Statistical Analysis Plan

NCT Number: NCT03196427

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

Study Number: Vedolizumab-2005

Document Version and Date: Final 4.0, 17 Jul 2025

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vedolizumab-2005

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

Long-term Safety With Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

PHASE 2b

Version**:** Final 4.0

Date**:** 17 July 2025

Prepared by:

[redacted]

Statistical and Quantitative Sciences

Based on:

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

1.2 Revision History

Version	Date	Person	Change
1.0	12 Aug 2019	[redacted]	
2.0	23 Feb 2024	[redacted]	[redacted]
3.0	1/30/25	[redacted]	- Revise header version number to match 1st page. - General clean-up (spacing, TOC page numbers updated.) - Table 6.2, drop duplicate endpoint of time to (first) fistula remission. - Additional updates per amended protocol V8. o [redacted] o Section 8.11.2. Update TEAE definition [redacted] o Revise interim analysis to be more flexible
4.0	7/17/25	[redacted]	- Section 5: o Revised endpoint wording for secondary endpoint maintenance of clinical response in CD to match definition in protocol Section 5.2.2. o [redacted] o Editorial changes and consolidation of definition for some secondary [redacted] o [redacted]

Version	Date	Person	Change
			[redacted] o Corresponding changes made in Section 7.8. - Section 7.1: [redacted] - Sections 7.1.4/7.8: [redacted] - Section 7.8.1: Total column added for general summaries of efficacy data. - Section 7.8.5: Clarification added for content of subgroup listings. - Section 7.9.1: [redacted] - Section 7.11.2: Frequent TEAE cutoff reduced from 5% to 3%. - Section 7.11.3: Added wording to include summaries of laboratory data by both conventional and SI units. - Section 9.2: Link for CDAI CDC growth chart(s) updated

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LIST OF ABBREVIATIONS

AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
IBD	inflammatory bowel disease
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
OL	open-label
PCDAI	Pediatric Crohn's Disease Activity Index
[redacted]	[redacted]
[redacted]	[redacted]
PTE	pretreatment event
PUCAI	Pediatric Ulcerative Colitis Activity Index
Q8W	once every 8 weeks
SAP	statistical analysis plan
SD	standard deviation
SES-CD	simple endoscopic score for Crohn's disease
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
WHODrug	World Health Organization Drug Dictionary

3.0 OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

To evaluate the efficacy of long-term vedolizumab IV in pediatric subjects with UC or CD.

- 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.
- To examine the effect of long-term vedolizumab IV treatment on health-related quality-of-life measurements in pediatric subjects with UC or CD.

To determine the effect of long-term vedolizumab IV treatment on patterns of growth and development in pediatric subjects with UC or CD.

3.3 [redacted]

[redacted]

4.0 STUDY DESIGN

Study Vedolizumab-2005 is a phase 2b, extension study to determine the long-term safety of vedolizumab IV in pediatric subjects with UC or CD who initiated vedolizumab treatment at 2 to 17 years of age, inclusive, in Study MLN0002-2003 (a phase 2, dose-ranging study). Up to 80 pediatric subjects who completed Study MLN0002-2003 and, at Week 22, achieved clinical response as defined by a reduction of partial Mayo score of ≥2 points and ≥25% from Baseline, or a reduction of the PUCAI of ≥20 points from Baseline for subjects with UC; or a reduction of the CDAI as defined by a ≥70-point decrease from Baseline or a decrease of PCDAI of ≥15 points for subjects with CD will be enrolled in the study. The study will also evaluate the effect of long-term vedolizumab IV treatment on the time to major IBD-related events (hospitalizations, surgeries, or procedures), health-related quality-of-life measurements, patterns of growth and development, [redacted] Subjects and investigators will remain blinded to the dose being administered through Week 32 of the study. If the subject experiences disease worsening, they may be eligible for dose escalation for subjects on the low dose of the appropriate weight group. If the subject is receiving the high dose for the appropriate weight group, they will not be eligible for dose escalation and will be discontinued from treatment. [redacted]. At Week 40 the blind will be lifted. A schematic of the study design is shown in Figure 4.a.

Assessment of eligibility for Vedolizumab-2005 will be determined and informed consent/pediatric assent for participation in Study Vedolizumab-2005 will be obtained on or after Week 14 through Week 22 of Study MLN0002-2003 based on the assessments of clinical response described above. Subjects in MLN002-2003 randomized to the low dose group who have not yet satisfied the criteria for clinical response at Week 14 will undergo a blinded dose escalation to the high dose group and will be re-evaluated for clinical response at Week 22 and eligibility to enter Vedolizumab-2005. The relevant clinical assessments from the Week 22 Visits of Study MLN0002-2003 will be used as the baseline assessments for Vedolizumab-2005. The majority of assessments in the extension study will be performed at 8-week intervals or at unscheduled visits when appropriate. [redacted] Safety assessments, [redacted], will be conducted as listed in the Schedule of Study Procedures in Appendix A of the study protocol. It is anticipated that the duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study. The subjects will attend a Final Safety Visit 18 weeks after the last dose of vedolizumab in Study Vedolizumab-2005. The end of study will be when the last subject completes their final safety visit 18 weeks after their last treatment in Study Vedolizumab-2005. During the safety follow-up period, if subjects transition to vedolizumab other than study drug, safety data will be collected until the 18-week safety follow-up visit (eg, 18 weeks after the last dose of study drug). Additionally, subjects will be required to

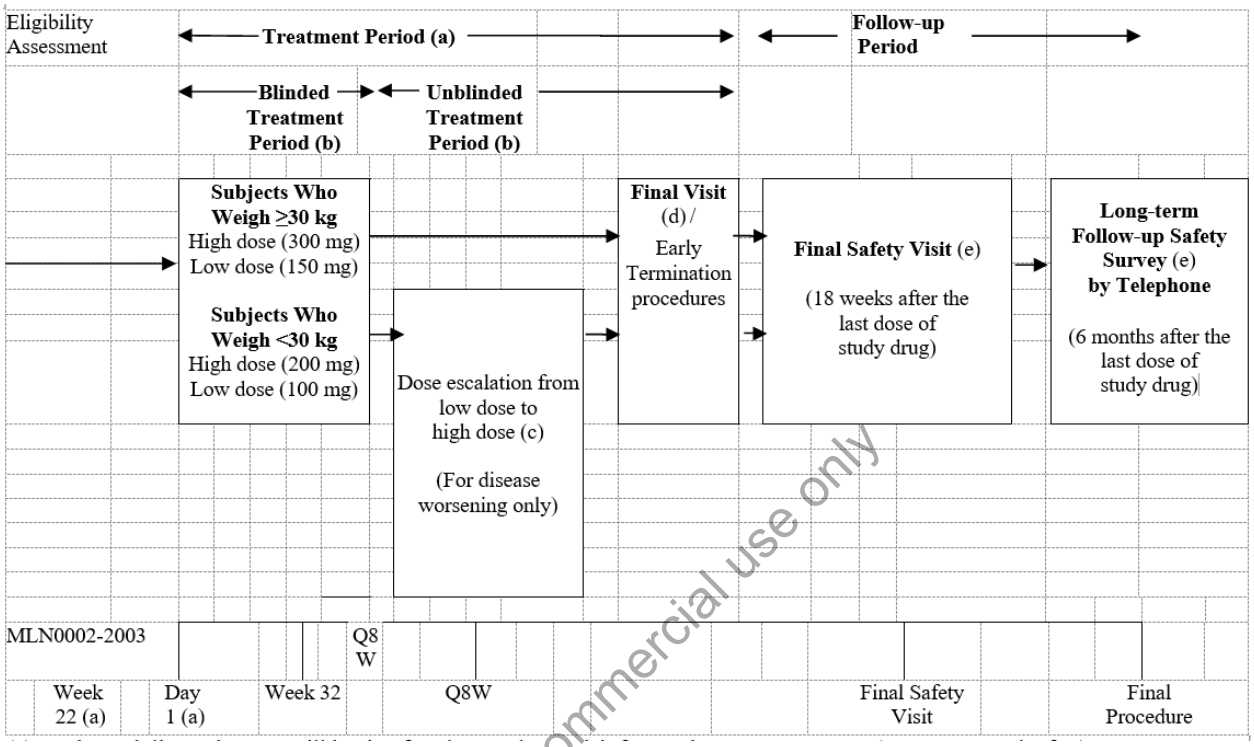
participate in a long-term follow-up safety survey by telephone, 6 months after their last dose of vedolizumab study drug.

Subjects will receive their first dose of vedolizumab IV in this study on Day 1, within 1 week of the MLN0002-2003 Week 22 assessments. At study entry, subjects will be administered the same blinded dose of vedolizumab IV that was received at Week 14 in Study MLN0002-2003 and will then continue to receive vedolizumab IV at a frequency of Q8W. The dosing algorithms for the high dose and low dose groups are summarized in Figure 4.b and Figure 4.c, respectively.

Subjects receiving the low dose (150 or 100 mg) of vedolizumab IV may be escalated to the high dose (300 or 200 mg) at any time during Vedolizumab-2005 if the subject demonstrates disease worsening by PUCAI/PCDAI at 2 consecutive visits (scheduled or unscheduled) (Figure 4.c). For UC subjects, disease worsening is 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 subjects, disease worsening is 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.

