Title: A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

NCT Number: NCT02790138

SAP Approve Date: 12 February 2021

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vedolizumab-4004

A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

Vedolizumab IV 300 mg in the Treatment of Chronic Pouchitis

PHASE 4

Version**:** Final V2.0 (Amendment 01)

Date**:** 12 February 2021

Prepared by:

PPD

Based on:

Protocol Version: Amendment 04

Protocol Date: 14 September 2020

Original SAP Date: 29 June 2020

1.1 Signatures

Study Number: **Vedolizumab-4004**

Study Title: A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

Version / Date: Final V2.0 / 12 February 2021

Approvals:

This document is signed electronically.
Electronic signatures can be found on the last page of this document.

PPD

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
anti-TNF	tumor necrosis factor-alpha antagonist
BMI	body mass index
CGQL	Cleveland Global Quality of Life
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CCI	[redacted]
CS	corticosteroids
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FC	fecal calprotectin
HLT	high level term
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
IPAA	ileal pouch anal anastomosis
IV	intravenous
LOCF	last observation carried forward
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
mPDAI	Modified Pouchitis Disease Activity Index
PML	progressive multifocal leukoencephalopathy
PMNL	polymorphic nuclear leukocyte infiltration
PDAI	Pouchitis Disease Activity Index
p.p.	percent points
PPS	per protocol set
PT	preferred term
PTE	pretreatment event
RB	rectal bleeding
CCI	[redacted]
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
CCI	[redacted]

SF	stool frequency
SI	International System of Units
SMQ	Standard MedDRA Query
SOC	system organ class
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
WHODrug	World Health Organization Drug

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective is to compare the efficacy of vedolizumab IV to placebo in terms of the percentage of subjects with chronic or recurrent pouchitis achieving clinically relevant remission.

4.2 Secondary Objectives

The secondary objectives are to assess the efficacy of vedolizumab IV by:

- Percentage of subjects achieving modified Pouchitis Disease Activity Index (mPDAI) <5 and a reduction of overall score by ≥2 points from baseline mPDAI.
- Percentage of subjects achieving Pouchitis Disease Activity Index (PDAI) <7 and a reduction of overall score by ≥3 points from baseline PDAI.
- Time to remission (defined as a PDAI score <7 and a decrease in PDAI score of ≥3 points from baseline).
- Percentage of subjects achieving a partial response (defined as reduction mPDAI score by ≥2 points from baseline).
- Change in PDAI endoscopic subscore.
- Change in PDAI histologic subscore.
- Change in total PDAI.
- Change in Inflammatory Bowel Disease Questionnaire (IBDQ) and Cleveland Global Quality of Life (CGQL).

4.3 Exploratory Objectives

CCI

[redacted]

4.4 Safety Objective

The safety objective is to assess the safety of vedolizumab IV in chronic or recurrent pouchitis.

4.5 Study Design

This is a phase 4, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vedolizumab IV 300 mg over a 34-week treatment period (with the last dose at Week 30) in subjects with a proctocolectomy and ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC) who have developed chronic or recurrent pouchitis.

Approximately 110 adult subjects with chronic or recurrent pouchitis were to be randomized to this study. Subjects must have developed chronic or recurrent pouchitis, defined as an mPDAI score ≥ 5 assessed as the average from 3 days immediately prior to the baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either (a) ≥ 3 recurrent episodes within 1 year prior to the Screening visit, each treated with ≥ 2 weeks of antibiotic or other prescription therapy, or (b) requiring maintenance antibiotic therapy taken continuously for ≥ 4 weeks immediately prior to the baseline Endoscopy Visit.

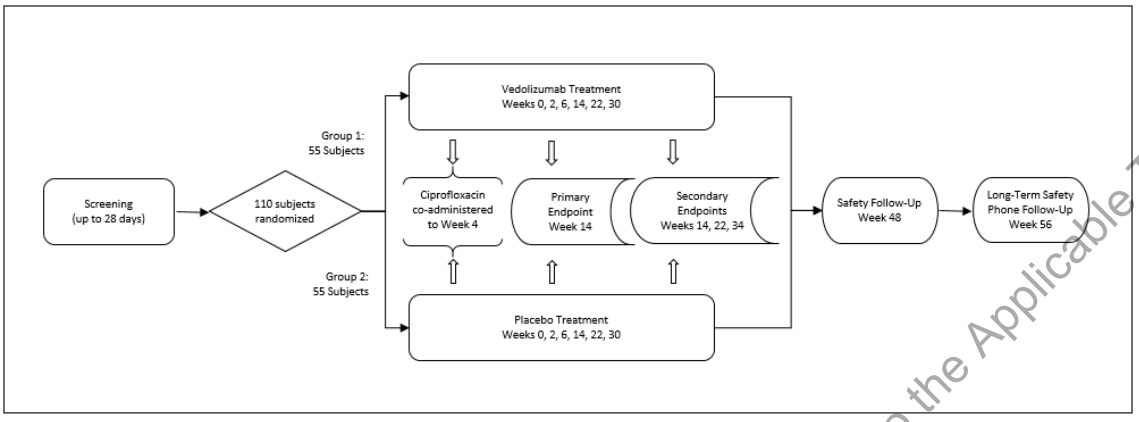
Eligible subjects were randomized at Day 1 in a 1:1 ratio to the following 2 treatment arms; subjects enrolled under protocol amendment 03 (or later) were randomized stratified by type of pouchitis (chronic or recurrent):

- Arm 1: Vedolizumab IV 300 mg dose at Week 0, 2, 6, 14, 22 and 30, administered as a 30-minute infusion;
- Arm 2: Placebo IV dose at Week 0, 2, 6, 14, 22 and 30, administered as a 30-minute infusion.

All subjects received concomitant antibiotic treatment with ciprofloxacin 500 mg twice daily through Week 4. Additional courses of antibiotics were allowed, as needed, for flares after Week 14. Final efficacy assessments were to be performed 4 weeks after the last study dose (Week 34). Additional safety follow-ups occurred 18 weeks after the last study dose (Week 48) and subjects were required to participate in a long-term follow-up safety survey by telephone, 26 weeks after the last dose of study drug (Week 56).

A schematic of the study design is included as Figure 4.a. A schedule of assessments is listed in Appendix A.

Figure 4.a Schematic of Study Design



5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary efficacy endpoint is clinically relevant remission after 14 weeks of treatment. Clinically relevant remission is defined as an mPDAI score < 5 and a reduction of overall score by ≥ 2 points from baseline.

5.2 Secondary Endpoints

Secondary endpoints include:

- Clinically relevant remission at Week 34 (last dosing at Week 30).
- PDAI remission (defined as PDAI score < 7 and a decrease in PDAI score by ≥ 3 points from baseline) at Week 14 and at Week 34.
- Time to PDAI remission (defined as a PDAI score < 7 and a decrease in PDAI score of ≥ 3 points from baseline).
- Partial mPDAI response (defined as decrease in mPDAI score by ≥ 2 points from baseline) at Week 14 and at Week 34.
- Change from baseline in PDAI endoscopic subscore at Weeks 14 and 34.
- Change from baseline in PDAI histologic subscore at Weeks 14 and 34.
- Change from baseline in Total PDAI score at Weeks 14 and 34.
- Change from baseline in IBDQ and CGQL at Weeks 14, 22 and 34.

5.3 Exploratory Endpoints

CCI

[redacted]

5.4 Safety Endpoints

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), serious adverse events (SAEs), vital signs and results of standard laboratory tests (clinical chemistry, hematology, coagulation and urinalysis).

5.5 Other Data and Variables Collected

Other data and variables collected and mapped to the study database include:

- Demographic data (see details in section 7.5)
- Baseline disease characteristics (see details in section 7.5)
- Medical history (see details in section 7.6)
- Prior and concomitant medications (see details in section 7.7)
- Study drug exposure (see details in section 7.8)
- Significant protocol deviations (see details in section 7.4.1)

6.0 DETERMINATION OF SAMPLE SIZE

The sample size was calculated based on the remission rate at 14 weeks.

Initially, the sample size was based on the observed remission rate in GEMINI 1 (MLN0002-C13006) in subjects with moderate to severe UC: the placebo group remission rate was 8%, the vedolizumab group rate was 23%; an effect size of 15%.

However, pouchitis is different from UC and a new assessment using published data was made to evaluate what would be a significant treatment effect. Based on 2 recent papers using the mPDAI as the primary endpoint [2,3], a placebo rate of 15% was estimated. A clinically significant effect was estimated to be of 25%, an average of the remission (complete response) observed in the 2 aforementioned papers (32% and 21% post-induction response, respectively) evaluating the effect of infliximab using the mPDAI.

An effect size of at least 25% would be considered clinically meaningful (i.e., a remission rate of 40% in subjects maintained on vedolizumab IV). Therefore, a total of 98 evaluable subjects (49 per treatment arm) is required to detect a 25% difference in the remission rate at the 2-sided significance level of 0.05 with 80% power. To account for attrition, 110 subjects were planned to be randomized (55 per treatment arm).

7.0 METHODS OF ANALYSIS AND PRESENTATION

This statistical analysis plan (SAP) version is an amendment to the SAP Version 1.0 (dated 29 June 2020) and is based on the study protocol, amendment 04, dated 14 September 2020 [1].

A blinded data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

7.1 General Principles

In general, unless stated otherwise below, all descriptive data summaries will be provided by treatment arm for the applicable analysis set. Where appropriate, variables will be further summarized by study visit and/or subgroups defined in section 7.1.6.

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. Confidence intervals (CIs) about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

For categorical variables, the number (and %) of subjects falling into each category will be presented. Percentages will be calculated based only on non-missing observations in the respective analysis set and will, in general, be displayed with 1 decimal place. The number of missing observations will be reported in category "Missing" (no percentage shown for this category). The same handling applies to similar categories like "not collected", "not applicable".

All CIs, statistical tests and resulting p-values will be reported as 2-sided unless otherwise stated; p-values will be displayed with 3 decimal places (p-values < 0.001 will be displayed as "< 0.001").

All study-related raw data and relevant derived data, as specified below, will be presented in data listings. The listings will be sorted by treatment arm and by subject. In general, listings will be done for all subjects randomized. Screen failure data will be grouped and presented at the end of data listings, where appropriate. When no data are available for a table or appendix, an empty page with the title will be produced with suitable text (e.g., "There were no subjects with markedly abnormal values of laboratory parameters.").

All statistical analyses will be conducted using SAS System® Version 9.4, or higher.

7.1.1 Study Definitions

The following treatment arm labels will be used in the outputs:

- Vedolizumab IV
- Placebo IV

Type of pouchitis:

The study protocol defines the type of pouchitis as follows:

- Chronic pouchitis is defined as pouchitis requiring maintenance antibiotic therapy taken continuously for ≥ 4 weeks immediately prior to the baseline endoscopy visit.
- Recurrent pouchitis is defined as ≥ 3 recurrent episodes of pouchitis within 1 year prior to screening, each treated with ≥ 2 weeks of antibiotic or other prescription therapy.

For the purpose of the analysis, the type of pouchitis will be determined based on the following criteria:

a) If the subject received a maintenance antibiotic therapy continuously for ≥ 26 days, that was started at least 26 days prior to start of study medication (Day 1, see section 7.1.2) and was continued until at least 7 days before screening (date of informed consent considered here), then the type of pouchitis is chronic.
Note: For the calculation of duration of immediate prior antibiotic use, the following should be applied:
   - only prior antibiotics for UC/pouchitis as defined below will be considered;
   - records of prior antibiotics with reported end date completely missing and not flagged as ongoing or as ended after the screening/informed consent date will be ignored (i.e. imputed end dates of those records not to be considered);
   - for prior antibiotics reported with a partial end date, that would be imputed as being after Day 1 (see section 7.1.2), the end date will be assumed as Day 1-1 (assume that antibiotic stopped before Day 1 as per protocol), unless the partial end date clearly indicates continuation after Day 1 (see details for end date imputations in section 7.1.8.2).

b) If the number of pouchitis episodes in the last 1 year prior to screening reported in the eCRF is ≥ 3, then the type of pouchitis is recurrent;

since the onset/end dates of the episodes within the last year are not recorded, it will be assumed they were treated appropriately.

c) If based on available data, both the criteria for chronic and recurrent pouchitis are met, then the type of pouchitis is set to chronic.

d) If neither of the criteria a) and b) above is met, recurrent pouchitis is assumed.

This definition will be revisited during blind data review.

Clinically relevant remission (mPDAI remission) is defined as mPDAI score < 5 and decrease of mPDAI score by ≥ 2 points from baseline.

PDAI remission is defined as PDAI score < 7 and decrease of PDAI score of ≥ 3 points from baseline.

Partial (mPDAI) response is defined as decrease of mPDAI score by ≥ 2 points from baseline.