No further dose escalation will be permitted beyond the high dose per weight category (300 or 200 mg) Q8W. Subjects who experience continued disease worsening during the extension study despite being administered the high dose of vedolizumab Q8W (300 or 200 mg) will be discontinued from the study. Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores when next assessed after the increased dose has been administered. After completion of the MLN0002-2003 study, subjects who have entered the Vedolizumab-2005 study and who qualify for a dose increase because of disease worsening will have their dose increased to the maximum allowable dose in the cohort determined by their weight at the time of non-response during the Vedolozumab-2005 study.

Figure 4.a Schematic of Vedolizumab-2005 Study Design



(a) Study Vedolizumab-2005 will begin after the Week 22 Visit for Study MLN0002-2003 (or up to 1 week after). Subjects who consent to participate in the extension study (Vedolizumab-2005) may continue blinded study dosing after MLN0002-2003 Week 22 End-of-Study Visit procedures have been completed.

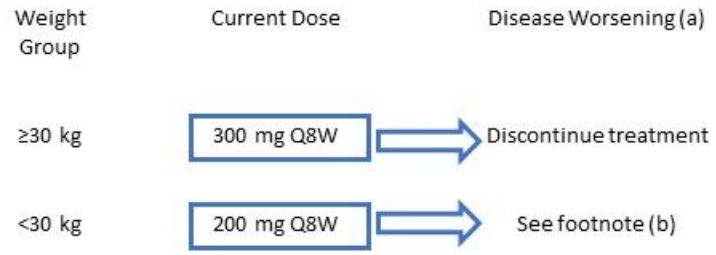
(b) Subjects will continue blinded study dosing through Week 32 of Study Vedolizumab-2005. If the subject experiences disease worsening, they may be eligible for dose escalation for subjects on the low dose of the appropriate weight group. If the subject is receiving the high dose for the appropriate weight group, they will not be eligible for dose escalation and will be discontinued from treatment. The dose will be unblinded at Week 40.

(c) If a subject demonstrates disease worsening by PUCAI/PCDAI (Section 7.8) at 2 consecutive visits (scheduled or unscheduled) they may be eligible for dose escalation. This information will be entered into IRT. Subjects eligible for a dose escalation will be dosed based on their weight at the time of nonresponse in Study Vedolizumab-2005. Subjects who were on the high dose for their current weight group will not be eligible for a dose escalation and will be discontinued from treatment. Subjects who show continued disease worsening despite dose escalation will be discontinued from the study. Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores 8 weeks after the increased dose has been administered.

(d) Duration of vedolizumab IV treatment will vary by subject on the basis of continued benefit but will be until vedolizumab IV is commercially available for pediatric indication(s) in the subject's country or until other drug access programs become available (whichever comes first), the subject turns 18 years of age and can be transitioned to commercial drug, the subject withdraws from the study, or the sponsor decides to close the study.

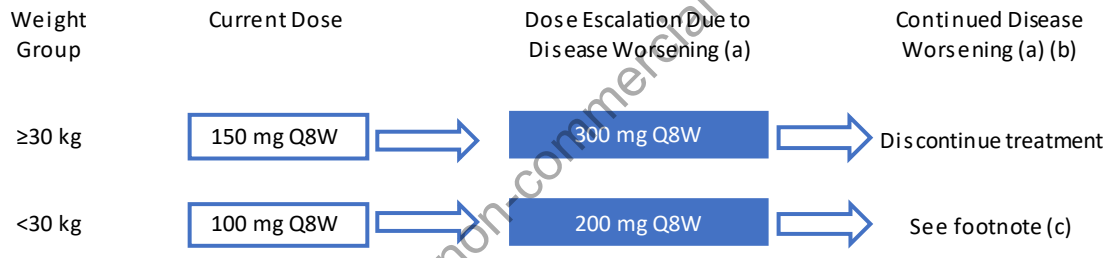
(e) Subjects will complete a Final Safety Visit 18 weeks after their last dose of study drug and participate in a long-term follow-up safety survey by telephone 6 months after the last dose of study drug.

Figure 4.b Schematic of Dosing Algorithm for Subjects in High Dose Groups in Open-label Period



(a) Definition of disease worsening: For UC, 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, 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.
(b) Subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse. If subjects weight has remained <30 kg at time of nonresponse, discontinue treatment. If subjects weight has increased to ≥30 kg at time of nonresponse, increase dose to 300 mg Q8W.

Figure 4.c Schematic of Dosing Algorithm for Subjects in Low Dose Groups in Open-label Period



(a) Definition of disease worsening: For UC, 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, 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.
(b) Continued disease worsening after a dose escalation is defined as no reduction in the elevated PCDAI or PUCAI scores 8 weeks after the increased dose has been administered.
(c) Subjects who have their dose increased based on nonresponse should be dosed based on weight at the time of nonresponse. If subjects weight has remained <30 kg at time of nonresponse, dose will increase to 200 mg Q8W. If subjects weight has increased to ≥30 kg at time of nonresponse, dose will increase to 300 mg Q8W.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

Percentage of subjects with treatment-emergent adverse events (TEAEs).

5.2 Secondary Endpoints

Table 5.1 lists the secondary endpoints and their definitions.

Table 5.1 Secondary Endpoints

Indication	Endpoint	Definition	Variable type
Secondary Endpoints			
UC	Maintenance of clinical response at Week 32, based on complete Mayo score*	A continued reduction in complete Mayo score of ≥3 points and ≥30% from the baseline (at initiation of MLN0002-2003) and continued decrease in rectal bleeding subscore of ≥1 point from baseline of MLN0002-2003, or absolute rectal bleeding subscore of ≤1 point at Week 32.	Binary
CD	Maintenance of clinical response at Week 32, based on SES-CD and CDAI	At Week 32, a 50% reduction in SES-CD score on endoscopy compared to the baseline endoscopy (at initiation of MLN0002-2003); and continued reduction in CDAI that is ≥70 point decrease from the baseline CDAI score at the initiation of MLN0002-2003.	Binary
UC and CD	Time to major IBD-related events	Time from study treatment start to first major IBD related hospitalization, surgery, or procedure	Time to event
	IMPACT-III	Change from baseline in IMPACT-III total and subscale scores at Week 24 and every 24 weeks thereafter.	Continuous
	Height velocity	Height velocity at Week 48 and every 48 weeks thereafter.	Continuous
	Height, weight, and body mass index (BMI)	Change from baseline in height, weight, and BMI at Week 24 and every 24 weeks thereafter.	Continuous
	Tanner scale	Achieving Tanner Stage V at or before age 16 (in females) or age 17 (in males)	Binary

* The definition for the endpoint maintenance of clinical response in UC is based on the definition of clinical response in Section 3.5 Study Definitions of the Protocol considering only the complete Mayo score.

5.3 [redacted]

Please see Table 5.2 for details of the [redacted]

Table 5.2 [redacted]

[redacted]

Table 5.2 [redacted]

[redacted]

5.4 [redacted]

[redacted]

[redacted]

Table 5.3 [redacted]

[redacted]

Table 5.3 [redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is estimated that up to 80 subjects (40 with UC and 40 with CD) who completed Study MLN0002-2003 will enter this study. No formal sample size calculations were performed for this study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® version 9.2 or higher.

Where appropriate, endpoints/variables will be summarized descriptively by study visit. For categorical variables, the count and proportions of each possible value will be tabulated by treatment groups. Percentages will be calculated out of the total number of subjects in the analysis set and by subgroups, when applicable. For continuous variables, the number of subjects with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be tabulated. Means and medians will be presented to 1 more decimal place than the recorded data. The SDs will be presented to 2 more decimal places than the recorded data.

Two-sided credible intervals will be computed using Jeffreys prior due to the expected small sample sizes and will be presented using the same number of decimal places as the point estimate. Jeffery's prior for a binomial parameter is beta distribution with both parameters of the beta distribution equal to 1/2. If n is the total number of subjects in a treatment group with x having positive outcomes then the posterior distribution of the binomial parameter will follow a beta distribution with parameters x+1/2 and n-x+1/2. The 2.5th and 97.5th percentile of the posterior beta distribution will provide the 95% credible interval. The exact 95% CI (e.g., Clopper-Pearson interval) will be presented as well.

Analysis windowing convention will be used to determine the analysis values for a given study visit for observed data analyses. Details are provided in Section 7.1.3.

7.1.1 Definition of Study Days

Day 1 will be defined as the day of first study drug administration in the Extension Study Vedolizumab-2005, as recorded on the electronic case report form (eCRF) dosing page.

Study day will be calculated relative to the date of the first dose of study drug administration in the Extension Study Vedolizumab-2005. Study days prior to the first dose of study drug will be calculated as:

Date of assessment/event – Date of first dose of study drug.

Study days on or after the first dose of study drug will be calculated as:

Date of assessment/event – Date of first dose of study drug + 1.

7.1.2 Baseline

Two baselines will be defined for the Extension Study Vedolizumab-2005:

- **Baseline at entry to Study MLN0002-2003** is defined as the last observed non-missing value before the first dose of study medication in Study MLN0002-2003.
- **Baseline at entry to Study Vedolizumab-2005** is defined as the last observed non-missing value before the first dose of study medication in Study Vedolizumab-2005. The relevant

assessments from the Week 22 Visit of Study MLN0002-2003 may be used as the baseline assessments.

Study Vedolizumab-2005 Day 1 predose Vedolizumab concentration will be the Week 22 trough concentration from Study MLN0002-2003.

Certain analyses of change from baseline will use baseline at entry to Study MLN0002-2003 as the reference for the calculation of change from baseline.

7.1.3 Definitions of Study Visit Windows

Subjects do not always adhere strictly to the visit timing stated in the protocol. Therefore, the designation of visits will be based on the day of evaluation relative to the start of study drug rather than the nominal visit recorded in the data. Accordingly, the study is divided into continuous, mutually exclusive analysis windows.

The rules provided in the tables (Table 7.1 and Table 7.2) below will be used for safety and efficacy data. The lower and upper bounds of each window are the approximate midpoints between the scheduled days for the current visit and its adjacent scheduled visits. The value used in analysis for by-visit summaries is the value within the specified window. If a subject has more than one measurement within an analysis window, the assessment closest to the target day will be used. In cases of ties between observations located on different sides of the target day, the later assessment will be used in analyses. In cases of ties located on the same side of the target day (i.e., more than one value for the same day), the mean of the values will be used for continuous parameters and the worst result will be chosen over a more positive one for categorical parameters.

Table 7.1 Analysis Visit Windows for Safety Data Evaluated by Visit*

Visit	Target Day	Vital Signs	Laboratory
Baseline1[a]	Day1a[a]		
Baseline2[b]	Day1b[b]	≤ 1	≤ 1
Week 8	Day 57	2 – 84	N/A
Week 16	Day 113	85 – 140	2 – 168
Week 24	Day 169	141 – 196	N/A
Week 32	Day 225	197 – 252	169 – 280
Week 40	Day 281	253 – 308	N/A
Week 48	Day 337	309 – 364	281 – 392
Week 56	Day 393	365 – 420	N/A
Week 64	Day 449	421 – 476	393 – 504
Week 72	Day 505	477 – 532	N/A
Week 80	Day 561	533 – 588	505 – 616
Week 88	Day 617	589 – 644	N/A
Week 96	Day 673	645 – 700	617 – 728

Table 7.1 Analysis Visit Windows for Safety Data Evaluated by Visit*

Visit	Target Day	Vital Signs	Laboratory
Week 104	Day 729	701 – 756	N/A
Week 112	Day 785	757 – 812	729 – 840
Week 120	Day 841	813 – 868	N/A
Week 128	Day 897	869 – 924	841 – 952
Week 136	Day 953	925 – 980	
Week 144	Day 1009	981 – 1036	953 – 1064
Week 152	Day 1065	1037 – 1092	N/A
Week 160	Day 1121	1093 – 1148	1065 – 1176
Week 168	Day 1177	1149 – 1204	N/A
Week 176	Day 1233	1205 – 1260	1177 – 1288
Week 184	Day 1289	1261 – 1316	N/A
Week 192	Day 1345	1317 – 1372	1289 –1400
Week 200	Day 1401	1373 – 1428	N/A
Week 208	Day 1457	1429 – 1484	1401 – 1512
Week 216	Day 1513	1485 – 1540	N/A
Week 224	Day 1569	1541 – 1596	1513 – 1624
Week 232	Day 1625	1597 – 1652	N/A
Week 240	Day 1681	1653 – 1708	1625 – 1736
Week 248	Day 1737	1709 – 1764	N/A
Week 256	Day 1793	1765 – 1820	1737 – 1848
Week 264	Day 1849	1821 – 1876	N/A
Increases every 8 weeks	Day (Week * 7) +1	Target day – 28 days to Target Day + 27 days	Target day – 56 days to Target day + 55 days
Follow-Up Safety Visit		Nominal Visit	Nominal Visit

*All visits without reference to a study refers to Vedolizumab-2005 visits.
[a] Baseline1 = Baseline at Vedolizumab-2003; Day1a = Day 1 at Vedolizumab-2003.
[b] Baseline2 = Baseline at Vedolizumab-2005; Day1b = Day 1 at Vedolizumab-2005.

Table 7.2 Analysis Visit Windows for Efficacy Data Evaluated by Visit*

Visit	Target Day	Partial Mayo Score, UCAI, [redacted] Steroid dosing	Endoscopy, CDAI, complete Mayo Score, SES-CD	[redacted] FCP	IMPACT-III
Baseline1[a]	Day1a[a]				
Baseline2[b]	Day1b[b]	≤ 1	≤ 1	≤ 1	≤ 1
Week 8	Day 57	2 – 84	N/A	N/A	N/A
Week 16	Day 113	85 – 140	N/A	N/A	N/A
Week 24	Day 169	141 – 196	N/A	N/A	2 – 252
Week 32	Day 225	197 – 252	2 – 392	N/A	N/A
Week 40	Day 281	253 – 308	N/A	N/A	N/A
Week 48	Day 337	309 – 364	N/A	2 – 504	253 – 420
Week 56	Day 393	365 – 420	N/A	N/A	N/A
Week 64	Day 449	421 – 476	N/A	N/A	N/A
Week 72	Day 505	477 – 532	N/A	N/A	421 – 588
Week 80	Day 561	533 – 588	393 – 728	N/A	N/A
Week 88	Day 617	589 – 644	N/A	N/A	N/A
Week 96	Day 673	645 – 700	N/A	505-840	589 – 756
Week 104	Day 729	701 – 756	N/A	N/A	N/A
Week 112	Day 785	757 – 812	N/A	N/A	N/A
Week 120	Day 841	813 – 868	N/A	N/A	757 – 924
Week 128	Day 897	869 – 924	729 – 1064	N/A	N/A
Week 136	Day 953	925 – 980	N/A	N/A	N/A
Week 144	Day 1009	981 – 1036	N/A	841 – 1176	925 – 1092
Week 152	Day 1065	1037 – 1092	N/A	N/A	N/A
Week 160	Day 1121	1093 – 1148	N/A	N/A	N/A
Week 168	Day 1177	1149 – 1204	N/A	N/A	1093 – 1260
Week 176	Day 1233	1205 – 1260	1065 – 1400	N/A	N/A
Week 184	Day 1289	1261 – 1316	N/A	N/A	N/A
Week 192	Day 1345	1317 – 1372	N/A	1177 – 1512	1261 – 1428
Week 200	Day 1401	1373 – 1428	N/A	N/A	N/A
Week 208	Day 1457	1429 – 1484	N/A	N/A	N/A
Week 216	Day 1513	1485 – 1540	N/A	N/A	1459 – 1596
Week 224	Day 1569	1541 – 1596	≥ 1401	N/A	N/A
Week 232	Day 1625	1597 – 1652	N/A	N/A	N/A
Week 240	Day 1681	1653 – 1708	N/A	1513-1848	1597 – 1764

Table 7.2 Analysis Visit Windows for Efficacy Data Evaluated by Visit*

Visit	Target Day	Partial Mayo Score, UCAI, [redacted] Steroid dosing	Endoscopy, CDAI, complete Mayo Score, SES-CD	[redacted] FCP	IMPACT-III
Week 248	Day 1737	1709 – 1764	N/A	N/A	N/A
Week 256	Day 1793	1765 – 1820	N/A	N/A	N/A
Week 264	Day 1849	1821 – 1876	N/A	N/A	1765 – 1932
Increases every 8 weeks	Day (Week * 7) +1	Target day – 28 days to Target day +27 days	Every 6 visits: Target day – 168 days to Target day + 167 days	Every 6 visits: Target day – 168 days to Target day + 167 days	Target day – 84 days to Target day + 83 days

*All visits without reference to a study refers to Vedolizumab-2005 visits.
[a] Baseline1 = Baseline at Vedolizumab-2003; Day1a = Day 1 at Vedolizumab-2003.
[b] Baseline2 = Baseline at Vedolizumab-2005; Day1b = Day 1 at Vedolizumab-2005.

7.1.4 Methods for Handling of Missing Efficacy Data

After Week 32, the conduct of an endoscopy and the assessment of the complete Mayo score (UC), CDAI and SES-CD (CD) were optional. Consequently, the modified Mayo score, and the binary response-type endpoints related to those optional assessments can only be determined for subjects/time points when those assessment were done. [redacted] Through the end of the treatment period, the missing efficacy data will be handled as follows:

1) Binary response-type endpoints:
In general, missing data for response-type endpoints up to and including Week 32 will be handled using the non-responder imputation method, i.e. any subject with missing information for determination of endpoint status up to Week 32 will be considered as a non-responder in the analysis. Missing response-type endpoints based on Mayo scores or CDAI due to missing diary data of subjects who were not required to complete a diary (at Week 32) per the protocol version they were enrolled under, will not be imputed (see also Section 7.8).
[redacted]

   a) For subjects who have completed or withdrawn by the time of interim data cut or at final analysis, the missing data for determination of the status of dichotomous efficacy endpoints will be handled as per the rules as in the paragraph above.

   b) [Interim analysis only] For ongoing subjects, missing data for determination of the status of dichotomous efficacy endpoints at the visits that have been reached by the time of

interim data cut will be imputed using the non-responder method. Data for future visits that have not been reached by the time of the interim data cut will not be imputed.

c) The two additional approaches for handling of missing data described below will be applied:

i) For subjects who have discontinued prematurely from the study, missing data for determination of the status of dichotomous efficacy endpoints at time points after their premature discontinuation will be handled as per the rules described in paragraph (1).