CCI [redacted]

CCI [redacted]

Relapse of pouchitis is defined as a worsening in the pouchitis symptoms after previous (documented) clinically relevant remission (mPDAI remission), identified by any of the following events:

- an adverse event with preferred term "Pouchitis" (MedDRA code 10036463), e.g. worsening of pouchitis, pouchitis flare (or similar)
- an adverse event flagged on the AE CRF page as related to flare
- worsening of pouchitis symptoms reported on the Flare CRF page
- start or change in concomitant medication flagged as for treatment of flare.

The corresponding date of relapse is the start/onset date of the respective event. The corresponding date of the (first) relapse ($date_{relapse}$) is the minimum of the start/onset dates of the aforementioned events after clinically relevant remission was achieved ($date_{mPDAI\ remission}$); the

CCI [redacted]

IBDQ remission is defined as a total IBDQ score of ≥170.

IBDQ (clinically meaningful) improvement, hereafter referred to as IBDQ improvement, is defined as a change from baseline by ≥ 16 points.

Corticosteroids (CS) for UC/pouchitis-related treatment will be identified by ATC codes A07EA, C05AA, H02AB, H02 with the following exception:

- CS with indication "asthma" and with route of administration reported as nasal or by inhalation are not considered UC/pouchitis-related treatment.

Antibiotics for UC/pouchitis-related treatment will be identified by ATC codes A07AA, J01-- (i.e., all ATC codes starting with J01) with the following exceptions:

- J01C, J01CA, J01CF, J01XE are not considered UC/pouchitis-related treatment;
- J01AA, J01FA, J01CR are only considered UC/pouchitis-related treatment if flagged in the eCRF as given for pouchitis or for a flare of pouchitis.

Prior anti-TNF treatment:

- Prior tumor necrosis factor-alpha antagonist (anti-TNF) treatment will be identified by the ATC 4th level (chemical) subgroup "TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS" (ATC code L04AB).
- Discontinuation of prior anti-TNF treatments for reasons "inadequate response", "loss of response", and "intolerance" will be considered failure of prior anti-TNF treatment.
  A subject with multiple prior anti-TNF therapies may have multiple reasons for failure.

Other relevant UC/pouchitis treatments:
Other relevant UC/pouchitis treatments will be identified by the following ATC codes A07DA, A07E, A07EC, A07FA, A16--, L01BB, L04AA, L04AC, L04AD, L04AX (L04-- are immunosuppressants).

Prior treatments started pre-/post-colectomy:
Classification of prior treatments will be done relative to the (imputed) date of colectomy (=IPAA).

a) A prior treatment that started on or after the date of the IPAA, and before Day 1, is considered "started post-colectomy".
   Note: this applies also to treatments that were started prior to IPAA, then stopped and started again on or after the date of the IPAA.

b) A prior treatment that was started before the IPAA is considered "started pre-colectomy".
   Note: this applies also to treatments that were started prior to IPAA and continued after IPAA.

Discontinuation of prior treatments for UC/pouchitis:
Discontinuation of prior treatments for UC/pouchitis for reasons "inadequate response", "loss of response", and "intolerance" will be considered failure of the prior treatment.
For prior UC/pouchitis treatments recorded on the "Medication History/Concomitant

Medications" eCRF form, the reason for discontinuation will be identified as "not recorded".
A subject with multiple prior treatments may have multiple reasons for failure.
Note: This is a generalization of the definition for prior anti-TNF treatments above.

7.1.2 Definition of Study Days

Study Day 1 (Day 1) is defined as the date on which a subject is administered the first dose of study medication. Other study days are defined relative to the Study Day 1 with Day -1 being the day prior to Study Day 1. Typically, the study day of an assessment (or event) is derived as:

study day = date of assessment/event – date of first dose of study medication + 1.

7.1.3 Definition of Baseline Values

Unless otherwise specified, baseline values are defined as the last observed value before the first dose/administration of study medication.

For procedures performed on the same day as the first dose of study medication (Day 1) that as per protocol were to be performed prior to the first dose of study medication, it is assumed that the procedures are performed prior to the administration of the study medication (and data is considered pre-treatment, baseline). If there is more than one baseline score, then the one closer to the date of randomization will be used for analyses.

7.1.4 Definition of Last Visit

In general, "last visit" is defined as the last available observation of a subject after the first dose of study medication until either Week 34 or the date of early discontinuation, whichever comes first.

7.1.5 Definition of Screen Failure

Screen failure subjects are subjects who signed the informed consent form (ICF) and were not enrolled in the study. The primary reason for screen failure is collected in the eCRF using the following categories:

- Pretreatment Event (PTE)/AE
- Did Not Meet Entrance Criteria
- Significant Protocol Deviation
- Lost to Follow-Up
- Voluntary Withdrawal
- Study Termination
- Other

7.1.6 Covariates and Subgroups

The following subgroups may be used in the data summaries, adaptations of the subgroup categories specified below might be applied as deemed necessary to achieve subgroups of reasonable size:

- Type of pouchitis:
  chronic pouchitis vs recurrent pouchitis (see definitions in section 7.1.1)
- Prior anti-TNF treatment started post-colectomy[(a)]:
  anti-TNF failure, anti-TNF used/no failure, anti-TNF not used (see definitions in section 7.1.1).
  [(a)] Note: this includes on prior treatments collected on the CRF form "UC Disease Last Antibiotic Medication and All Prior Biologics".
  A subject with multiple prior anti-TNF treatment courses post-colectomy who experienced at least one failure will be categorized as "anti-TNF failure".
- Prior anti-TNF exposure (for UC or pouchitis):
  anti-TNF naïve vs anti-TNF experienced
- baseline severity based on mPDAI[(b)]:
  5 to 8 (moderately active)
  9 to 12 (severely active)
  [(b)] Note: If there are < 8 subjects with a baseline mPDAI<5 after adjudication of the PDAI endoscopy ulceration score, they will be excluded from this subgroup analyses; otherwise they will be analyzed as a separate subgroup.
- baseline severity based on PDAI[(c)]:
  < 7 (quiescent)
  7 to 12 (moderately active)
  13 to 18 (severely active)
  [(c)] Note: if there are < 8 subjects in a subgroup, analysis of this subgroup will be omitted; subjects with missing PDAI at baseline will be excluded from this subgroup analyses.
- baseline polymorphic nuclear leukocyte infiltration (PMNL) based on PDAI:
  0 - 1 = none/mild
  ≥ 2 = moderate/severe + crypt abscess
- time from IPAA to start of treatment: < 7 years vs ≥ 7 years
- baseline FC: ≤ 250 µg/g vs > 250 µg/g
- baseline CRP: ≤ 5 mg/L vs > 5 mg/L

7.1.7 Definition of Study Visit Windows

The visit windows to be used in the data analysis are shown in Table 7.a. However, these windows will be reviewed (and adapted as deemed necessary) during the blind data review.

Unless otherwise specified, data will be allocated to and summarized for the respective study visits according to the actual assessment date and the analysis visit windows below. Furthermore, the following additional ordered rules will be applied to identify an analysis record/value to be used in the analysis and summaries:

- Data recorded within one of the analysis visit windows below will be used in the analysis for the respective scheduled visit; data recorded at days outside the defined visit windows will not be included in the by-visit summaries.
- Data identified on the eCRF as coming from an "unscheduled" visit will be eligible for windowing.
- If a subject has more than one measurement within an analysis window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the later assessment will be used in analyses. In case of ties located on the same side of the target day (e.g., 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 (e.g., an abnormal vital signs value will be chosen over a normal vital sign value).

Table 7.a Visit Windows for Efficacy and Safety Variables

Visit	Target Day	Visit Window (days) per Protocol	Analysis Visit Window (days)
Baseline[a]	1	--	-42 – 1
Week 2	15	±2	±4 (11 – 19)
Week 4	29	±2	±4 (25 – 33)
Week 6	43	±2	±7 (36 – 50)
Week 14	99	±3	±14 (85 – 113)
Week 22	155	±7	±14 (141 – 169)
Week 30[b]	211	±7	±14 (197 – 224)
Week 34[c]	239	±7	±14 (225 – 253) (m)PDAI: ±28 (211 – 267)
Week 48	337	±7	±21 (316 – 358)
Week 56	393	±7	±21 (372 – 414)

[a] The formal lower boundary of the Baseline visit is Day -28 consistent with the protocol defined screening period; however, screening assessment done up to 14 days earlier (Day -42) will be considered for the determination of a baseline value.

[b] The formal upper boundary of Week 30 window would be Day 225; data reported on Day 225 will be allocated to Week 34.

[c] mPDAI/PDAI assessments performed on/between days 211 to 267 will be considered for the analysis of Week 34.

Note: Baseline, Week 14 and Week 34 are planned visits for pouchitis assessments (PDAI).

The following additional rule(s) do(es) apply:

- All assessments, including the assessments that do not fit within any defined analysis visit window, will be listed. Data recorded at days outside the above visit windows will be shown in the data listings as "unscheduled" visit; data recorded at early discontinuation will be shown as "early termination".

7.1.8 Handling of Missing Data

In general, missing data will not be imputed. Exceptions and rules for these exceptions are summarized hereafter:

- The general handling of missing (m)PDAI data is described in section 7.1.10; additional handling missing (m)PDAI data is described in the respective subsections of section 7.9.
- The general handling of subjects with missing efficacy data for (determination of) a response-type endpoints described in section 7.9.1.1; additional handling of those cases in sensitivity analyses is described in section 7.9.6.1.
- Missing data for AE onset and end dates will be imputed as described in section 7.1.8.1.
- Missing data for concomitant medication start and stop dates will be imputed as described in section 7.1.8.2.
- A (partially) missing IPAA date will be imputed as described in section 7.1.9.

Further missing data handling rules are described in the respective sections as applicable.

7.1.8.1 Conventions for Missing or Incomplete Adverse Event Dates

A missing or incomplete AE onset date will be imputed according to the following conventions:

1. If an onset date is missing, the imputed onset date will be imputed as the first non-missing valid date from the following list (in order of precedence):
   - First study medication date
   - Informed consent date.
2. If an onset date is incomplete, the derived onset date will be calculated following:
   - 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.
   - Missing day and month, but year present: the day and month will be imputed as the 30th 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.

A missing or incomplete AE end date will be imputed according to the following conventions:

1. If an end date is missing (and AE not flagged as ongoing), the end date will be imputed as the last study assessment date. If the AE start date is after the last study assessment, the end date will be imputed as the AE start date.
2. If an end date is incomplete, the derived end date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the last date of the month (for example, February 2019 will be imputed as 28th February 2019).
   - Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.

7.1.8.2 Conventions for Missing Concomitant Medication Dates

Start and stop dates for all concomitant medications are collected on the eCRF. However, in case of missing or partial information in these dates, the following rules will be used:

If the medication start date is (partially) missing:

- If the day is missing, the start day will be the first day of the month.
- If the day and month are missing, and year is the same as in the date of first dose of study medication, the start day will be the first day of the month corresponding to 90 days prior to the date of first dose of study medication (if the month of first dose is Jan, Feb, or Mar, the start day will be 1 Jan of that year instead).
- If the day and month are missing, and the year is not the same as the year of first dose of study medication, the start day will be 1st Jan of that year.
- If the year is missing, the start year will be the minimum of year of the first site visit and the year of the ICF date.
- If the entire date is missing:
  - If the eCRF indicates that the medication ended prior to the ICF date, then the medication start date will be imputed as ICF date - 1.
  - Otherwise the start date will be imputed as minimum of the date of first dose of study medication (Day 1) and the medication end date.

If the medication end date is (partially) missing and medication is not flagged as "ongoing":

- If the day is missing:
  - In general, the end date will be the last day of the month reported. If the eCRF indicates the medication ended prior to ICF date, and month is the month of ICF, the end date will be imputed as ICF date - 1.

- If the day and month are missing:
  - If the year is the same as the date of last assessment, then the end date day will be imputed by the last day of the month during which the last assessment occurred.
  - If the year is not the same as the year of the last assessment, then the end date will be imputed as 31st December of that year.
- If the year is missing or the entire date is unknown, the end year will be the year in which the last assessment occurred (further imputation according to the rules for partial dates above). If information collected on the CRF indicates that the medication ended prior to the ICF date, the medication end date will be imputed as ICF date - 1.