For subjects who have completed the study or completed the study early and transitioned to the commercial drug (at age 18), missing data for determination of their status of dichotomous efficacy endpoints will not be imputed for time points after their time of study treatment completion (EOT). Instead, those subjects will be excluded from the analyses of such endpoints for the time points after their study treatment completion (observed data up to EOT+126 days will be included in the analysis).

ii) For subjects who have completed or withdrawn from the study, the missing data for determination of the status of dichotomous efficacy endpoints after completion or withdrawal will not be imputed, and subjects will not be counted in the denominator for those time points (observed-data analysis).

2) Continuous endpoints:
Missing data for the continuous efficacy endpoints complete, modified, and partial Mayo score, CDAI, and SES-CD will not be imputed. [redacted] Other continuous endpoints will be summarized using observed data analyses only.

[redacted]

[redacted]

Other missing data handling methods may be explored as appropriate.

7.1.5 Conventions for Missing Adverse Event Dates

Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or SAEs, a missing or incomplete onset date will be imputed according to the following conventions:

1. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
   a) First study medication date.
   b) Consent date (for SAEs only).
2. If an onset date is incomplete, the derived onset date will be calculated following:
   a) Missing day, but month and year present: the day will be imputed as the 15th of the month. If the month and year are equal to the month and year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
   b) Missing day and month, but year present: the day and month will be imputed as the 30th of June of the year. If the year is equal to the year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
   c) If the imputed AE onset date occurs after the database lock date, the imputed AE onset date will be imputed as the database lock date.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

3. If an end date is missing, the derived end date will be imputed as the last assessment date assuming that the last assessment occurs after the AE start. If the last assessment occurs prior to the AE start date, the derived end date will be imputed as the AE start date.
4. If an end date is incomplete, the derived end date will be calculated following:
   a) Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month.

      Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.

   b) If the imputed AE end date occurs after the database lock date, the imputed AE end date will be imputed as the database lock date.

7.1.6 Conventions for Missing Concomitant Medication Dates

Start and stop dates for medication history and concomitant medications are collected on the eCRF. Definitions of medication history and concomitant medications are defined in Section 7.6. Missing or partial dates for medication history will not be imputed. However, in case of missing or partial dates for concomitant medications, the following rules will be used:

If the start date is partial or unknown:

- If the day is missing, the start day will be the first day of the month.
- If the month is missing, the start month will be the month corresponding to month of the first dose of study drug.
- If the year is missing, the start year will be the minimum of the year of the first clinic visit or the year of the informed consent date.
- If the entire date is unknown, the start date will be the date of first dose of study drug.

If the stop date is partial, unknown or "ongoing":

- If the day is missing, the stop day will be the last day of the month reported.
- If the month is missing, the stop month will be to the month during which the last assessment occurred.
- If the year is missing or the entire date is unknown or if the medication is "ongoing", the stop year will be the year in which the last assessment occurred.

No dates will be imputed for previous medications.

7.1.7 Conventions for Calculation of Mayo Score

The Mayo scoring system is a composite index of 4 disease activity variables (see Appendix A for details):

- Stool frequency
- Rectal bleeding
- Findings on endoscopy
- Physician's global assessment (PGA)

Each variable is scored individually on an integer scale of 0 to 3, with higher scores indicating greater disease activity. The individual components of the Mayo score are stool frequency, rectal bleeding, findings on endoscopy, and the physician's global assessment (PGA). The Partial Mayo score is calculated analogously but excludes the endoscopy subscore. The modified Mayo score is calculated analogously but excludes the PGA subscore.

Mayo scores will be derived from first principles. All subscores should be rounded to the nearest integers. Apply rounding as final subscores are created and prior to calculation of total score. The day prior, day of and day after endoscopy cannot be used for subject Diary entry because of the required bowel prep for the procedure.

It shall be noted, that the modified Mayo score derived in this study is not fully compliant with the modified Mayo score as per the draft FDA UC Guidance 2022 (Ulcerative Colitis: Developing Drugs for Treatment, Guidance for Industry, April 2022); as per the Mayo scoring system used in this study (see Mayo Score Calculation Worksheet in 9.1, Appendix A), an endoscopic score of 1 includes mild friability.

7.1.7.1 GEMINI Approach

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

1. Use the date of the visit where PGA was performed to identify analysis visit using the analysis visit windowing rules defined in Section 7.1.3.
2. Identify PGA result (subscore).
3. Identify the endoscopy subscore (based on adjudicated data) using the analysis visit windows.
4. Calculate rectal bleeding subscore and stool frequency subscore:
   a) Select the Diary data completed by the subject from 7 days prior to the visit date identified in (1).
   b) Merge in endoscopy dates (including dates of attempted endoscopy) and set diary data one day prior, on the day and one day after the endoscopy to missing.
   c) For Screening visit, if less than 3 days of data remain then a subscore cannot be calculated. Otherwise, sum the 3 most recent non-missing results and divide by 3. Subjects who have

less than 3 days of Diary data during Screening are not eligible for enrollment and the subscore will be considered missing.

d) For post-Screening visits, sum the 3 most recent non-missing results and divide by 3. If only 2 non-missing results remain, then sum the 2 most recent non-missing results and divide by 2. If less than 2 days of diary data are available, the subject will be categorized as a non-responder and the subscore will be considered missing.

5. Calculate total score:

a) For complete Mayo, sum the PGA subscore, endoscopy subscore, rectal bleeding subscore and stool frequency subscore. All 4 subscores must be available.

b) For partial Mayo, sum the PGA subscore, rectal bleeding subscore and stool frequency subscore. All 3 subscores must be available.

Table 7.3 [redacted]

Table 7.3 [redacted]

[redacted]

7.1.7.2 Draft FDA UC Guidance (2016) Approach

The complete Mayo and partial Mayo will also be calculated per draft FDA UC Guidance (August 2016). The efficacy endpoints based on complete, partial, or modified Mayo scores at Week 6, Week 14, and Week 22 will be derived using this approach as sensitivity analysis.

1. Use the date of the visit where PGA was performed to identify analysis visit using the analysis visit windowing rules defined in Section 7.1.3.
2. Identify PGA result (subscore).
3. Identify the endoscopy subscore (based on adjudicated data) using the visit windows.
4. Calculate rectal bleeding subscore and stool frequency subscore:
   a) Select the Diary data completed by the subject from 7 days prior to the visit date identified in (1).
   b) Merge in endoscopy dates (including dates of attempted endoscopy) and set diary data one day prior, on the day and one day after the endoscopy to missing.
   c) For Screening visit, if less than 3 days of data remain then a subscore cannot be calculated. Otherwise, sum the 3 most recent non-missing results and divide by 3. Subjects who have less than 3 days of Diary data during Screening are not eligible for enrollment and the subscore will be considered missing.
   d) For post-Screening visits, sum the 3 most recent consecutive non-missing results and divide by 3. For subjects who do not have 3 consecutive days of non-missing Diary data but have at least 4 days of data available in the last 7-day period prior to the visit, the non-missing scores from the total number of available days in the last 7-day period will be averaged. If less than 3 consecutive days or 4 days of Diary data in the last 7-day period are available, the subject will be categorized as a non-responder and the subscore will be considered missing.
5. Calculate total score:
   a) For complete Mayo, sum the PGA subscore, endoscopy subscore, rectal bleeding subscore and stool frequency subscore. All 4 subscores must be available.
   b) For partial Mayo, sum the PGA subscore, rectal bleeding subscore and stool frequency subscore. All 3 subscores must be available.

Table 7.4 [redacted]

Table 7.4 [redacted]

[redacted]

Table 7.4 [redacted]

[redacted]

7.1.8 Conventions for Calculation of CDAI Scores

The CDAI score is the summation of 8 components, including number of liquid or very soft stools, abdominal pain, general well-being, extra-intestinal manifestations of Crohn's Disease, Lomotil/Imodium/opiates for diarrhea usage, abdominal mass, hematocrit level, and body weight (see Appendix B for details). Minor modifications are made to the CDAI to facilitate its use in children, e.g., replacing "standard weight" by "ideal weight for height" (Griffiths et al, 2005).

7.1.8.1 GEMINI Approach

Number of liquid or very soft stools, abdominal pain, and general well-being are self-reported via subject electronic diary entries. To calculate subscores at each visit, the diary data from the 10 days prior to the date of CDAI calculation were used and the following rules were applied:

1. Identify the date of the Clinician CDAI completion date from the Diary system.
2. Calculate the 3 Diary subscores (liquid/soft stool frequency, abdominal pain and general wellbeing) as follows.
    a. Select the diary data from 10 days prior to the CDAI completion date identified in (1).
    b. Merge in endoscopy video dates (including dates of attempted endoscopy video) and set diary data one day prior, on the day and one day after the endoscopy to missing.
    c. For number of liquid or very soft stools only, if any of the 7 most recent days of diary data have stool frequency values greater than 24, set the value for the stool record for that day to missing.
    d. For Screening, if less than 7 days of non-missing data remain, then a subscore cannot be calculated; otherwise, the subscore is calculated as the sum of the most recent 7 days of non-missing diary.
    e. For post-screening visits:

i. If less than 4 days of diary data is non-missing, then a subscore cannot be calculated.

ii. If 4, 5 or 6 days of diary is non-missing, the subscore is calculated as {average of non-missing diary from available days ×7} rounding to the nearest integer.

iii. If 7 or more days of diary is non-missing, the subscore is calculated as sum of the most recent 7 days of non-missing diary.

Table 7.5 [redacted] Table 7.6 [redacted]. Subject diaries can be completed 14 days prior to the eligibility visit. Any on-study colonoscopies and/or MRE are taken into account such that the diary data from the day prior, day of, and day after are excluded from the visit's CDAI calculation.