Special handling of (partially) missing medication end dates for antibiotics given for UC/pouchitis started before Day 1 will be applied; the general imputation rules defined above will be used with the following exceptions:

- If the exact end date is unknown and available information does indicate that the antibiotic is continued after the ICF date but does not indicate that the antibiotic is continued after Day 1, it will be assumed that the antibiotic was stopped prior to Day 1 as per protocol, and the end date will be imputed as Day 1 – 1 as described below.
- If the day is missing:
  - In principle, the general rule for that case defined above will be applied.
  - However, if month/year of the partial medication end date are the same as of Day 1, the end date will be imputed as Day 1 – 1 (if Day 1 is the 1st of a month, the end date will be imputed as Day 1).
- If the day and month are missing (i.e. only year is reported):
  - In principle, the general rule for that case defined above will be applied.
  - However, if the year of the partial end date is the same as of Day 1, and
    a) end of medication is not flagged as ongoing after ICF, then assume as ended prior to ICF and the end date will be imputed as ICF date – 1;
    b) end of medication is flagged as ongoing after ICF or as ended after ICF, then the end date will be imputed as Day 1 – 1.
- If the entire end date is unknown:
  - If the start date is before the ICF date and end of medication is not flagged as ongoing/ended after ICF, then assume the medication ended prior to ICF and impute the end date as ICF date – 1.
  - If the start date is before the ICF date and end of medication is flagged as continued after ICF date (ongoing at ICF or ended after ICF), the end date will be imputed as Day 1 – 1.

– If the start date is after the ICF date (but before Day 1), an there is no indication that the medication was continued after Day 1, the end date will be imputed as Day 1 – 1.

7.1.9 Convention for Calculation of Time since IPAA

Time since IPAA is calculated as the number of years from IPAA date to first dose date (Day 1):

$$\frac{\text{date}_{\text{first dose}} - \text{date}_{\text{IPAA}} + 1}{365.25}$$

If the IPAA date is partially missing, the following rules will take effect:

- Missing day, but month and year are present: the day will be imputed as the 15th day of the month.
- Missing day and month, but year is present: the day and month will be imputed as 30th June of the year.

7.1.10 Conventions for Calculation of PDAI and mPDAI Scores

The Pouchitis Disease Activity Index (PDAI) is an objective and quantitative criterion for pouch inflammation after IPAA, consisting of the 3 subdomains clinical symptoms, endoscopic inflammation and acute histologic inflammation. Each subdomain is scored from 0 to 6, the total PDAI score is the sum of the 3 subscores and has a range of 0 to 18. The clinical symptoms are based on a patient diary completed for 3 days prior to endoscopy or bowel preparation for endoscopy. The average of the completed diary entries is taken for PDAI calculation, where at least one non-missing day needs to exist. A cutoff of 7 for differentiation between 'pouchitis' (≥7 points) and 'no pouchitis' (<7 points) is established. See Appendix B for more details.

The modified Pouchitis Disease Activity Index (mPDAI) consists of PDAI subdomains clinical symptoms and endoscopic inflammation; the mPDAI score has a range of 0 to 12. A cutoff of 5 differentiates subjects with pouchitis (mPDAI ≥5) from subjects without pouchitis (mPDAI <5). See Appendix C for more information.

The PDAI (and so the mPDAI) was to be assessed at baseline (Screening/ Visit 1), Week 14 and Week 34. Scores for all individual PDAI components were to be entered in the eCRF and the original mPDAI and PDAI total scores were derived based on these eCRF entries. In addition, the original central reader assessments of the 6 endoscopic inflammation components and the 2 acute histologic inflammation components will be captured in the study database.

For the purpose of the data analysis, the following rules will be applied used:

- Clinical symptoms:
  For the 4 clinical symptoms, generally, the scores entered in the eCRF will be used for the calculation of the clinical symptoms subscore. If the score of a clinical symptom is missing in the eCRF, it should be attempted to derive the symptom score from the corresponding patient diary entries.

- Endoscopic inflammation:
  For the 6 PDAI endoscopy components, the central reader data will be used to derive the endoscopic inflammation subscore (i.e., eCRF data will not be used).
  In case adjudication of the endoscopy ulceration score was done in context of the endoscopy additional (re-assessment) introduced in protocol amendment no. 4, the adjudicated ulceration score will be used in the calculation of the endoscopic inflammation subscore.
  However, the original ulceration score will be kept and reported/listed as well.
- Acute histologic inflammation:
  For the 2 PDAI histology components, the central reader data will be used to derive the acute histologic inflammation subscore (i.e., eCRF data will not be used).
- mPDAI total score:
  The mPDAI total score will be calculated as the sum of the clinical symptoms subscore and endoscopic inflammation subscore which are derived according to the rules above.
- PDAI total score:
  The PDAI total score will be calculated as the sum of all 3 subscores (clinical symptoms, endoscopic inflammation, acute histologic inflammation) which are derived according to the rules above.
- Where multiple assessments for a PDAI component are available for a visit (i.e., within the defined analysis window), the latest assessment will be used for the calculation of the respective subscores and total scores. Consequently, the assessment date of the last component/domain included in the calculation of a domain subscore or the total scores will be used as the analysis date for the domain subscore and total scores.
  For the endoscopic and the histologic items, the date the endoscopy was performed or histology biopsy taken, respectively, will be considered the date of assessment.
- PDAI assessments performed at early discontinuation (of study drug) that fall into the respective analysis window will be considered for analysis.
- Handling of missing data for these calculations is described below.

<u>Missing data handling for PDAI:</u>

- For the "as observed" summaries described in section 7.9.2, no missing (m)PDAI data will be imputed and only reported data will be summarized. For other data summaries and analyses imputation methods described below are to be applied.
- Imputation of completely missing mPDAI and PDAI assessments:
  Imputation of completely missing mPDAI and PDAI assessments will be done as described in the respective subsection of section 7.9.
- Imputation of partially missing mPDAI and PDAI assessments:
  Individual (m)PDAI components at *baseline* will not be imputed; thus, the respective PDAI domain subscore and the total PDAI score (and total mPDAI score, if applicable)

are missing for baseline.
Individual (m)PDAI components at *post-baseline time points* will be imputed using last-observation carried forward (LOCF); for this baseline data and unscheduled data (e.g. reported at early discontinuation) will be considered. Consequently, the respective PDAI domain subscore and the total PDAI score (and total mPDAI score, if applicable) will be derived using the imputed individual components.

Note:

In context of the blind data review the PDAI component scores need to be reviewed and verified against the source data; potential inconsistencies will need to be identified and their handling will be defined prior to database lock. This includes but is not limited to the following:

- Verification of scoring of clinical symptoms as per eCRF (supposed to be the average over 3 last diary days) against patient reported diary data.
- Verification of presence/absence of endoscopic findings as per eCRF against central reader raw data (the eCRF does not distinguish between absence and missing as only symptoms present are reported).
- In case of early termination, PDAI results might be reported on Early Termination page but not on Week 14 or Week 34, allocation of the Early Termination records to the respective target visits Week 14 and Week 34 to be defined.

7.1.11 Multiple Comparisons/Multiplicity

No adjustment of the statistical significance level is necessary to account for the futility analysis (see details in section 7.13).

Inferential comparisons between the two treatment arms are planned for multiple endpoints and two analysis populations. The study was powered for the difference in the primary endpoint and the analysis of the two populations for the primary efficacy endpoint is considered sensitivity analysis, therefore no multiplicity adjustment is needed.

No multiplicity adjustment for inferential testing of the secondary and exploratory endpoints is considered; therefore, p-values from those tests will be presented as nominal p-values only and have to be interpreted as such.

7.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- The safety analysis set (SAF) will consist of all randomized subjects who received at least 1 dose of study medication. Subjects will be analyzed according to the treatment actually received.
- The full analysis set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug. The FAS will be used as the primary analysis population for efficacy. Subjects will be analyzed according to the treatment they were randomized to.

- The per protocol set (PPS) will include all subjects in the FAS who do not have any major protocol violations. Major protocol violations that lead to exclusion of a subject from the PPS are listed in Section 7.4.2.

In addition, the populations "all screened subjects", "screening failures" and "all randomized subjects" may be used for particular data summaries.

If any subjects are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis prior to data base lock but all randomized subjects will be presented in the subject listings.

7.3 General Study Information and Disposition of Subjects

General study information and subject eligibility will be summarized as follows:

- Study information, including the date first subject signed the ICF, date of first and last study drug dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Regulatory Activities (MedDRA) version used, World Health Organization Drug (WHODrug) dictionary version used and SAS® version used for the data analysis.
- Demographic data for screen failures, showing age, gender, race, ethnicity.
- Eligibility for randomization, including number of subjects screened, number of subjects eligible/not eligible for randomization, and primary reason for subjects not eligible for randomization.

Subject disposition will be summarized for all randomized subjects as follows:

- Subjects randomized by geographical region (Western Europe, North America), country and site.
- Number (and %) of subjects who were randomized but not treated, if applicable
- Number (and %) of subjects who received study drug (at least once)
- Number (and %) of subjects who completed the study drug
- Number (and %) of subjects who prematurely discontinued (permanently) study drug and the reason for discontinuation. The reasons for discontinuation include PTE/AE, significant protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy, lack of efficacy and other.
- Number (and %) of subjects who completed Week 14*.
- Number (and %) of subjects who completed Week 34*.
- Number (and %) of subjects who completed all planned study visits.
- Number (and %) of subjects who prematurely discontinued the study and the reason for discontinuation.

* Week 14/Week 34 visits are considered completed when a subject's last visit with pouchitis assessment (at least one mPDAI subdomain assessed) was done in the respective visit window or thereafter.

In addition, incidence of protocol deviations and subject eligibility for the analysis sets will be summarized:

- Incidence of significant protocol deviations by category (see also section 7.4.1).
- Incidence of major protocol violations by category (see also section 7.4.2).
- Number (and %) of subjects eligible for each analysis set;
  Reasons for exclusion from analysis sets will be listed.

Corresponding subject data listings to be provided:

- All subjects: inclusion/exclusion criteria responses by subject
- Screen failures: screening and demographic data captured for screen failures
- Randomized subjects: date of ICF date, date of screening, date of randomization, further randomization information, date of first dose, last dose and last study visit.
- Randomized subjects who did not meet at least one inclusion criteria or who did meet at least one exclusion criteria will be listed.
- Subjects excluded from analysis sets will be listed including the reason for exclusion.

7.4 Significant Protocol Deviations and Major Protocol Violations

7.4.1 Significant Protocol Deviations

Significant protocol deviations were to be collected on the eCRF throughout the study conduct. Significant protocol deviations will be summarized for all randomized subjects using the following categories:

- Entry Criteria
- Concomitant Medication
- Procedures Not Performed Per Protocol (Primary Endpoint or Safety Related)
- Study Medication
- Withdrawal Criteria

A corresponding subject data listing, grouped by study site, will be provided.

Note: Study monitors informed that also several non-significant deviations had been reported in the study database (via the eCRF). Therefore, all deviations reported in the study database will be reviewed and re-assessed regarding their significance in context of the blind data review.

7.4.2 Major Protocol Violations

Major protocol violations that lead to exclusion from the PPS include the following categories:

- Randomized, but not treated
- Received wrong study medication (at least once)
- Missing baseline mPDAI score
- mPDAI score < 5 at baseline (considering the adjudicated endoscopy ulceration score)
- Missing Week 14 mPDAI score

Further major protocol violations might be identified in context of the blind data review. Major protocol violations will be summarized by means of a frequency table. A corresponding subject data listing, grouped by study site, will be provided.

7.5 Demographic and Other Baseline Characteristics

Generally, demographic and baseline characteristics will be summarized for all subjects randomized and for all analysis sets (SAF, FAS and PPS). If all subjects randomized and the SAF are identical, only one (combined) summary will be provided (with population title All randomized subjects / Safety Analysis Set). If two or all sets of SAF, FAS or PPS are identical, summaries can be combined accordingly. All summaries will be done by treatment arm and overall (in the respective analysis set).

Table 7.b lists the demographic and general baseline variables that will be tabulated.

Table 7.b Demographic and Baseline Characteristics

Demography (unit)	Summarized as	Categories
Age (years)	Continuous and Categorical	< 35 years 35 to < 65 years ≥ 65 years
Gender	Categorical	Male Female
Ethnicity	Categorical	Hispanic or Latino Non-Hispanic and Latino Not Collected
Race[a]	Categorical	American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Multiracial
Height (cm)	Continuous	
Weight (kg)	Continuous	
Body Mass Index (BMI) (kg/m^2)	Continuous and Categorical	Underweight (BMI< 18.5) Normal (BMI 18.5 to < 25.0) Overweight (BMI 25.0 to < 30.0) Obesity (BMI ≥ 30.0)
Smoking Classification	Categorical	Never-smoker Current smoker Ex-smoker
Female Reproductive Status	Categorical	Postmenopausal Surgically Sterile Female of Childbearing Potential N/A (Subject is male)[b]

[a] recorded on the eCRF. Subjects who identify themselves as more than one race on the eCRF will be classified as Multiracial for tabulation and will be included only in the multiracial category.

[b] Category "N/A" will be excluded from calculations of percentages for the other categories.

The BMI will be derived as body weight (kg) / height (m)^2 using the last body weight measurement prior to first dose of study medication (usually at Day 1) and the height measured at Visit 1 (Screening).

Table 7.c lists the pouchitis related baseline variables that will be tabulated.