The subscore is calculated by multiplying the factor appropriate for the item.

- For stool, the factor is 2.
- For abdominal pain, the factor is 5.
- For general well-being, the factor is 7.

3. Extra-intestinal manifestations of Crohn's Disease Subscore: total number of checked items from Diary data, and multiply by a factor of 20.
4. Lomotil/Imodium/opiates for diarrhoea Subscore: Subscore is 1 if "Yes" is selected; subscore is 0 if "No" is selected. Multiply by a factor of 30.
5. Abdominal Mass Subscore: subscore is 0 if "None" is selected, subscore is 2 if "Questionable" is selected, and subscore is 5 if "Definite" is selected. Multiply by a factor of 10.
6. Calculate Hematocrit Subscore as follows:
    a. For the Screening Visit, identify the most recent non-missing Hematocrit (%) results with the sample collection date prior to the CDAI completion date in (1)
    b. For post-screening visits, identify the Hematocrit (%) results using the visit windows defined in Section 7.1.2.
    c. For male subjects, the subscore is calculated as the maximum of {47- Hematocrit (%), 0} rounding to the nearest integer. For female subjects, the subscore is calculated as the maximum of {42- Hematocrit (%), 0} rounding to the nearest integer.
    d. The haematocrit subtotal is then multiplied by a factor of 6 to determine the haematocrit subscore. If the haematocrit subtotal is 0, the haematocrit subscore is set to 0.

7. Body Weight Subscore

    a. Identify the weight in kilogram (kg) using the visit windows defined in Section 7.1.2.

    b. Identify the standard weight using subject's gender, age and height according to Appendix B. Minor modifications are made to the CDAI by replacing "Standard Weight" by "Ideal Weight for Height". See Appendix B for details.

    c. Calculate the subscore using the formula below, rounding to the nearest integer. If the body weight subscore is < -10, the body weight subscore is set to -10.

$$\left[1 - \left(\frac{\text{Body Weight}}{\text{Ideal Weight for Height}}\right)\right] \times 100$$

8. Calculate total CDAI score for a study visit as the sum of the 8 subscores at that particular study visit. If any of the 8 subscores is missing, the total CDAI score cannot be calculated and the total CDAI score for that study visit will be set to missing.

Table 7.5 [redacted]

[redacted]

Table 7.6 [redacted]

[redacted]

7.1.9 Conventions for Calculation of SES-CD

The SES-CD has been shown to be comparable to the Crohn's Disease Endoscopic Index of Severity and a straightforward scoring system for Crohn's disease (see Appendix C for details).

The SES-CD total score ranges from 0 to 56 and is the sum of 4 variables (i.e., size of ulcers [cm], ulcerated surface [%], affected surface [%], and presence of narrowing) across 5 bowel segments (i.e., rectum, descending and sigmoid colon, transverse colon, ascending colon, and

ileum). Each variable is coded from 0 to 3 based on severity, where 0 is none or not severe and 3 is the most severe case, with the sum of the scores for each variable ranging from 0 to 15, except for presence of narrowing. Presence of narrowing ranges from 0 to 11 since a severity of 3 represents a narrowing which a colonoscope cannot pass and, thus, can only be observed once among the bowel segments. The segmental SES-CD score is the sum of the 4 variables for each bowel segment and can range from 0 to 12, where each individual variable score ranges from 0 to 3.

7.1.10 [redacted]

[redacted]

7.1.11 [redacted]

[redacted]

7.2 Analysis Sets

7.2.1 Enrolled Set

The enrolled set will have all subjects enrolled in this study.

7.2.2 Full Analysis Set (FAS)

The full analysis set (FAS) will include all enrolled subjects who receive at least 1 dose of study drug in Vedolizumab-2005 and will be used in the efficacy analysis.

7.2.3 Safety Analysis Set (SAF)

The safety analysis set (SAF) will include all enrolled subjects who receive at least 1 dose of study drug in Vedolizumab-2005, as in the FAS, and will be used in the safety analysis.

7.2.4 [redacted]

[redacted]

7.3 Disposition of Subjects

Disposition of subjects will be presented based on the subjects enrolled. If the enrolled set and FAS are the same, then presentation will use the FAS in all summaries.

The following summaries of subject disposition will be produced:

Summary of Eligibility for Treatment in Vedolizumab-2005

This summary will include the number of subjects eligible for treatment and the number of subjects not eligible for treatment along with the primary reason for not being eligible (i.e. screen failures).

Number of Subjects treated by Site and Dose Regimen

This summary will be performed by the factors: previous exposure/failure of TNF-α antagonist therapy or naïve to TNF-α antagonist therapy, indication (UC, CD) and weight group at entry (≥30 kg, <30 kg) to Vedolizumab-2003.

Disposition of Subjects

This summary will be performed on the enrolled set and will summarize subjects treated, subjects completing or prematurely discontinuing study drug along with the primary reason for study drug discontinuation.

Significant Protocol Deviations

This summary will be performed on the Enrolled Set and will summarize the significant protocol deviations captured on the electronic case report form by dose regimen and overall.

Analysis Sets

The analysis sets defined in Section 7.2 will be summarized.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by dose regimen at entry to Vedolizumab-2005, by indication and overall for each weight group (at entry to

Vedolizumab-2003) based on the Vedolizumab-2005 enrolled set. The baseline summary will include descriptive statistics for age, height, weight and body mass index and counts and percentages for weight groups (≥30 kg, <30 kg), gender, ethnicity, race, substance use and geographical region. Note that age, height, weight and body mass index will be based on the data collected at entry to Vedolizumab-2005 and everything else will be based on the data collected at entry to Vedolizumab-2003. For continuous variables, summary statistics (non-missing values, mean, median, SD, minimum and maximum) will be generated. For categorical variables, the counts and percentages of each possible value will be generated.

Baseline disease characteristics (at the entry to Vedolizumab-2003 and at the entry to Vedolizumab-2005) will be summarized for each indication separately by dose regimen (at entry to Vedolizumab-2005) and overall. The summaries will include descriptive statistics for disease duration, baseline disease activity (based on complete Mayo, partial Mayo and PUCAI for UC and CDAI, PCDAI and SES-CD for CD), baseline number of liquid or very soft stools subscore and abdominal pain subscore from CDAI for CD, baseline fecal calprotectin and baseline [redacted]. Counts and percentages will also be presented for baseline stool frequency subscore, rectal bleeding subscore, endoscopic subscore and physician's global assessment subscore from Mayo for UC (0, 1, 2, 3 for all subscores) and anti-TNF history (naïve, exposed/failed).

The relevant assessments from the Week 22 Visit of Study MLN0002-2003 may be used as the baseline assessments at the entry of Vedolizumab-2005. The assessments of complete Mayo score and SES-CD from the Week 14 visit of Vedolizumab-2003 may be used as the baseline assessments at the entry to Vedolizumab-2005.

Baseline characteristic categories for UC and CD are summarized in Table 7.7 and Table 7.8, respectively.

Table 7.7 Baseline Characteristics for UC

Baseline Characteristics	Summarized as	Categories
Disease duration	Continuous and Categorical	< 1 year ≥ 1 to < 3 years ≥ 3 to < 7 years ≥ 7 years
Baseline fecal calprotectin (µg/g)	Continuous and Categorical	≤ 250 µg/g > 250 µg/g and ≤ 500 µg/g > 500 µg/g
[redacted]		
Prior TNF History	Categorical	Naïve Exposure

Table 7.7 Baseline Characteristics for UC

Baseline Characteristics	Summarized as	Categories
		Failure
Baseline Mayo score	Continuous	
Baseline disease activity based on complete Mayo	Categorical	Mild (<6) Moderate (6 to 8) Severe (9 to 12)
Baseline partial Mayo score	Continuous	
Baseline disease activity based on partial Mayo	Categorical	Mild (2-4) Moderate (5-6) Severe (7-9)
Baseline PUCAI	Continuous	
Baseline disease activity based on PUCAI	Categorical	Mild (10-34) Moderate (35-64) Severe (65-85)
Baseline stool frequency subscore from Mayo	Categorical	0, 1, 2, 3
Baseline rectal bleeding subscore from Mayo	Categorical	0, 1, 2, 3
Baseline endoscopic subscore from Mayo	Categorical	0, 1, 2, 3
Baseline physician's global assessment subscore from Mayo	Categorical	0, 1, 2, 3

Baseline Mayo scores and subscores calculated using the GEMINI approach.

Table 7.8 Baseline Characteristics for CD

Baseline Characteristics	Summarized as	Categories
Disease duration	Continuous and Categorical	< 1 year ≥ 1 to < 3 years ≥ 3 to < 7 years ≥ 7 years
Baseline fecal calprotectin (µg/g)	Continuous and Categorical	≤ 250 µg/g > 250 µg/g and ≤ 500 µg/g > 500 µg/g
[redacted]		
Prior TNF History	Categorical	Naïve

Table 7.8 Baseline Characteristics for CD

Baseline Characteristics	Summarized as	Categories
		Exposure Failure
Baseline CDAI score	Continuous	
Baseline disease activity based on CDAI	Categorical	>330 ≤330
Baseline PCDAI	Continuous	
Baseline disease activity based on PCDAI	Categorical	Mild (11-30) Moderate to Severe (>30)
Baseline SES-CD	Continuous	
Baseline disease activity based on SES-CD	Categorical	Moderate (7-15) Severe (>15)
Baseline number of liquid or very soft stools subscore from CDAI	Continuous	
Baseline abdominal pain subscore from CDAI	Continuous	

All demographic, baseline characteristics and baseline disease characteristics will be listed.

7.5 Medical History and Concurrent Medical Conditions

The FAS will be used for all summaries in this section.

Medical history is defined as any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Medical history will be coded using MedDRA Version 26.1 (or higher) and will be summarized by system organ class and preferred term, by dose regimen (at entry to Vedolizumab-2005) and overall.

Concurrent medical conditions are defined as any significant conditions or diseases relevant to the disease under study that were ongoing at signing of informed consent. Concurrent medical conditions will be coded using MedDRA Version 26.1 (or higher) and will be summarized by system organ class and preferred term, by dose regimen (at entry to Vedolizumab-2005) and overall.

Medical history and concurrent medical conditions will be presented in data listings.

7.6 Medication History and Concomitant Medications

The SAF will be used for all summaries in this section.

Medication history and concomitant medications will be summarized by preferred name.

Medication history is defined as any medication relevant to eligibility criteria stopped at or within 1 month prior to signing of informed consent. Medication history will be coded using WHODrug 2023 (or higher) and will be summarized by preferred medication name, by dose regimen (at entry to Vedolizumab-2005) and overall.

Prior biologic history for the treatment of UC or CD is defined as prior biologic medications stopped at or prior to signing of informed consent for Vedolizumab-2003. Prior biologic history will be coded using WHODrug 2023 (or higher) and will be summarized for each indication separately by preferred medication name, by dose regimen (at entry to Vedolizumab-2005) and overall.

Concomitant medications are defined as any drugs used in addition to the study medication from Day 1 through the end of the study. Concomitant medications will be coded using WHODrug 2023 (or higher).

Baseline for the above refers to the baseline visit for Vedolizumab-2005. Each category of concomitant medications will be summarized by preferred medication name, by dose regimen (at entry to Vedolizumab-2005) and overall.

7.7 Study Drug Exposure and Compliance

The SAF will be used for all summaries in this section.

Completed infusions are defined as infusions where the total amount of study drug is infused. The number of completed infusions will be summarized by dose regimen and overall.

The extent of exposure to Vedolizumab in Vedolizumab-2005 will be calculated by the duration between the first and last dose of study drug plus 18 weeks (126 days) in order to account for the known duration of detectable vedolizumab serum concentration after the last dose, i.e.

Date of last dose of Vedolizumab – Date of first dose of Vedolizumab + 1 + 126 days.

The extent of exposure will be summarized using descriptive statistics by dose group and overall for each indication separately.

The number and percentage of subjects administered each dose level (100mg, 200mg, 150mg, 300mg) at each visit will be summarized using the total number of subjects enrolling in Vedolizumab-2005 in each indication and by weight group as the denominator, excluding those subjects who drop out at specific visits (to ensure that subjects who are not continuing on these visits will not be included in the percentage calculation).

Compliance will be calculated as follows:

(# of completed infusions) / total number of planned infusions * 100, or

(# of completed or partial infusions) / total number of planned infusions * 100.

7.8 Efficacy Analysis

Efficacy analyses will be performed using the FAS and are exploratory; no formal statistical comparisons will be made.

For response-type binary efficacy endpoints based on Mayo, CDAI [redacted] scores, subject having missing data for determination of binary endpoint (i.e., missing data for the component of the respective scale) at any time point will be handled as described in section 7.1.4.

The following is to be considered in the analysis of the aforementioned binary response-type endpoints at Week 32:

- Due to differences in the protocol versions (e.g., versions amendment #4 and amendment #5), completion of a daily symptom diary to inform the calculation of Mayo or CDAI scores was not mandatory for all subjects. Hence, Mayo scores/CDAI scores missing at Week 32 due to missing corresponding diary data for subjects enrolled under protocol versions not requiring diary completion should be handled specifically and excluded from the denominator (non-response imputation is not appropriate).

All response-type binary efficacy endpoints will be summarized for each indication separately by weight group/dose group on the FAS. Both 95% Jeffrey interval and exact 95% CI (e.g., Clopper-Pearson interval) will be presented.

7.8.1 Presentation of Efficacy Data

Efficacy data collected during the blinded treatment period (i.e., through Week 32) will be summarized according to the last treatment regimen (i.e., highest dose received) through Week 32 in study Vedolizumab-2005, regardless of previous dose escalation in study Vedolizumab-2003.

The "100mg, 200mg, 150mg, 300mg" dose groups will include subjects without any dose escalation from the entry to Vedolizumab-2005 through Week 32.

The "Escalated to 200mg" dose group will include subjects receiving 100mg at the entry to Vedolizumab-2005 and being escalated to 200mg as the highest dose through Week 32.

The "Escalated to 300mg" dose group will include subjects receiving 100mg, 150mg, and/or 200mg at the entry to Vedolizumab-2005 and being escalated to 300mg as the highest dose through Week 32.

For example, the following 6 mutually exclusive groups during the blinded treatment period:

100mg only	200mg only	150mg only	300mg only	Escalated to 200mg	Escalated to 300mg	Total

Efficacy data collected during the unblinded or open-label (OL) treatment period will be summarized according to the last treatment regimen received during OL treatment period (i.e., highest dose received) considering dose escalation(s), regardless of previous dose escalation in study Vedolizumab-2003 or blinded treatment period in study Vedolizumab-2005.

The "100mg, 200mg, 150mg, 300mg" dose groups will include subjects without any dose escalation from Week 32 of Vedolizumab-2005 throughout the OL treatment period.

The "Escalated to 200mg" dose group will include subjects receiving 100mg at Week 32 of Vedolizumab-2005 and being escalated to 200mg as the highest dose throughout the OL treatment period.

The "Escalated to 300mg" dose group will include subjects receiving 100mg, 150mg, and/or 200mg at Week 32 of Vedolizumab-2005 and being escalated to 300mg as the highest dose throughout the OL treatment period.

For example, the following 6 mutually exclusive groups during the unblinded or open-label (OL) treatment period:

100mg only	200mg only	150mg only	300mg only	Escalated to 200mg	Escalated to 300mg	Total

7.8.2 Secondary Efficacy Endpoints

The number and percentage (together with 95% CI) of UC subjects who, at Week 32, achieve and maintain clinical response based on complete Mayo score (derived using the Gemini Approach, see Section 7.1.7.1), will be presented by weight group (at entry to Vedolizumab-2005) and dose regimen (at entry to Vedolizumab-2005) for UC subjects.

The number and percentage (together with 95% CI) of CD subjects who, at Week 32, achieve and maintain clinical response based on SES-CD score and CDAI score, will be presented by weight group and dose regimen (at entry to Vedolizumab-2005) for CD subjects.

Time to major IBD-related events (hospitalizations, surgeries, and procedures) will be summarized both by proportion and utilizing Kaplan-Meier methods. Each indication (hospitalization, surgeries, procedures and combined) will be summarized by proportion of subjects with the indication (at any point during the study.) Kaplan-Meier estimates will be presented as yearly rates for the combined indication (hospitalizations, surgeries, or procedures) regardless of the dose regimen received. Subjects without documented IBD-related events before reaching the end of study will be censored at the date of last assessment/visit/contact, whichever occurs last.

7.8.2.1 Sensitivity Analysis

For UC, sensitivity analysis will be performed for secondary efficacy endpoints using the conventions of calculating the complete Mayo score per draft FDA UC guidance (2016) described in Section 7.1.7.2.

For UC and CD, a sensitivity analysis will be performed for the two secondary efficacy endpoints which will not apply the missing value assumptions from section 7.1.4.

Additional sensitivity analyses may be conducted as appropriate.

7.8.3 [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

7.8.4 [redacted]

[redacted]

7.8.5 Subgroup Analysis

For each indication separately, subgroup analyses will be performed for secondary [redacted] endpoints via data listings. The subject level data by subgroup will be presented by weight group and dose regimen for each indication as appropriate.

Subgroup of Interest	Subgroup Categories of Interest
Anti-TNF History	Naïve, Exposed/Failed
Exposed to High Dose	Yes (Including randomized and escalated to high dose)
Subjects requiring dose escalation	Yes

A listing showing subject level efficacy status (clinical response and remission based on the different scores applicable for each indication) over time, grouped by prior weight group/dose regimen and anti-TNF history status will be provided.

A similar listing will be provided for subjects exposed to high dose of vedolizumab.

In the subgroup of subjects who required dose escalation (i.e. subjects who experience disease worsening and qualify for escalation), clinical response and remission status (based upon PUCAI/PCDAI) at all visits subsequent to dose escalation will be listed by disease indication, weight category and visit at which dose escalation occurred.

7.9 [redacted]/Pharmacodynamic Analysis

7.9.1 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

7.10.1 Health-Related Quality-of-Life

IMPACT-III total and subscale scores (based on 6-domain scoring system) and their changes from Vedolizumab-2005 baseline will be summarized descriptively by weight and dose group and visit as observed for each indication separately using the FAS.

IMPACT-III total and subscale data during the blinded treatment period will be presented based on the last treatment regimen (i.e. the highest dose received), in the same way as for efficacy data. Similarly, the IMPACT-III total and subscale data during the OL treatment period will be summarized according to the last treatment regimen received during OL treatment period (i.e., highest dose received) considering dose escalation(s), as was done for the efficacy data.