Table 7.c Pouchitis Related Baseline Characteristics

Characteristics (unit)	Summarized as	Categories
Type of pouchitis	Categorical	Chronic pouchitis Recurrent pouchitis
Time since IPAA[a]	Continuous and Categorical	< 1 year 1 to < 3 years 3 to < 7 years ≥ 7 years
Baseline mPDAI[b]	Continuous and Categorical	< 5 (quiescent) 5 to 8 (moderately active) 9 to 12 (severely active)
Baseline PDAI[c]	Continuous and Categorical	< 7 (quiescent) 7 to 12 (moderately active) 13 to 18 (severely active)
Baseline stool frequency (from PDAI)	Categorical	0 = Usual postoperative stool frequency 1 = 1-2 stools/day > postoperative usual 2= 3 or more stools/day > postoperative usual
Baseline polymorphic nuclear leukocyte infiltration (PMNL; from PDAI)	Categorical	0 = none 1 = mild 2 = moderate + crypt abscess 3 = severe + crypt abscess
CCI [redacted]		
Prior anti-TNF exposure (for UC or pouchitis)[e]	Categorical	anti-TNF naïve anti-TNF experienced
Prior anti-TNF started post-colectomy[f]	Categorical	anti-TNF failure by reason: inadequate response, loss of response, intolerance anti-TNF used/no failure anti-TNF not used
Concomitant use of corticosteroids (for UC or pouchitis) at baseline	Categorical	Yes No
Baseline CRP (mg/L)	Continuous and Categorical	≤ 2.87 mg/L > 2.87 mg/L to ≤ 5 mg/L > 5 mg/L to ≤ 10mg/L > 10 mg/L
Baseline FC (µg/g)	Continuous and Categorical	≤ 250 µg/g > 250 µg/g to ≤ 500 µg/g > 500 µg/g

[a] See section 7.1.9 for calculation rule.

[b] See Appendix C for details on score derivation.

[c] See Appendix B for details on score derivation.

[d] See Appendix E for details on score derivation.

[e] Considering any prior use of anti-TNF for UC or pouchitis as recorded on the "UC Disease Last Antibiotic Medication and All Prior Biologics" or "Medication History/Concomitant Medications" CRF pages. See also section 7.1.1.

[f] Considering prior use of anti-TNF started post IPAA as recorded on the "UC Disease Last Antibiotic Medication and All Prior Biologics"; reasons for discontinuation "inadequate response", "loss of response", and "intolerance" are considered anti-TNF treatment failure. See also section 7.1.1 and section 7.1.6 for further details.

7.6 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that stopped at or prior to the time of ICF. Concurrent medical conditions are defined as significant ongoing conditions or diseases present at signing of ICF; the investigated disease "pouchitis" is not considered a concurrent medical condition. Both medical history and concurrent medical conditions will be summarized using the SAF (by treatment arm and overall).

Medical history and concurrent medical conditions will be coded using the MedDRA dictionary (MedDRA 23.0 Mixed). Medical history and concurrent medical conditions will be summarized by system organ class (SOC) and preferred term (PT), showing the number (and %) of subjects with medical history or condition (by SOC and PT); the tables will be sorted in alphabetic order by SOC and in decreasing frequency based on the total number of reports by PTs within each SOC. The denominator used for calculating the percentages will be the total number of subjects in the SAF (within treatment arm and overall, respectively). A subject having multiple reports the same PT will be counted only once for that PT. Similarly, a subject with multiple reports within the same SOC (even with different PTs) will be counted only once for that SOC.

The listings for medical history and concurrent medical condition data will contain at least one record per subject indicating if there was any medical history or concurrent condition reported, and, where applicable, showing the details of the medical history or concurrent medical condition (e.g., SOC, PT, start and end dates).

In addition, surgical and disease history related to UC (recorded separately in the eCRF) will be listed.

7.7 Medication History and Concomitant Medications

Medication history and concomitant medications were to be recorded in the eCRF. Reported medications will be grouped as follows:

- Prior medications: medications started prior to Day 1
- Concomitant medications: medications ongoing at Day 1 or started on or after Day 1 and before the end of study participation/early discontinuation

All medications will be coded using the WHODrug dictionary (01 March 2016 Expanded version).

Summaries of prior medications and concomitant medications will be provided based on the SAF and will present the number and percentage of subjects (using the total number of subjects in the treatment arm as the denominator) by therapeutic classification, subclassification, and preferred medication name. Therapeutic classification and subclassification terms will be sorted alphabetically; preferred medication names will be sorted using decreasing frequency across treatment arms.

Medications for treatment of UC or pouchitis (including worsening and flares) will primarily include antibiotics, corticosteroids, anti-TNFs and other relevant UC/pouchitis treatment (see

definitions in section 7.1.1); in addition, other medications flagged on the respective eCRF pages as "specifically for pouchitis" or "for treatment of flare" will be included.

Failure of prior treatment for UC or pouchitis will be identified as specified for prior anti-TNF treatments (see section 7.1.1), namely discontinuation reasons "inadequate response", "loss of response", and "intolerance" will be considered failure.

For the first 4 weeks, ciprofloxacin is given as companion antibiotic according to protocol; this companion antibiotic will not be considered as concomitant treatment as such. Ciprofloxacin will be considered as concomitant treatment in the following cases:

- Ciprofloxacin taken prior to the Week 4 visit (i.e. on or after Day 1) in addition to the companion antibiotic (i.e. total daily dose is higher than as per protocol).
- Ciprofloxacin taken after the later of Day 29 / actual Week 4 visit date.
  (e.g., if Week 4 visit was one Day 23, all ciprofloxacin up to Day 29 will be considered as companion antibiotic; if Week 4 visit was on Day 35, all ciprofloxacin up to Day 35 will be considered as companion antibiotic).

The following additional medication summaries will be provided for the FAS and PPS populations:

Prior UC/Pouchitis Medications

- Prior medications for UC and prior biologics (for UC/pouchitis) grouped by therapeutic classification, subclassification.
  (as collected on eCRF form "UC Disease Last Antibiotic Medication and All Prior Biologics", complemented by any such medication recorded as prior medication on the "Medication History/Concomitant Medications" eCRF form)
- Prior medications for UC/pouchitis started post-colectomy (= after IPAA) grouped by therapeutic classification, subclassification.
  (as collected on eCRF form "UC Disease Last Antibiotic Medication and All Prior Biologics", complemented by any such medication recorded as prior medication on the "Medication History/Concomitant Medications" eCRF form)
- Summary of reasons for failure/discontinuation and primary reason of intolerance of prior medications for UC/pouchitis started post-colectomy (= after IPAA) grouped by therapeutic classification, subclassification.
  (as collected on eCRF form "UC Disease Last Antibiotic Medication and All Prior Biologics", complemented by any such medication recorded as prior medication on the "Medication History/Concomitant Medications" eCRF form; for prior medications for UC or pouchitis recorded on the "Medication History/Concomitant Medications" eCRF form, the reason for discontinuation will be identified as "not recorded").
  A subject with multiple prior treatment courses within the same treatment class (therapeutic classification or subclassification) who experienced at least one failure in the treatment class will be counted as "failure" for the respective treatment class.

Concomitant Pouchitis Medications

- Concomitant medications for the treatment of pouchitis/worsening of pouchitis/flares grouped by therapeutic classification, subclassification.
  Intake of the companion antibiotic medication (ciprofloxacin 500 mg twice daily) during the first 4 weeks as per protocol will not be included in this summary. However, if this medication was continued after 4 weeks* or re-started after Week 4* or given for a flare/worsening, it will be included and counted in the summary.
  *Note: 4 weeks and Week 4 here refer to the later of the actual Week 4 visit date and Day 29 (see above).
- Use of concomitant corticosteroids (CS) for pouchitis using frequency tables showing number (and %) of subjects with/without CS use by visit (baseline/Day 1, Week 14, Week 34), where the reference day for baseline is Day 1 and for Week 14/34 is the day of the corresponding mPDAI assessment.
- Use of concomitant antibiotics for pouchitis (excluding the companion antibiotic medication given per protocol up to Week 4) using frequency tables showing number (and %) of subjects with/without antibiotics use by visit (baseline/Day 1, Week 14, Week 34), where the reference day for baseline is Day 1 and for Week 14/34 is the day of the corresponding mPDAI assessment.

Separate listings for medication history and concomitant medications will be produced by site and subject number. In addition, antibiotic medications and/or prior biologics related to UC (recorded separately in the eCRF) will be listed.

7.8 Study Drug Exposure

Study drug exposure will be summarized based on the SAF, FAS and PPS.

The following exposure data summaries will be provided (by treatment arm):

- Number (and %) of subjects by total number of intravenous infusions received
- Number (and %) of subjects who received any incomplete infusion (a subject has received complete infusion if the total amount was infused as per data collected in eCRF)
- Descriptive statistics for the total vedolizumab dose (mg) received in the study
- Descriptive statistics for duration of exposure (days)
- Frequency table for duration of exposure, showing the number (and %) of subjects according to the following categories: <20 weeks, 20 to <24 weeks, 24 to <32 weeks, 32 to <40 weeks, 40 to <48 weeks and ≥48 weeks.

For subjects randomized to vedolizumab IV, the duration of exposure will be calculated as:

date of last dose – date of first dose + 1 + 126,

where adding 126 days accounts for 5 times the half-life of vedolizumab IV. For subjects randomized to the placebo arm, the duration of exposure will be calculated as:

date of last dose – date of first dose + 1.

All study drug administration and accountability data will be listed.

7.9 Efficacy Analysis

This section describes the analyses to be conducted on the primary, secondary and additional endpoints related to efficacy.

7.9.1 General Consideration for the Efficacy Data Analysis

The primary efficacy analyses will be done based on the FAS, i.e., in general, all efficacy endpoints will primarily be summarized and analyzed for the FAS. Analyses of selected mPDAI and PDAI based endpoints (e.g., clinically relevant [mPDAI] remission, PDAI remission, partial mPDAI response, sustained mPDAI remission, sustained PDAI remission) will be repeated for the PPS. Further sensitivity analyses are described in section 7.9.6.1. The PDAI was to be assessed at baseline (Screening/ Visit 1), Week 14 and Week 34. All summaries will be provided by treatment arm and visit, if applicable.

Subjects for whom the total PDAI score at baseline cannot be calculated due to missing PDAI component or subscore will be excluded from the response analyses for PDAI remission, sustained PDAI remission, CCI [redacted] and analysis of time to PDAI remission and summaries of changes in the respective PDAI subscore(s) and changes in the respective PDAI component(s). However, data from such subjects will be included in the descriptive PDAI summaries by visit.

All efficacy data (originally reported data and derived outcomes) will be listed.

7.9.1.1 Analysis of Response-type Endpoints

For response-type efficacy endpoints (such as the primary endpoint), frequency tables will be provided, showing

- the number and proportion (%) of subjects achieving and not achieving the response (by treatment arm, visit)
- corresponding 2-sided 95% CIs for the response rate (by treatment arm, visit)
- difference in response rates (expressed in percent points [p.p]) between treatment arms (vedolizumab – placebo) and corresponding 95% CI

If not stated otherwise, the 95% CIs will be calculated using the exact method. Visit here typically refers to post-baseline visits (i.e., if not specifically mentioned those tables will be provided only for post-baseline visits).

The difference in response rate between the treatments will be tested using a chi-squared test and the (2-sided) p-value reported. If the number of responders or non-responders in either of the two treatment arms is too small (i.e., ≤5), the exact method (i.e., Fisher's Exact test) will be performed instead.

In order to account for the stratified randomization, response rates will be additionally analyzed stratified by type of pouchitis using the Cochran-Mantel-Haenszel (CMH) test, showing the relative risks (of response, relative to placebo) and 95% confidence limits overall (common) and for the two levels of type of pouchitis, and the p-value for association between treatment and response from the CMH statistics. This additional analysis will only be done for the endpoints mPDAI remission and PDAI remission (at Week 14 and Week 34) for the FAS and PPS, and only if the number of responders and non-responders in both treatment arms is sufficiently large (i.e., >5); this analysis will not be done for any subgroup analyses.

In these analyses, all subjects with missing data for determination of response status at a time point will be considered as a non-responder (non-response imputation).

This applies, in particular, to the following endpoints: clinically relevant remission (mPDAI remission), PDAI remission, partial mPDAI response.

7.9.1.2 Analysis of Other Categorical/Ordinal Endpoints

For categorical and ordinal efficacy endpoints other than response-type efficacy endpoints, frequency tables will be provided, showing the number and proportion (%) of subjects per category by treatment arm and visit (see details for standard frequency tables in in section 7.1).

7.9.1.3 Analysis of Continuous Endpoints

Continuous efficacy endpoints (observed values) and their change from baseline will be summarized descriptively by treatment arm and visit (see details for descriptive statistics in section 7.1).

Where required, e.g. for secondary efficacy endpoints, changes from baseline to relevant visits in both treatment arms will be compared using the Wilcoxon rank-sum tests; the (Wilcoxon-Mann-Whitney) odds estimator and its 95% CI and the Hodges-Lehmann estimate for difference (location shift) with its 95% CI will be presented.