Missing data will not be imputed.

7.10.2 [redacted]

[redacted]

[redacted]

7.10.3 Growth and Development

Change from Vedolizumab-2005 baseline in height (based on the height of subjects when they enroll in the Vedolizumab-2005 study), [redacted], height velocity (change in height divided by the duration (time between the two height measures)), weight, and BMI will be summarized as observed descriptively by visit and initial dose regimen (at entry to Vedolizumab-2005) and visit using the FAS. Missing data will not be imputed.

The number and percentage of subjects achieving Tanner stage 5 at or before age 16 years (females) or 17 years (males) will be summarized by visit and initial dose regimen (at entry to Vedolizumab-2005) using the FAS. Missing data will not be imputed. Shift tables for Tanner stage at each nominal visit relative to Vedolizumab-2005 baseline, for each domain separately, will be provided, based on the FAS.

7.10.4 [redacted]

[redacted]

7.10.5 COVID-19

If there are unavoidable circumstances that impact the ability to conduct study procedures, the method of contingency measure will be summarized for reason for missing data, methods of contact, and alternative dose administration. All the data collected for COVID-19 Impact will be listed.

7.11 Safety Analysis

The primary objective of the study is to determine the safety profile of long-term vedolizumab IV treatment in pediatric subjects with UC or CD. The primary endpoint is the incidence of TEAEs. Safety analyses will be performed using the SAF. Safety data will be summarized by dose regimen and various subgroups including by indication (UC or CD). No statistical inference will be made for safety analyses.

7.11.1 Safety Data

Safety data in blinded treatment period (up to Week 32) and OL treatment period will be combined and summarized according to the last actual treatment regimen received during study Vedolizumab-2005 (i.e., highest dose received) considering dose escalation(s), i.e., according to the following 6 mutually exclusive groups. Safety treatment can also be presented as indication as appropriate.

The "Escalated to 200 mg" dose group will include subjects previously receiving 100mg.

The "Escalated to 300mg" dose group will include subjects previously receiving 100mg, 150mg, and/or 200mg.

100mg only	200mg only	150mg only	300mg only	Escalated to 200mg	Escalated to 300mg

7.11.2 Adverse Events

The number and percentage of subjects with TEAEs, [redacted], AEs leading to discontinuation, and SAEs that occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug will be summarized by MedDRA system organ class, high level term, and preferred term. TEAEs will also be summarized by severity and by relationship to study drug. Separate summaries will be generated for treatment-related AEs overall and by severity. Exposure-adjusted incidence rates will also be analyzed.

The number of exacerbations (recorded as AEs) with reappearance in blood in the stools will be summarized descriptively by dose regimen.

A Treatment-emergent AE (TEAE) is either an AE whose date of onset occurs on or after the first dose of study drug, or an already-present AE that worsens 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 (126 days, accounting for 5 times the half-life of vedolizumab).An

overview of TEAEs will be provided by dose group and overall, summarizing the number of events and the number and percentage of subjects with the following:

- TEAEs.
- Serious TEAEs (SAEs).
- TEAEs related to study drug.
- SAEs related to study drug.
- Severe TEAEs.
- TEAEs leading to study drug discontinuation.
- TEAEs leading to study discontinuation.
- AEs leading to death.

The number and percentage of subjects with the following categories of TEAEs will be summarized by MedDRA system organ class, high level term and preferred term, by dose regimen and overall:

- TEAEs.
- Drug-related TEAEs.
- Drug-related serious TEAEs
- TEAEs leading to study drug discontinuation.
- SAEs.
- [redacted]

The number and percentage of subjects with the most frequent TEAEs occurring in at least 3% of subjects in any dose regimen will be summarized by preferred term, and overall.

The number and percentage of subjects with the most frequent non-serious TEAEs occurring in at least 3% of subjects in any dose regimen will be summarized by system organ class and preferred term, and overall.

The number and percentage of subjects with the following categories of TEAEs will be summarized by MedDRA system organ class, high level term and preferred term, by severity, dose regimen and overall:

- TEAEs.
- Drug-related TEAEs.
- The following AE data will be listed:
- AEs.

- AEs leading to study discontinuation.
- Serious TEAEs.
- AEs resulting in death.
- AEs occurring more than 30 days post treatment.

7.11.3 Clinical Laboratory Evaluations

Change from baseline in clinical chemistry laboratory tests will be summarized by dose regimen (based on the baseline treatment group) and visit in separate tables for conventional and SI units. The same will be done for Hematology laboratory tests.

The number and percentage of subjects with markedly abnormal values for laboratory tests will be summarized for post-baseline data based on SI units using section 9.7 Appendix G Criteria for Identification of Markedly Abnormal Laboratory Values and Vital Sign Values.

Shifts of laboratory test results (low, normal, high) from baseline will be summarized by visit and dose regimen.

The number and percentage of subjects with elevated liver enzyme laboratory parameters (including ALT, AST, alkaline phosphatase and bilirubin) will be summarized by dose regimen.

All laboratory results will be presented in data listings.

7.11.4 Vital Signs

Change from baseline in vital signs will be summarized by dose regimen at baseline and visit.

The number and percentage of subjects with markedly abnormal values of vital signs will be summarized by visit and dose regimen.

All vital signs data will also be listed.

7.11.5 12-Lead ECGs

Not applicable.

7.11.6 Other Observations Related to Safety

[redacted].

7.12 Interim Analysis

Several interim analyses may be conducted to support future pediatric studies. These may occur 1) when all subjects in the ≥30 kg weight group have completed Week 32 or withdrawn from the study or 2) when all subjects in the <30 kg weight group have completed Week 32 or withdrawn from the study. The purpose of conducting interim analyses would be to gain intermediate information on [redacted], efficacy, and safety and results may be used to inform design and dose

selection for other pediatric studies. There is no intention for early trial termination based on the results of the interim analysis (other than safety concerns).

Interim analyses will be carried out by an independent statistical team not involved in daily activities of the study. The analyses presented will be a subset of those planned for the full study report.

7.13 Changes in the Statistical Analysis Plan

[redacted]

SAP was updated to reflect Protocol version 7 dated 8 March 2023 and update the below:

1. Extended analysis visit derivation to beyond 5-year period.
2. [redacted]

For V3.0:

- General formatting (header, spacing, etc) cleanup
- Dropped duplicate endpoint
- SAP was updated to reflect Protocol V8.
  - Definitions for TEAE [redacted] revised per program standard
  - [redacted]
  - Revised interim analysis to be more flexible

For V4.0

- Section 5 – Analysis Endpoints:
  - Wording of secondary endpoint maintenance of clinical response in CD adapted to match protocol wording and criteria in protocol Section 5.2.2.
  - [redacted]
  - Editorial changes and consolidation of definition for some secondary and additional endpoints.
  - [redacted]
  - Corresponding changes were made in Section 7.8 and its subsections.
- [redacted]

- Sections 7.1.4/7.8: Clarification added for handling of missing efficacy data based on Mayo score or CDAI score at Week 32, specifically for study subjects who were not required to complete a daily symptom diary based on the protocol version under which they were enrolled, and after Week 32.
- Section 7.8.1: Total column added for general summaries of efficacy data.
- Section 7.8.5: Clarification added for content of subgroup listings.
- Section 7.9.1: [redacted]
- Section 7.11.2: Frequent TEAE cutoff reduced from 5% to 3%.
- [redacted]
- Section 9.2: Link for CDAI CDC growth chart(s) updated

8.0 REFERENCES

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8. Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol 2012;52(10):1601-6.

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9.0 APPENDICES

9.1 Appendix A Mayo Score Calculation Worksheet

Complete and partial Mayo Scoring "Points to Remember"	
The Mayo Score is widely used in clinical trials to assess Ulcerative Colitis disease activity. It is a combination of two patient-reported and two physician-determined components. The partial Mayo Score includes only the Stool Frequency, Rectal Bleeding, and PGA subscores. (Does not include endoscopy)	
Sub Scores	
Stool Frequency **(Patient)** **0 = Normal number of stools for this patient** **1 = 1 to 2 stools more than normal** **2 = 3 to 4 stools more than normal** **3 = 5 or more stools more than normal**	Stool frequency **WILL:** ➢ Be derived from patient reported diary data in IVRS and will be the average of 3 days prior to visit ➢ Be variable from patient to patient. Instruct patients to set the baseline of "normal" to whatever is "normal" for them. (eg, A patient normally has 1 stool per day and today has had 4 stools. Therefore the patient has had 3 more than "normal", which yields a value of 2 for that day) ➢ Be defined as the passage of solid or liquid fecal material. Episodes of incontinence count. A non-productive trip to the bathroom or the simple passage of gas **DO NOT COUNT** as a stool.
Rectal Bleeding **(Patient)** **0 = No blood seen** **1 = Streaks of blood with stool less than half the time** **2 = Obvious blood with stool most of the time** **3 = Blood alone passes**	Rectal bleeding **WILL:** ➢ Be derived from patient reported diary data in IVRS and will be the average of 3 days prior to visit ➢ Represent the most severe bleeding of the day. Hemorrhoidal bleeding **DOES NOT COUNT.**
Findings on Endoscopy **(Physician)** **0 = Normal or inactive disease** **1 = Mild disease (erythema, decreased vascular pattern, mild friability)** **2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)** **3 = Severe disease (spontaneous bleeding, ulceration)**	Findings on Endoscopy **WILL:** ➢ Be documented by photographic evidence ➢ Be classified by the worst affected segment if mucosal appearance varies ➢ Be characterized as follows • Moderate: Bleeds to touch (forceps applied to colonic mucosa for 1 second) • Severe: Bleeds spontaneously ➢ Endoscopy should be performed by the same endoscopist for any given patient

Physician's Global Assessment **(Physician)** **0 = Normal** **1 = Mild disease** **2 = Moderate disease** **3 = Severe disease**	Physician's Global Assessment **WILL:** ➢ Be based on the patient's overall status on the day of visit ➢ Reflect how the patient is doing at present. Assessment **SHOULD NOT** reflect past disease severity or complexity or the number/kinds of medications the patient is receiving. ➢ Be based on the • Other 3 components of the Mayo score • Patient's recollection of abdominal discomfort and general sense of well-being • Patient's performance status, fecal incontinence, and mood • Physician's observations and physical exam findings ➢ Reflect disease activity, **NOT** disease severity (eg. **Do not** automatically give a high PGA to patients with pancolitis or severe/complicated disease, or patients requiring multiple medications.)
• Subscores representing the average of 3 days of patient diary data can be obtained from the IVRS subscore report. If calculated manually, **subscores should be rounded to the nearest integer.** • The Mayo score is equal to the sum of the subscores.	