7.9.1.4 Analysis of Time-To-Event Endpoints

For time-to-event endpoints, the time to event (in days) from first dose of study medication (Day 1) will be derived as

$$\text{time (days)} = \text{date of event} - \text{date of Day 1} + 1.$$

The time to event will be analyzed using Kaplan-Meier product limit methods, with subjects that do not experience the event during the study being censored at the time of the last corresponding assessment or date of last record (week 34 or early discontinuation), as applicable. Summaries will present the total number (and %) of subjects with event, total number of cases censored; the time to event will be summarized by estimates of 25^{th}, 50^{th} (median), and 75^{th} percentiles with 95% CIs, and the range (min, max); in addition, cumulated number of subjects with event by appropriate time points and corresponding Kaplan-Meier estimates (with 95% CI) and number of subjects at risk by time point will also be summarized.

The survival analysis will be supplemented with a corresponding Kaplan-Meier plot (by treatment arm, using an appropriate time scale) to illustrate the time to event, showing also the number of subjects at risk at the time points (at baseline and at the time points corresponding to the summary table).

7.9.2 Overall PDAI and mPDAI Summaries

The primary and most of the secondary efficacy are based on the PDAI and mPDAI, assessed at baseline/screening, Week 14 and Week 34. The PDAI (and mPDAI) scores and components and their changes from baseline will be summarized as described below for the FAS and the PPS. In general, all scores are integer scores and therefore, minimum and maximum values will be displayed without decimals. Details for response-type frequency tables, (standard) frequency tables and descriptive statistics can be found in sections 7.9.1.1, 7.9.1.2 and 7.9.1.3, respectively.

mPDAI total score (summaries for overall populations and subgroups specified in section 7.9.3)

a) descriptive statistics, as observed
(for FAS and PPS overall, including inferential statistics as described in section 7.9.1.3)

b) descriptive statistics, LOCF applied (only for the FAS);
(for FAS overall, including inferential statistics as described in section 7.9.1.3)

c) frequency table with categories < 5 (quiescent), 5 to 8 (moderately active), 9 to 12 (severely active), as observed

d) response-type frequency table with categories < 5 (remission), ≥ 5 (active), non-response imputation applied as described in section 7.9.1.1

PDAI total score (summaries for overall populations and subgroups specified in section 7.9.4)

a) descriptive statistics, as observed
(for FAS and PPS overall, including inferential statistics as described in section 7.9.1.3)

b) descriptive statistics, LOCF applied (only for the FAS)
(for FAS overall, including inferential statistics as described in section 7.9.1.3)

c) frequency table with categories < 7 (quiescent), 7 to 12 (moderately active), 13 to 18 (severely active), as observed

d) response-type frequency table with categories < 7 (remission), ≥ 7 (active), non-response imputation applied as described in section 7.9.1.1

PDAI domains and components

Clinical symptoms

- Clinical symptoms subscore

  a) descriptive statistics, as observed
  (for FAS and PPS overall, including inferential statistics as described in section 7.9.1.3)

b) descriptive statistics, LOCF applied (only for the FAS)
(for FAS overall, including inferential statistics as described in section 7.9.1.3)

- Stool frequency (SF)
  a) frequency table with categories 0 = "usual postoperative frequency", 1 = "1-2 stools/day more than usual", 2 = "≥ 3 stools/day more than usual" (observed data, no imputation applied)
  b) response-type frequency table with categories 0 = "usual postoperative frequency", ≥1 = "more than usual"
  c) response-type frequency table with categories 0 = "usual postoperative frequency", ≥1 = "more than usual", for the subpopulation having an SF score > 0 at baseline
  d) response-type frequency table with categories ≤1 = "≤ 2 stools/day more than usual postoperative frequency", 2 = "≥ 3 stools/day more than usual" (without inferential statistics)
  e) response-type frequency table with categories ≤1 = "≤ 2 stools/day more than usual postoperative frequency", 2 = "≥ 3 stools/day more than usual", for the subpopulation having an SF score > 1 at baseline (without inferential statistics)
- Rectal bleeding (RB)
  a) frequency table with categories 0 = "none or rare", 1 = "present daily" (observed data, no imputation applied)
  b) response-type frequency table with categories 0 = "none or rare", 1 = "present daily" (without inferential statistics)
  c) response-type frequency table with categories 0 = "none or rare", 1 = "present daily", for the subpopulation having an RB score > 0 (i.e. rectal bleeding present daily) at baseline (without inferential statistics)
- Clinical components fecal urgency or abdominal cramps, fever:
  frequency tables with categories as per PDAI (see Appendix B)

Endoscopic inflammation

- Endoscopic inflammation subscore
  a) descriptive statistics, as observed
  (for FAS and PPS overall, including inferential statistics as described in section 7.9.1.3)
  b) descriptive statistics, LOCF applied (only for the FAS)
  (for FAS overall, including inferential statistics as described in section 7.9.1.3)

- Endoscopic component ulceration
  a) frequency table with categories 0 = "absent", 1 = "present" (observed data, no imputation applied)
  b) response-type frequency table with categories 0 = "absent", 1 = "present" (without inferential statistics)
  c) response-type frequency table with categories 0 = "absent", 1 = "present", for the subpopulation having an ulceration score > 0 (i.e. ulceration present) at baseline (without inferential statistics)
- Endoscopic components friability, loss of vascular pattern, edema: frequency tables with categories 0 = "absent", 1 = "present"
- Note: no specific summaries for components granularity and mucus exudates

Note: For the components of endoscopic inflammation, the central reader data should be used and not the eCRF data (the eCRF only captured presence, thus missing and absence cannot be distinguished).

Acute histologic inflammation

- Acute histologic inflammation subscore
  a) descriptive statistics, as observed
  (for FAS and PPS overall, including inferential statistics as described in section 7.9.1.3)
  b) descriptive statistics, LOCF applied (only for the FAS)
  (for FAS overall, including inferential statistics as described in section 7.9.1.3)
- Histologic inflammation components polymorphic nuclear leukocyte infiltration and ulceration per low power field:
  frequency tables with categories as per PDAI (see Appendix B)

Further summaries and analyses of the primary and secondary efficacy endpoints related to the PDAI are described in sections 7.9.3 and 7.9.4. Further summaries and analyses of individual PDAI components are described in section 7.9.6. In general, the summaries and analyses of and outcome/endpoint or component described in this section and the later section should be grouped together and, where possible, be shown in the same table.

7.9.3 Primary Efficacy Endpoint

The primary endpoint is clinically relevant (mPDAI) remission (defined as an mPDAI score < 5 and a reduction of mPDAI score by ≥ 2 points from baseline) at Week 14.

Let p_v and p_p describe the proportion of subjects achieving the primary endpoint (i.e., of Week 14 mPDAI remitters) in the vedolizumab and placebo arms, respectively. The null and alternative hypotheses for the primary efficacy endpoint are:

H_0: $p_v = p_p$

H_1: $p_v \neq p_p$

The primary endpoint (a response-type endpoint) will be summarized and analyzed as described in section 7.9.1.1 based on the FAS (primary analysis) and the PPS (sensitivity analysis). The primary inferential analysis for testing the hypothesis is the chi-squared test described in section 7.9.1.1. Related descriptive summaries are described in section 7.9.2.

Corresponding subgroup analyses will be done for subgroups by type of pouchitis, prior anti-TNF failure for pouchitis (started post-colectomy), prior anti-TNF exposure, baseline severity based on mPDAI, baseline PMNL, time from IPAA to start of treatment, baseline FC, baseline CRP (see definitions in section 7.1.6). Results from those subgroup analyses will be illustrated by means of forest plots for the treatment difference in response rates with corresponding 95% CI by subgroup.

7.9.4 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be summarized and analyzed as described below based on the FAS (primary analysis); analyses will be repeated for the PPS (sensitivity analysis) as indicated below. Related descriptive summaries for PDAI-based endpoints are already described in section 7.9.2.

Corresponding subgroup analyses for subgroups by type of pouchitis, prior anti-TNF failure for pouchitis (started post-colectomy), prior anti-TNF exposure, baseline severity based on mPDAI, baseline PMNL, time from IPAA to start of treatment, baseline FC, baseline CRP (see definitions in section 7.1.6) will be done for the endpoints mPDAI remission at Week 34, PDAI remission at Week 14 and Week 34, and partial mPDAI response at Week 14 and Week 34. Analyses for PDAI remission at Week 14 and Week 34 will also be repeated for subgroups by baseline severity based on PDAI. Results from those subgroup analyses will be illustrated by means of forest plots for the treatment difference in response rates with corresponding 95% CI by subgroup.

Clinically relevant (mPDAI) Remission at Week 34

The secondary endpoint clinically relevant (mPDAI) remission at Week 34 will be summarized and analyzed as described in section 7.9.1.1 based on the FAS and the PPS.

PDAI Remission at Week 14 and at Week 34

PDAI remission (defined as a PDAI score < 7 and a decrease in PDAI score of ≥ 3 points from baseline) at Week 14 and at Week 34 will be summarized and analyzed as described in section 7.9.1.1 based on the FAS and the PPS.

Time to PDAI Remission

The time point of PDAI remission is defined as the first visit on which the PDAI score is < 7 and a decrease in the PDAI score of ≥ 3 points from baseline occurred (=$Visit_{remission}$). The time to PDAI remission is then derived using the date of $Visit_{remission}$ and summarized and analyzed as

described in section 7.9.1.4 based on the FAS. Subjects who did not achieve PDAI remission, will be censored at the time of their last PDAI assessment; if a subject's last PDAI assessment is the baseline assessment, the subject will be censored at Day 1. Cumulated event counts, KM estimates and number at risk will be shown for the Week 14 and Week 34 visits (considering the last day of the respective analysis windows defined in section 7.1.7).

Cox proportional hazards regression will be performed to explore the effect of prognostic factors. Prognostics factors include type of pouchitis, prior anti-TNF failure for pouchitis (started post-colectomy), prior anti-TNF exposure, time from IPAA, baseline severity based on mPDAI, baseline severity based on PDAI, baseline PMNL, baseline FC, baseline CRP (for all factors use same categories as for subgroup analyses of the primary endpoint, see also section 7.1.6), age (< 35 years vs ≥ 35 years), gender, BMI (< 30 vs ≥ 30 kg/m^2). This regression analysis will be done for the FAS and the PPS.

Adjustments for baseline imbalances on key prognostic factors (listed above) will be made using Cox regression.

Partial mPDAI Response at Week 14 and at Week 34

Partial mPDAI response (defined as a reduction in mPDAI score by ≥2 points from baseline) at Week 14 and at Week 34 will be summarized and analyzed as described in section 7.9.1.1 based on the FAS and the PPS.

Changes in PDAI Subscores

Total PDAI and PDAI subscores (mPDAI score, clinical symptoms, endoscopic inflammation and histologic inflammation) and their changes will be summarized as described in section 7.9.2. In addition, the changes in these scores from baseline to Week 14 and to Week 34 will be analyzed as described in section 7.9.1.3 (including inferential statistics for the FAS and PPS overall populations).

All summaries and analyses will be done for the FAS and the PPS based on observed data; for the FAS analyses will be repeated with missing data imputed using the last observation carried forward (LOCF) approach applied (thereby considering data from unscheduled visits or early termination).

IBDQ

The IBDQ is an instrument used to assess quality of life in adult subjects with IBD. It includes 32 questions on 4 domains: bowel systems (10 items), emotional function (12 items), social function (5 items) and systemic function (5 items). Subjects are asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224 (see calculation rules in Appendix G). The IBDQ was to be assessed at Day 1 (baseline), Week 14, Week 22 and Week 34.

The total IBDQ score and domain scores and their respective changes from baseline to Week 14, Week 22 and Week 34 will be summarized descriptively as described in section 7.9.1.3

(including inferential statistics for the FAS and PPS overall populations, only for the total IBDQ score).

In addition, IBDQ remission and IBDQ improvement will be summarized by visit, by means of response-type frequency tables as described in section 7.9.1.1 (without inferential statistics).

All IBDQ summaries will be provided once based on observed data (FAS and PPS) and once with missing data imputed using LOCF (FAS only).

CGQL

The CGQL was developed as a quality-of-life indicator specifically for subjects with IPAA. It includes three components (current quality of life, current quality of health and current energy level), each scored on a scale of 0 (worst) to 10 (best). The CGQL utility score will be derived as the sum of the component scores divided by 30; the CGQL is recorded with a patient diary which is completed for 3 days prior to endoscopy or bowel preparation for endoscopy. The Fazio score is assessed as the average of the completed CGQL utility scores, where at least one non-missing day needs to exist (see further details in Appendix F). The CGQL was to be assessed at Day 1 (baseline), Week 14, Week 22 and Week 34.

The Fazio score and change from baseline to Week 14, Week 22 and Week 34 will be summarized descriptively as described in section 7.9.1.3 (including inferential statistics), once based on observed data (FAS and PPS) and once with missing data imputed using LOCF (FAS only).

7.9.5 Exploratory Efficacy Endpoints

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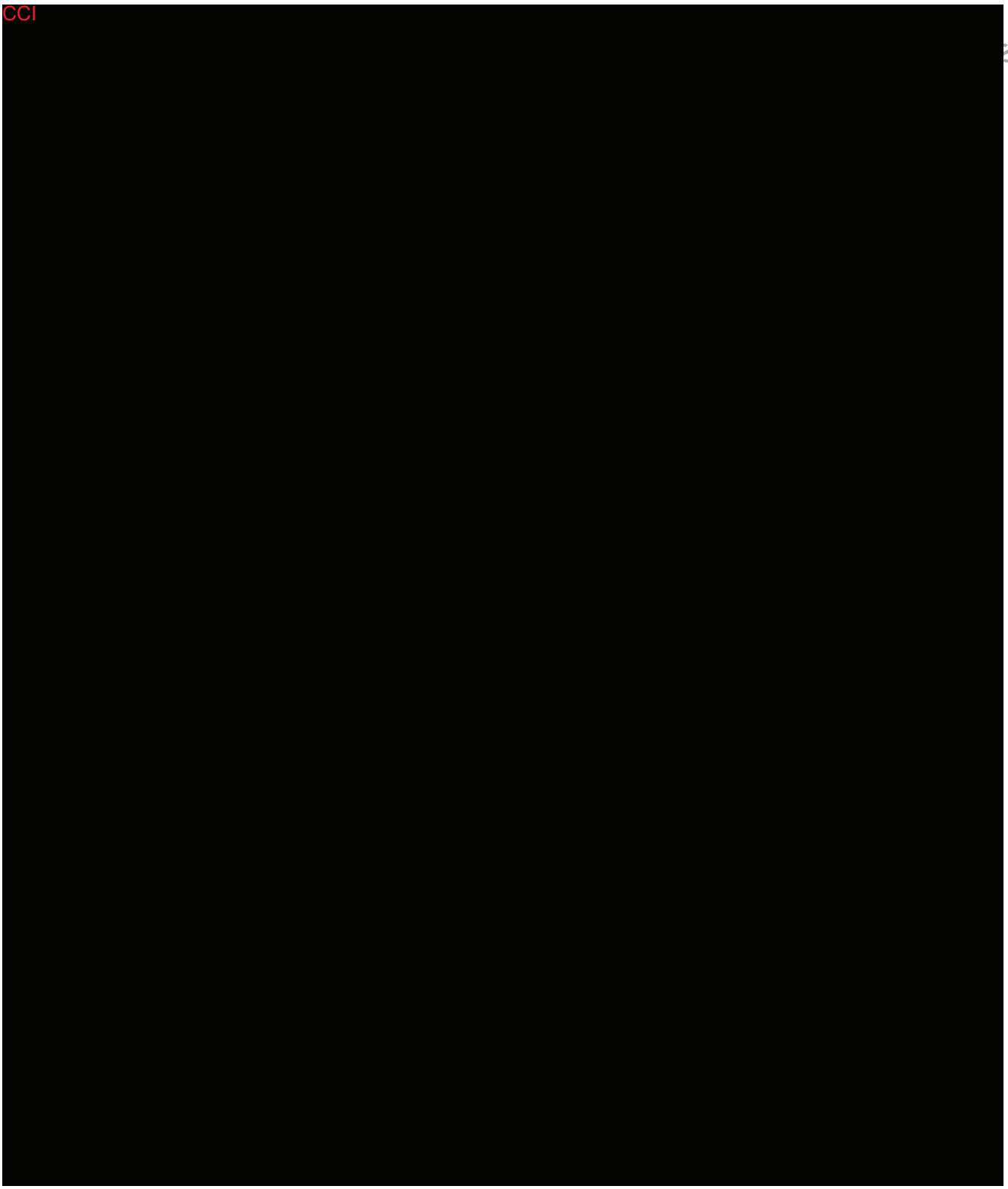
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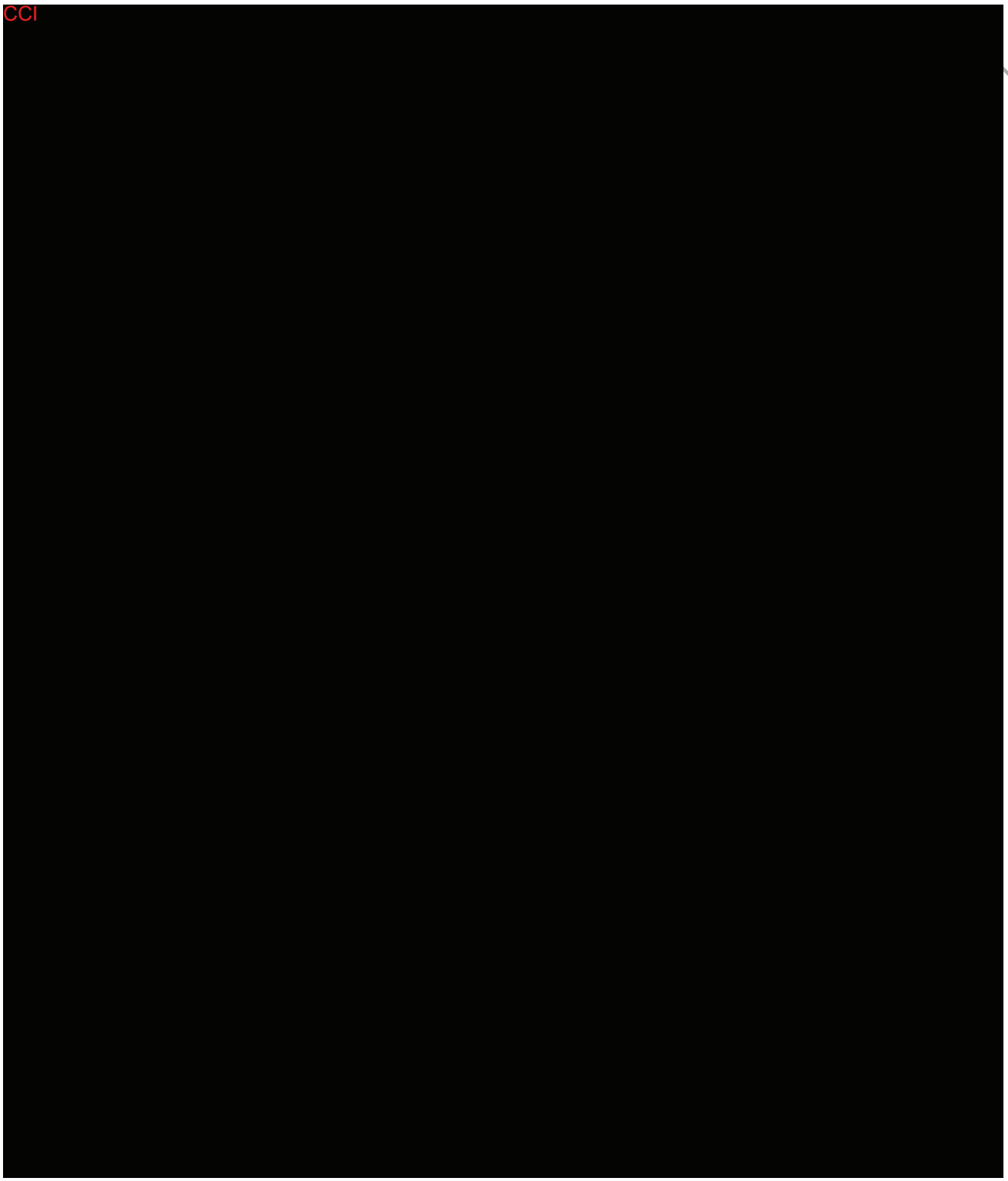

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7.9.6 Sensitivity Analyses and Additional Analyses

7.9.6.1 Sensitivity Analyses

Sensitivity analyses are considered for the following endpoints:

- Clinically relevant (mPDAI) remission at Week 14 and Week 34
- PDAI remission at Week 14 and Week 34
- Partial mPDAI response at Week 14 and at Week 34
- Sustained mPDAI remission
- Sustained PDAI remission

At first, the analyses for the aforementioned endpoints as described in sections 7.9.3, 7.9.4 and 7.9.5. will be repeated based on the PPS. In case, major differences between the results for the FAS and the PPS are detected for these endpoints, analysis of further efficacy endpoints based on the PPS might be warranted.

To assess the impact of dropouts and missing data for response-type efficacy endpoints listed above, further sensitivity analysis will be performed in addition to the initial non-response imputation approach described in section 7.9.1.1. and applied to the respective response-type frequency tables and analyses:

1) Impute all missing data using LOCF
2) Hybrid approach:
    a. Interim missing data (e.g. Week 14 missing, but Week 34 data present) will be imputed using LOCF.
    b. Missing data after study drug discontinuation will be imputed based on the primary reason for study drug discontinuation:
    missing data after study drug discontinuations due to AE or lack of efficacy will be imputed using the non-response imputation (as done in the initial approach);

missing data after study discontinuations for other reasons will be imputed using LOCF.

3) Non-response imputation for use of concomitant antibiotics prior to Week 14:
In addition to the general non-response imputation for missing data in the initial analysis, subjects with use of concomitant antibiotics relevant for UC/pouchitis (see section 7.1.1), other than the companion antibiotic given per protocol up to Week 4, prior to Week 14 (date of Week 14 endoscopy) will be imputed as non-responders at Week 14 and Week 34 for the aforementioned efficacy endpoints.

Independently from the three approaches described above, missing individual PDAI components will be imputed as described in section 7.1.10. Those analyses will be done initially based on the FAS. If large deviations from the results of the initial analyses are identified, they might be repeated based on the PPS and further sensitivity analyses with different missing data imputation methods might be considered.

7.9.6.2 Additional Analyses

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Due to large number of centers with small number of patients recruited, appropriate pooling of centers by the following geographical regions will be done:

- Europe (all European countries)
  - Central Europe (UK, Belgium, Germany, the Netherlands)
  - Southern Europe (France, Italy, Spain)
- North America (US/Canada)
  - USA
  - Canada

Appropriate summaries for the aforementioned response-type endpoints by region will be provided and corresponding forest plots for the treatment difference in response rates with corresponding 95% CI by region will be plotted (for the FAS population only).

If the graphical exploration yields substantial differences between the region/centers, the exploration will be repeated for the PPS and corresponding summary statistics will be produced for both populations. Additionally, these endpoints might be analyzed additionally accounting for region/center (regions/centers with alike effects might be grouped accordingly).

7.10 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.11 Other Outcomes

Not applicable.

7.12 Safety Analysis

Safety analyses include AEs, clinical laboratory values, vital signs and electrocardiograms (ECGs). All safety summaries will be based on the SAF, and if not mentioned otherwise will show results by treatment arm.

7.12.1 Adverse Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed ICF to participate in a study, but prior to administration of any study medication. An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a study medication. Treatment-emergent adverse events (TEAEs) will be defined as any AE that occurs after the first dose of study medication (on or after Day 1) and up to the last dose of study medication plus applicable follow up (18 weeks = 126 days from the date of last dose).

Adverse events were to be recorded throughout the study with assessment of intensity (mild, moderate, severe), relationship to study medication (related, not related) and seriousness (SAE or not). Further AE information collected include onset and end of AE, type (pretreatment or AE), relationship to study procedure, actions taken concerning study medication, and outcome. PTEs and AEs will be coded using MedDRA, Version 23.0 Mixed.

The overview of TEAEs will be summarized using the number of events as well as the number and percentage of subjects with TEAEs. All other TEAE summaries provide the number and percentage of subjects with event, with events grouped by MedDRA system organ class (SOC), high level term (HLT), and preferred term (PT).

Most frequent TEAEs are defined as events that occur in at least 5% of subjects within either treatment arm. Exposure adjusted incidence rates will be derived as incidence per 100 subject years.