9.2 Appendix B Crohn's Disease Activity Index (CDAI)

Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		×2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0=none, 1=mild, 2=moderate, 3=severe (reported on the 7 days immediately prior to the study visit)		×5	
General well-being	7-day total of daily general well-being scores on a 4-point scale: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible (reported on the 7 days immediately prior to the study visit)		×7	
Extra-intestinal manifestations of CD	Total number of checked boxes (check all that apply): □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis □ Anal fissure, fistula, or abscess □ Other fistula □ Fever over 37.8°C during past week		×20	
Lomotil/Imodium/ opiates for diarrhea	Yes=1 No=0		×30	
Abdominal mass	None=0 Questionable=2 Definite=5		×10	
Hematocrit (%)(a)	Males: subtract value from 47 Females: subtract value from 42		×6	
Body weight (b)	(1 – (body weight/ ideal weight for height))×100		×1	
Final score			Add totals:	

Source: Adapted from: Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70 (3):439-44.
(a) If hematocrit subtotal <0, enter 0.
(b) If body weight subtotal <-10, enter -10.

To facilitate the use of CDAI in children, "Standard Weight" is replaced by "Ideal Weight for Height" (Griffiths et al, 2005). Ideal Weight for Height is calculated as follows:

(1) Find the child's measured height to determine the percentile for that height by gender and age, using Centers for Disease Control and Prevention Stature-for-Age growth chart.

https://www.cdc.gov/growthcharts/cdc-data-files.htm

(2) The child's Ideal Weight for Height is the weight on the same percentile in (1) for the child's gender and age, using Centers for Disease Control and Prevention Weight-for-Age growth chart. For example, for a boy's height at the 25th percentile for his age, his ideal weight will be considered to also be the 25th percentile weight for his age.

See above linkNumeric example: for a 2-year old boy with measured height of 84cm and measured weight of 11kg, his height of 84cm is at the 25th percentile for his age per CDC Stature-for-Age chart. His ideal weight will be the 25th percentile for 2-year old boys per CDC Weight-for-Age chart, which is 11.78 kg. This boy's body weight subscore of CDAI will be $(1 - \frac{11}{11.78}) \times 100 = 7$.

9.3 Appendix C Simple Endoscopic Score for Crohn's Disease (SES-CD)

The SES-CD is a validated endoscopic activity score used to assess the status and change of mucosal lesions in patients with CD (Daperno et al, 2004). The score assesses 4 variables in up to 5 segments to yield its final result.

	Simple Endoscopic Score for Crohn's Disease values			
Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø >2 cm)
Ulcerated surface (%)	None	<10%	10-30%	>30%
Affected surface (%)	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Ø, Diameter.

Source: Adapted from Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60(4):505-12.

The SES-CD score chart permits assessment of each variable by segment and across the entire ileum plus colon, as well as calculation of a total score.

	Ileum	**Right Colon**	**Transverse Colon**	**Left Colon**	**Rectum**	**Total**
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surface (0-3)						
Presence and type of narrowings						
					Total SES-CD =	

9.4 Appendix D PUCAI

Time period for evaluation:

- Answers should reflect a daily average of the last 2 days;
- however, if clinical conditions are changing rapidly (eg, during intense intravenous therapy), the most recent 24 hours should be considered; and
- for patients undergoing colonoscopy, answers should reflect the 2 days before bowel clean out was started.

	Item	Points
1	**Abdominal pain**	
	no pain	0
	pain can be ignored	5
	pain cannot be ignored	10
2	**Rectal bleeding**	
	None	0
	small amount only, in <50% of stools	10
	small amount with most stools	20
	Large amount	30
3	**Stool consistency of most stools**	
	Formed	0
	Partially formed	5
	Completely unformed	10
4	**Number of stools per 24 hours**	
	0-2	0
	3-5	5
	6-8	10
	>8	15
5	**Nocturnal stools (any episode causing wakening)**	
	No	0
	Yes	10
6	**Activity level**	
	No limitation of activity	0
	Occasional limitation of activity	5
	Severe restricted activity	10
	SCORE	**Total Max 85**

Source: Turner D, Otley AR, Mack D, et al. Development and evaluation of a Pediatric Ulcerative Colitis Activity Index (PUCAI): a prospective multicenter study. Gastroenterology. 2007; 133: 423

9.5 Appendix E PCDAI

History (recall 1 week)				
Abdominal pain				
None				0
Mild (brief episodes, not interfering with activities)				5
Moderate/severe (frequent or persistent, affecting activities)				10
Stools				
0-1 liquid stools, no blood				0
2-5 liquid or up to 2 semi-formed with small blood				5
Gross bleeding, >6 liquid stools or nocturnal diarrhoea				10
Patient functioning, general well-being (Recall, 1 week)				
No limitation of activities, well				0
Occasional difficulties in maintaining age appropriate activities, below par				5
Frequent limitation of activities, very poor				10
EXAMINATION				
Weight				
Weight gain or voluntary weight loss				0
Involuntary weight loss 1-9%				5
Weight loss >10%				10
Height				
<1 channel decrease (or height velocity >-SD)				0
>1<2 channel decrease (or height velocity <-1SD>-2SD)				5
>2 channel decrease (or height velocity <-2SD)				10
Abdomen				
No tenderness, no mass				0
Tenderness, or mass without tenderness				5
Tenderness, involuntary guarding, definite mass				10
Peri-rectal disease				
None, asymptomatic tags				0
1-2 indolent fistula, scant drainage, tenderness of abscess				5
Active fistula, drainage, tenderness or abscess				10
Extra-intestinal manifestations (Fever >38.5 x 3 days in week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum)				
none				0
one				5
two				10
LABORATORY				
Hematocrit (%)				
<10 years	11-14 (male)	11-19 (female)	15-19 (male)	
>33	>=35	>=34	>=37	0
28-33	30-34	29-33	32-36	2.5
<28	<30	<29	<32	5
ESR (mm/hr)				
<20				0
20-50				2.5
>50				5
Albumin (g/L)				
>35				0
31-34				5
<30				10

9.6 [redacted]

[redacted]

9.7 Appendix G Criteria for Identification of Markedly Abnormal Laboratory Values and Vital Sign Values.

Hematology—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
Hemoglobin	<0.8 × LLN,	>1.2 × ULN
Hematocrit	<0.8 × LLN,	>1.2 × ULN
RBC count	<0.8 × LLN,	>1.2 × ULN
WBC count	$<2.0 \times 10^3/\mu L$	>1.5 × ULN
Platelet count	$<70 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$

RBC=red blood cell, WBC=white blood cell. LLN=lower limit of normal, ULN=upper limit of normal.

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
ALT	--	>3x ULN
AST	--	>3x ULN
GGT	--	>3x ULN
Alkaline phosphatase	--	>3x ULN
Total bilirubin	--	>2.0 mg/dL
Albumin	<2.5 g/dL	--
Total protein	<0.8x LLN	>1.2x ULN
Creatinine	--	>2.0 mg/dL
Sodium	<130 mEq/L	>150 mEq/L
Potassium	<3.0 mEq/L	>6.0 mEq/L
Bicarbonate	<8.0 mmol/L	--
Chloride	<75 mmol/L	>126 mmol/L
Calcium	<1.50 mmol/L	>3.25 mmol/L
Glucose	≤2.8 mmol/L	≥20 mmol/L
Phosphorous	<0.52 mmol/L	>2.10 mmol/L
CPK	--	>5x ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, CPK=creatine phosphokinase, LLN=lower limit of normal, ULN=upper limit of normal.

9.8 Appendix H Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	Bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	°C	< 35.6	>37.7
	°F	<96.1	>99.9

9.9 Appendix I IBD-Related Events

Any hospitalization, surgery, and procedure will be adjudicated to be IBD-related or not by Takeda. The adjudication will be stored in the clinical data base and used for the time to IBD-related event analysis.

Approval signature:

[redacted]

[redacted], Gastrointestinal and Inflammation (GI2) Statistics

Signature Page for MLN0002-2005-Statistical-Analysis-Plan-v4.0_final
Title: Vedo-2005 SAP v4.0

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