The following outputs will be produced for TEAEs overall:

- Overview of TEAEs, showing the number (and %) of subjects with and number of TEAEs (number of events) overall, TEAEs overall by intensity, TEAEs overall by drug relationship, TEAEs leading to study drug discontinuation, serious TEAEs overall, serious TEAEs by drug relationship, serious TEAEs leading to study drug discontinuation, and the number of deaths.
- Number (and %) of subjects with and number of TEAEs by SOC, HLT and PT
- Exposure-adjusted* TEAEs by SOC, HLT, and PT
- Subject mapping of TEAEs by SOC, HLT, and PT

- Number (and %) of subjects with and number of TEAEs leading to study drug discontinuation by SOC, HLT and PT
- Subject mapping of TEAEs leading to study drug discontinuation by SOC, HLT, and PT
- Number (and %) of subjects with and number of serious TEAEs by SOC, HLT and PT
- Exposure-adjusted* serious TEAEs by SOC, HLT, and PT
- Subject mapping of serious TEAEs by SOC, HLT, and PT
- Number (and %) of subjects with and number of most frequent TEAEs by SOC, HLT and PT
- Number (and %) of subjects with and number of most frequent non-serious TEAEs by SOC, HLT and by PT
- Number (and %) of subjects with and number of drug-related TEAEs by SOC, HLT and PT
- Intensity of TEAEs by SOC, HLT and PT
- Intensity of drug-related TEAEs by SOC, HLT and PT

* For the expose-adjusted TEAE tables the exposure-adjusted incidence rate (incidence per 100 subject years) will be summarized. For the purpose of this analysis,

- the exposure-adjusted incidence rate is defined as the number of subjects with AEs (with onset during the exposure interval) divided by the total exposure time of the subjects (in a treatment arm)
- for both treatment arms,
  a subject's exposure interval is defined as [date of first dose; date of last dose + 126 days] and the corresponding exposure time as date of last dose – date of first dose + 1 + 126.

The following summaries will be provided for TEAEs related to a flare:

- Overview of TEAEs related to a flare, showing the number (and %) of subjects with and number of TEAEs related to a flare overall, TEAEs related to a flare overall by intensity, TEAEs related to a flare overall by drug relationship, TEAEs related to a flare leading to study drug discontinuation, serious TEAEs related to a flare overall, serious TEAEs related to a flare by drug relationship, serious TEAEs related to a flare leading to study drug discontinuation.
- Number (and %) of subjects with and number of TEAEs related to a flare by SOC, HLT and PT
- Number (and %) of subjects with and number of TEAEs related to a flare leading to study drug discontinuation by SOC, HLT and PT
- Number (and %) of subjects with and number of serious TEAEs related to a flare by SOC, HLT and PT

- Number (and %) of subjects with and number of drug-related TEAEs related to a flare by SOC, HLT and PT
- Intensity of TEAEs related to a flare by SOC, HLT and PT

The following pretreatment event summaries will be provided:

- Number (and %) of subjects with and number of pretreatment events by SOC, HLT and PT
- Number (and %) of subjects with and number of serious pretreatment events by SOC, HLT and PT

For the number (and %) of subjects with TEAEs in above summaries, subjects who reported the same TEAE multiple times will be counted only once per PT; similarly, subjects who reported multiple TEAEs falling in the same HLT or SOC will be counted only once per HLT or SOC, respectively. For the intensity summaries, if a subject reported multiple TEAEs coded to the same SOC or HLT or PT then the maximum intensity reported will be considered. If the intensity for a TEAE is missing, it will be counted as "severe" in the summaries, but in listings will be shown as missing. Similarly, for the summary of drug-related TEAEs, for subjects with multiple reports of the same PT (or within HLT or SOC), the worst case reported for the PT (within HLT or SOC) will be considered. If the drug-relationship for a TEAE is missing, it will be counted as "related" in the summaries, but in listings will be shown as missing.

Data listings will be provided for pretreatment events, TEAEs overall*, TEAEs related to a flare, TEAEs leading to study drug discontinuation*, serious TEAEs*, and AEs resulting in death*. *In those listings, TEAEs related to a flare will be flagged.

7.12.1.1 Adverse Events of Special Interest

Based on the mechanism of action of vedolizumab, the following 5 AEs of special interest (AESIs) have been predefined with corresponding MedDRA search criteria. Standard MedDRA Query (SMQ) below refer to MedDRA V23.0 SMQ.

Hypersensitivity Reactions including Infusion-Related Reactions (IRRs)

Possible IRRs will be identified using the following MedDRA search criteria:

- Anaphylactic/anaphylactoid shock conditions SMQ (broad)
- Angioedema SMQ (broad)
- Hypersensitivity SMQ (broad)
- Infusion related reaction HLT

An AE that is indicated as an infusion site reaction in the eCRF will also be considered an IRR AESI.

Suspected Progressive Multifocal Leukoencephalopathy (PML)

Suspected PMLs will be identified within the Infection and Infestation SOC using the following MedDRA search criteria:

- Human polyomavirus infection PT
- JC virus infection PT
- JC virus CSF test positive PT
- Leukoencephalopathy PT
- Polyomavirus test positive PT
- JC polyomavirus test positive PT
- Progressive multifocal leukoencephalopathy PT

Liver Injury

Reports of liver injury will be identified using the following MedDRA search criteria:

- Cholestasis and jaundice of hepatic origin SMQ (broad)
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (broad)
- Hepatitis, non-infectious SMQ (broad)
- Liver related investigations, signs and symptoms SMQ (narrow)
- Liver infections SMQ (broad)

Malignancies

Reports of malignancy will be identified using the following MedDRA criterion:

- Neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC.
- An AE that is indicated as malignancy in the eCRF will also be considered an AESI.

Serious Infections

Reports of infection, flagged as serious TEAE, will be identified using the following MedDRA criterion:

- Infections and infestations SOC.

Incidence of the 5 AESIs will be summarized showing the number (and %) of subjects with and the number of events by SOC, HLT and PT.

7.12.2 Clinical Laboratory Evaluations

The laboratory parameters for serum chemistries, hematology, stool and urinalysis shown in Table 7.d were recorded in this study. Refer to Appendix A for scheduled measurements for clinical laboratory tests.

Table 7.d Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**
RBC	ALT	Bilirubin
WBC with differential*	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	AST	Ketones
Platelets	Total bilirubin	Leukocyte esterase
PT/INR	Total protein	Nitrite
	Creatinine	pH
	Blood urea nitrogen	Protein
	Creatine kinase	Specific Gravity
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	

Other:
HIV
Hepatitis panel, including HBsAg and anti-HCV

Serum	**Urine**	**Stool**
QuantiFERON for TB CRP	hCG (for pregnancy in female subjects of childbearing potential only)	Fecal calprotectin
beta hCG (for pregnancy in female subjects of childbearing potential only) FSH, if menopause is suspected (Screening visit only)		*C difficile*

*WBC differential to include lymphocytes, monocytes, basophils, eosinophils, and neutrophils.

FSH =follicle-stimulating hormone, GGT= γ-Glutamyl transferase, hCG =human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells.

In general, clinical laboratory parameters will be presented using the International System of Units (SI) unless otherwise stated. For test results not reported in SI units, the conversion to SI units will be done in the derived analysis data sets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived dataset. All data summaries will be based on the values using these preferred SI units. If a lab test with quantitative results has a value that is reported using a non-numeric

qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Continuous laboratory parameters tabulated using summary statistics for observed values and change from baseline by visit (baseline, each post baseline visit and last visit). Categorical laboratory parameters (e.g. urinalysis) will only be listed.

Criteria for markedly abnormal values (MAV) of laboratory parameters are listed in Appendix H. For laboratory parameters with available criteria, incidence of MAVs will be summarized as follows:

- Overview table with number (and %) of subjects with any MAV reported overall and by visit
- For each laboratory parameter for which at least one MAV was reported: a summary table for number (and %) of subjects with MAV by visit.

If both the baseline and on-treatment values of a parameter are beyond the MAV limit for that parameter, then the on-treatment value will be considered a MAV only if it is more extreme than was the baseline value.

In addition, the number (and %) of subjects with elevated liver function tests Alanine Aminotransferase, Aspartate Aminotransferase and Alkaline Phosphatase will be summarized separately.

All laboratory parameters will be listed, with values outside the normal ranges flagged as above "(H)" or below "(L)"; additionally, MAV values will be flagged (either as "(H#)" or "(L#)").

7.12.3 Vital Signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, body temperature (in °C), weight (in kg), and respiration rate were measured at the time points indicated in the schedule of study procedures (refer to Appendix A).

For each vital sign parameter, the observed values and change from baseline will be summarized by visit (including last visit) using descriptive statistics.

Criteria for MAV of vital signs (SBP, DBP, pulse and body temperature) are listed in Appendix I. For these vital signs parameters, incidence of MAV the number (and %) of subjects with MAV will be summarized by visit.

Vital signs data will be listed with markedly abnormal values (MAVs) flagged, either as "(H#)" for values exceeding the upper criterion or as "(L#)" for values exceeding the lower criterion.

7.12.4 12-Lead ECGs

Overall ECG interpretation category (within normal limits, abnormal but not clinically significant and abnormal clinically significant) are collected by the eCRF at Screening and occasional post-baseline unscheduled visits. ECG interpretations will be listed only.

7.12.5 Other Observations Related to Safety

Other safety related data recorded include the following data. The following additional safety data will only be collected by the eCRF when triggered by an adverse event. For those data appropriate data listings will be provided:

- Physical examinations
- Liver function tests (increase, sign and symptoms, event history and test results)
- Infections (details of infection, their diagnostic tests, cause/origin, history preceding events and associated symptoms) will also be listed.
- Malignancy (status based on diagnostic tests, stage, the risk factors and additional details)
- Results from the PML checklist that includes the PML criteria, their response, symptoms, result and abnormality; data will be listed (by visit) only for subjects with any abnormality reported.
- Results from the PML algorithm; data will be listed (by visit) only for subjects with any abnormality reported

7.13 Futility Analysis

A futility analysis was planned to be performed after a total of 50 subjects (25 subjects per treatment arm) have been randomized and completed Week 14 assessment of the primary efficacy endpoint (mPDAI remission).

Since it was not intended stop the study early on the grounds of efficacy based on the results from this futility analysis, no adjustment to the statistical significance level is necessary for the final analysis.

This futility analysis is described in a separate analysis plan (dated 12 October 2018).

7.14 Changes in the Statistical Analysis Plan

The following changes from protocol concerning the statistical analysis were applied:

- The wording "Percentage of subjects with…" or "Percentage of subjects achieving…" in the definition of response-type primary and secondary efficacy endpoints was removed to clarify that the respective event itself is considered the endpoint.
- The wording of some study endpoints was slightly altered for purpose of clarification; these alterations do not have an impact on the analysis of the endpoints.
- In order to be consistent and to not include any subjects that didn't receive any dose of study drug the definition of the FAS is adapted to 'all randomized subjects who receive at least 1 dose of study drug'.

- In the protocol, further analysis of time to PDAI remission in both treatment arms using the log-rank test was specified. This analysis has been removed due to the lack of accuracy of this endpoint (PDAI remission only assessed at Week 14 and Week 34).
- For the purpose of the analysis, the definition of type of pouchitis was refined and adapted to be determined based on data/information captured in the eCRF (see section 7.1.1).
- During blind data review two subjects were identified that were reported with total mPDAI baseline scores ≥ 5 as per the initial endoscopy reading but having a total mPDAI baseline score < 5 based on the adjudicated PDAI ulceration score. Those subjects will be included in the FAS population but excluded from the PPS and from subgroup analyses by baseline severity based on mPDAI.
- During blind data review it was identified that several subjects have used concomitant antibiotics other than the companion antibiotic given per protocol prior to Week 14. Therefore, a sensitivity analysis of the key response-type efficacy endpoints has been added in which subjects for those the concomitant use of antibiotics prior to Week 14 is reported/identified will be considered as non-responder (see section 7.9.6.1).
- The initially planned subgroup analysis by failure of prior anti-TNF treatment for pouchitis was refined to a subgroup analysis by failure of prior anti-TNF treatment started post-colectomy (see section 7.1.6).

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8.0 REFERENCES

1. A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST), Amendment 03, Takeda Development Center Americas, Inc., Protocol Vedolizumab-4004, Protocol Amendment 04, 14 September 2020.
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3. Barreiro-de Acosta M, Garcia-Bosch O, Souto R, Manosa M, Miranda J, Garcia-Sanchez V, et al. Efficacy of infliximab rescue therapy in patients with chronic refractory pouchitis: a multicenter study. Inflammatory bowel diseases 2012;18(5):812-7.
4. A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST), Futility Analysis Plan, Final, 12 October 2018.

9.0 APPENDICES

Appendix A Schedule of Study Procedures

	Screening	Treatment							Final Endoscopy Visit or ET	Safety Follow-Up (a)	Post-Study
Study Day/Week:	**Days -28 to -1**	**Wk0/ Day 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 14**	**Wk 22**	**Wk 30 (EOT)**	**Wk 34 (EOS)**	**Wk 48 (or 18 weeks post-tx if ET)**	**Phone Wk 56 (or 26 weeks post-tx if ET)**
Visit Windows (Days):			**±2**	**±2**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number:	**1 (b)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 (c) /ET**	**10**	**11**
Informed Consent (d)	X										
Inclusion/Exclusion Criteria	X	X									
Demographics	X										
Medical/Surgical History	X (e)										
UC/Pouchitis Disease History	X										
Concomitant Medications/Procedures (f)	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X		
Weight & Height	X (g)	X	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X	X		
ECG	X										
IBDQ		X				X	X		X		
CGQL		X				X	X		X		
mPDAI	X (h)					X			X		
PDAI	X (h)(i)					X			X		
Pouch Endoscopy with Biopsy	X					X			X		
Hematology	X	X				X		X	X		
Serum Chemistry and Other Laboratory Tests	X	X				X		X	X		
HIV/Hepatitis panel	X (j)										
Urinalysis	X	X				X		X	X		
CRP	X	X				X		X	X		
FSH (k)	X										
Tuberculosis QuantiFERON or Skin Test	X										
C difficile test	X										
Serum Pregnancy Test (l)	X								X		
Urine Pregnancy Test (l)		X (m)	X (m)	X	X (m)	X (m)	X (m)	X (m)		X	
Fecal Calprotectin Assay	X	X (m)				X	X	X	X		
Study Drug Dosing (IV) (n)		X	X		X	X	X	X			
Ciprofloxacin		X	X	X (o)		X (o)	X (o)	X (o)			

	Screening	Treatment							Final Endoscopy Visit or ET	Safety Follow-Up (a)	Post-Study
Study Day/Week:	**Days -28 to -1**	**Wk0/ Day 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 14**	**Wk 22**	**Wk 30 (EOT)**	**Wk 34 (EOS)**	**Wk 48 (or 18 weeks post-tx if ET)**	**Phone Wk 56 (or 26 weeks post-tx if ET)**
Visit Windows (Days):			**±2**	**±2**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number:	**1 (b)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 (c) /ET**	**10**	**11**
PML Checklist	X	X (m)	X (m)	X	X (m)	X (m)	X (m)	X (m)	X	X	
Provide PML Wallet Card		X							X		
PTE Assessment (f)	X	X									
AE/SAE Assessment (f)		X	X	X	X	X	X	X	X	X	
Long-Term Follow-Up Questionnaire											X
Access IWRS to Obtain Subject ID	X										
Access IWRS for Randomization		X									
Access IWRS to Register Visit	X	X	X		X	X	X	X	X		

Wk=Week.

(a) If subject is male or subject is postmenopausal and cannot attend the site for the safety follow-up visit, the safety follow-up visit may be conducted via phone.

(b) Once informed consent is obtained, listed procedures may be performed at any time during the screening period.

(c) Perform Visit 9 procedures if subject withdraws before Week 34.

(d) Informed consent process can begin prior to Visit 1, for example, if washout from medications is required.

(e) Smoking/nicotine usage status will be captured as part of medical history.

(f) Record adverse events, PTEs and medications from the time of signing the ICF.

(g) Height collected only at Visit 1.

(h) Clinical mPDAI and PDAI scores (patient reported symptoms) will be assessed as average from 3 days immediately prior to baseline endoscopy (or bowel preparation for endoscopy). Recording will be facilitated by a paper diary.

(i) Clinical and endoscopic PDAI scores for Visit 2 will be the scores obtained during Screening and the histologic score will be added when available to complete the full PDAI score.

(j) Hepatitis and HIV testing only done at the Screening Visit.

(k) Only if menopause is suspected.

(l) Only required for women of child bearing potential.

(m) To be performed before dosing.

(n) Subjects should be observed for 2 hours following the first 2 infusions, at a minimum and 1 hour after each subsequent infusion for monitoring hypersensitivity reactions.

(o) All subjects will receive ciprofloxacin 500 mg twice daily through Week 4. Additional antibiotics will be allowed, as needed, for flares after Week 14.

Appendix B The Pouchitis Disease Activity Index (PDAI)

Criteria		Score	Subtotal
Clinical[a]	**Stool Frequency**		
	Usual postoperative stool frequency	0	
	1-2 stools/day > postoperative usual	1	
	3 or more stools/day > postoperative usual	2	
	Rectal Bleeding		
	None or rare	0	
	Present daily	1	
	Fecal urgency or abdominal cramps		
	None	0	
	Occasional	1	
	Usual	2	
	Fever (temperature >37.8°C)		
	Absent	0	
	Present	1	
Endoscopic inflammation	Edema	1	
	Granularity	1	
	Friability	1	
	Loss of vascular pattern	1	
	Mucus exudates	1	
	Ulceration	1	
Acute histologic inflammation	**Polymorphic nuclear leukocyte infiltration**		
	None	0	
	Mild	1	
	Moderate + crypt abscess	2	
	Severe + crypt abscess	3	
	Ulceration per low power field (mean)		
	0%	0	
	<25%	1	
	25-50%	2	
	>50%	3	
			PDAI Score

[a] The clinical symptoms are based on a patient diary completed 3 days prior to endoscopy or bowel preparation for endoscopy. The average of the completed diary entries is taken for PDAI calculation, where at least one non-missing day need to exist.

Appendix C The Modified Pouchitis Disease Activity Index (mPDAI)

Criteria		Score	Subtotal
Clinical[a]	**Stool Frequency**		
	Usual postoperative stool frequency	0	
	1-2 stools/day > postoperative usual	1	
	3 or more stools/day > postoperative usual	2	
	Rectal Bleeding		
	None or rare	0	
	Present daily	1	
	Fecal urgency or abdominal cramps		
	None	0	
	Occasional	1	
	Usual	2	
	Fever (temperature >37.8°C)		
	Absent	0	
	Present	1	
Endoscopic inflammation	Edema	1	
	Granularity	1	
	Friability	1	
	Loss of vascular pattern	1	
	Mucus exudates	1	
	Ulceration	1	
			mPDAI Score

[a] The clinical symptoms are based on a patient diary completed 3 days prior to endoscopy or bowel preparation for endoscopy. The average of the completed diary entries is taken for mPDAI calculation, where at least one non-missing day need to exist.

CCI

CCI

Appendix F The Cleveland Global Quality of Life (CGQL) Instrument (Fazio Score)

Component	Scale
Current Quality of Life	0 (worst) to 10 (best)
Current Quality of Health	0 (worst) to 10 (best)
Current Energy Level	0 (worst) to 10 (best)
CGQL Utility Score[a]	(sum of components)/30
Fazio Score[b]	Average of utility scores from 3 days prior to endoscopy

[a] If there are any missing components the CGQL utility will also be missing.

[b] The Fazio score is assessed as the average of the completed CGQL utility scores, where at least one non-missing day need to exist.

Appendix G Quality of Life Questionnaires: IBDQ

Sub-score	Calculation
IBDQ Bowel symptoms score	Sum of (Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, Q29), Ranging from 10 to 70, 10 questions
IBDQ Emotional function score	Sum of (Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31, Q32), Ranging from 12 to 84, 12 questions
IBDQ Social function score	Sum of (Q4, Q8, Q12, Q16, Q28), Ranging from 5 to 35, 5 questions
IBDQ Systemic symptoms score	Sum of (Q2, Q6, Q10, Q14, Q18), Ranging from 5 to 35, 5 questions
Note: For each component score above, if 50% or less of the component score is missing at a visit, the MEAN of the remaining component score will be imputed as the value for the missing component score. If more than 50% of the component score is missing for the item, the imputed value will be set to missing.	
IBDQ score	Sum of (bowel, emotion, social, system)
Note: If any of the component score is missing at a visit, the imputed value will be set to missing.	

Appendix H Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology

			Conventional Units			Takeda Preferred SI Units	
Parameter	**Gender**	**Age**	**Units**	**Markedly Abnormal Value**		**Units**	**Markedly Abnormal Value**
Red Blood Cells	Both	Adult	$\times 10^6$ cells/µL	< 0.8 × LLN, > 1.2 × ULN		$\times 10^{12}$ cells/L	< 0.8 × LLN, > 1.2 × ULN
White Blood Cells	Both	Adult	$\times 10^3$ cells/µL	<2.0, > 1.5 × ULN		$\times 10^9$ cells/L	<2.0, > 1.5 × ULN
Hemoglobin	Both	Adult	g/dL	< 0.8 × LLN, > 1.2 × ULN		g/L	< 0.8 × LLN, > 1.2 × ULN
Hematocrit	Both	Adult	%	< 0.8 × LLN, > 1.2 × ULN		Fraction of 1	< 0.8 × LLN, > 1.2 × ULN
Platelets	Both	Adult	$\times 10^3$/µL	< 70, > 600		$\times 10^9$ /L	< 70, > 600
Segmented Neutrophils (Absolute)	Both	Adult	$\times 10^3$ cells/µL	< 0.5 × LLN, > 1.5 × ULN		$\times 10^9$ cells/L	< 0.5 × LLN, > 1.5 × ULN
Segmented Neutrophils (Relative)	Both	Adult	%	< 0.5 × LLN, > 1.5 × ULN		Fraction of 1	< 0.5 × LLN, > 1.5 × ULN
Lymphocytes (Absolute)	Both	Adult	$\times 10^3$ cells/µL	< 0.5 × LLN, > 1.5 × ULN		$\times 10^9$ cells/L	< 0.5× LLN, > 1.5 × ULN
Lymphocytes (Relative)	Both	Adult	%	< 0.5 × LLN, > 1.5 × ULN		Fraction of 1	< 0.5 × LLN, > 1.5 × ULN
Monocytes (Absolute)	Both	Adult	$\times 10^3$ cells/µL	> 2 × ULN		$\times 10^9$ cells/L	> 2 × ULN
Monocytes (Relative)	Both	Adult	%	> 2 × ULN		Fraction of 1	> 2 × ULN
Eosinophils (Absolute)	Both	Adult	$\times 10^3$ cells/µL	> 2 × ULN		$\times 10^9$ cells/L	> 2 × ULN
Eosinophils (Relative)	Both	Adult	%	> 2 × ULN		Fraction of 1	> 2 × ULN
Basophils (Absolute)	Both	Adult	$\times 10^3$ cells/µL	> 3 × ULN		$\times 10^9$ cells/L	> 3 × ULN
Basophils (Relative)	Both	Adult	%	> 3 × ULN		Fraction of 1	> 3 × ULN
PT	Both	Adult	Sec	> 1.5 × ULN		Sec	> 1.5 × ULN
INR†	Both	Adult	NA	> 1.5		NA	> 1.5

LLN=lower limit of normal or lower reference limit; ULN=upper limit of normal or upper reference limit
† Values are for subjects without anticoagulation, based on the normal range provided above for PT.

Serum Chemistry

Parameter	Gender	Age (years)	Conventional Units			Takeda Preferred SI Units	
			Units	Markedly Abnormal Values		Units	Markedly Abnormal Value
Alanine Aminotransferase	Both	Adult	U/L	>3 × ULN		U/L	>3 × ULN
Albumin	Both	Adult	g/dL	< 2.5		g/L	< 25
Alkaline Phosphatase	Both	>20	U/L	>3 × ULN		U/L	>3 × ULN
Aspartate Aminotransferase	Both	Adult	U/L	>3 × ULN		U/L	> 3 × ULN
Total Bilirubin	Both	Adult	mg/dL	> 2.0		µmol/L	> 34.2
Total Protein	Both	Adult	g/dL	< 0.8 × LLN, > 1.2 × ULN		g/L	< 0.8 × LLN, > 1.2 × ULN
Creatinine	Both	Adult	mg/dL	> 2		µmol/L	> 177
Blood Urea Nitrogen	Both	Adult	mg/dL	> 30		mmol/L	> 10.7
Creatine Kinase	Both	Adult	U/L	>5 × ULN		U/L	>5 × ULN
γ-Glutamyl Transferase	Both	Adult	U/L	>3 × ULN		U/L	>3 × ULN
Potassium (serum)	Both	Adult	mEq/L	< 3.0, > 6.0		mmol/L	< 3.0, > 6.0
Sodium	Both	Adult	mEq/L	< 130, > 150		mmol/L	< 130, > 150
Direct Bilirubin	Both	Adult	mg/dL	>2 × ULN		µmol/L	>2 × ULN
Calcium	Both	Adult	mg/dL	< 27, > 58.6		mmol/L	< 1.50, > 3.25
Uric Acid	Both	Adult	mg/dL	> 13.0		µmol/L	> 773
Glucose	Both	Adult	mg/dL	< 50, > 350		mmol/L	< 2.8, > 19.4
Magnesium	Both	Adult	mg/dL	< 1.2, > 3.0		mmol/L	< 0.5, > 1.2
Phosphorus	Both	Adult	mg/dL	< 1.6, > 6.2		mmol/L	< 0.52, > 2.000
Chloride	Both	Adult	mEq/L	< 75, > 126		mmol/L	< 75, > 126

LLN=lower limit of normal or lower reference limit; ULN=upper limit of normal or upper reference limit

†Any abnormal values should be interpreted with the ratio progesterone/estrogen and SHBP values: Higher levels of SHBP lower levels of free progesterone.

Appendix I Criteria for Identification of Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic Arterial Pressure	mmHg	<85	>180
Diastolic Arterial Pressure	mmHg	<50	>110
Pulse	bpm	<50	>120
Body Temperature	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Document Originator Approval	12-Feb-2021 19:51 UTC
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