Statistical Analysis Plan

NCT Number: NCT02743806

Title: Entyvio (Vedolizumab IV) Extended Access Program in Ulcerative Colitis and Crohn's Disease

Study Number: Vedolizumab-4013

Document Version and Date: 2.0 (24 February 2023)

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1 TITLE PAGE

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vedolizumab-4013 (Main Study)

Entyvio (Vedolizumab IV) Extended Access Program
in Ulcerative Colitis and Crohn's Disease

PHASE 3b/4

Version: Final 2.0 (Amendment 1)
Date: 24-FEB-2023

Prepared by:

[redacted], Takeda Statistical and Quantitative Sciences, GI Statistics

Based on:

Protocol Version: Amendment 7
Protocol Date: 02 September 2021

1.1 Approval Signatures

Study Title: Entyvio (Vedolizumab IV) Extended Access Program in Ulcerative Colitis and Crohn's Disease (XAP Main Study)

Approvals:

DocuSigned by:
[redacted]
24-Feb-2023 | 10:50:41 CET

[redacted], GI Statistics
Statistical and Quantitative Sciences, Data Sciences Institute
Takeda Pharmaceuticals International AG

Date

DocuSigned by:
[redacted]
28-Feb-2023 | 09:13:29 EST

[redacted], Head GI Statistics,
Statistical and Quantitative Sciences, Data Sciences Institute
Takeda Pharmaceuticals Inc.

Date

DocuSigned by:
[redacted]
24-Feb-2023 | 19:02:08 JST

[redacted] DipPharmMed
[redacted], I obal Medical Affairs
Takeda Pharmaceuticals International AG

Date

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3 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
CRP	C-reactive protein
CS	corticosteroids
COVID	Coronavirus disease
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
HBI	Harvey Bradshaw index
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IMM	immunosuppressant
IV	intravenous
IVRS	interactive voice response system
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PT	preferred term
Q4W	every 4 weeks
Q8W	every 8 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TLFs	tables, listings, and figures
UC	ulcerative colitis
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary
XAP	open-label extended access program

4 OBJECTIVES

4.1 Primary Objectives

Primary objectives of the XAP Main Study:

To monitor ongoing safety in subjects with ulcerative colitis (UC) and Crohn's disease (CD) and to provide access to vedolizumab for qualifying subjects who, in the opinion of the investigator, continue to derive benefit from vedolizumab and for whom continued treatment with vedolizumab is desired because there is no other comparable product available or the subject may be expected to develop worsening of disease if they were to modify treatment.

Objectives of the XAP-PK substudy are not subject of this document.

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

Not applicable.

4.4 Safety Objective

See primary objective in section 4.1.

4.5 Study Design (XAP Main Study)

This is a multinational, multicenter, phase 3b/4, open-label extended access program (XAP) study to monitor ongoing safety and provide access to vedolizumab for qualifying subjects who have successfully completed participation in qualifying vedolizumab clinical studies (C13008 [GEMINI LTS], patients with CD or UC, and MLN0002-3028 [Versify], patients with CD). Subjects in the C13008 study may have been rolled over into the study from a prior clinical study (C13004, C13006, C13007, C13008) and been treated with vedolizumab before enrollment into C1300 or may have been enrolled and first treated with vedolizumab in the C13008 study ('de-novo' patients).

A subject was eligible to be enrolled in the XAP study when he/she received vedolizumab during participation in a qualifying study, and, in the opinion of the investigator, is experiencing and expected to derive continued clinical benefit with vedolizumab every 4 weeks (Q4W) or every 8 weeks (Q8W) dosing regimen but not having access to commercially available vedolizumab after completion of the qualifying study.

Eligible subjects were to be rolled over from the qualifying study into the XAP study (i.e., enrolled into the XAP study). Subjects are/were to have their XAP enrollment visit in conjunction with the final dosing visit of the qualifying study or, if that is/was not possible, at the latest before or on their final safety follow-up visit of the qualifying study

A subject is/was to remain in the XAP study until vedolizumab being available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until the subject's withdrawal, whichever is sooner.

If vedolizumab becomes commercially available to a subject for Q8W dosing but the subject has not been stable on that regimen for the previous 6 months, the subject should only exit the XAP study if vedolizumab is commercially available to the subject at the previous, more frequent dosing regimen. If vedolizumab is not commercially available at the previous dosing regimen, the subject is/was to remain in the XAP study until the subject is stable for 6 months and can move to commercially available Q8W dosing of vedolizumab.

Within 60 days of the subject having access to commercially available vedolizumab, the subject should have the final study infusion visit. Subjects should report for a safety follow-up visit 18 weeks after their final study infusion.

Subjects will be considered to have regularly completed the XAP study once transitioned to commercially available and reimbursed product.

4.5.1 Study Treatment

Study subjects were to receive the following open-label study treatment:

- vedolizumab IV 300 mg every 8 weeks (Q8W)
  (IV infusion over approximately 30 minutes)

The first dose of vedolizumab in this study should occur 8 weeks (± 7 days) after the last vedolizumab dose in the qualifying study. If indicated, the time to the first dose of vedolizumab in this study could have been extended but was to be performed no later than the safety follow-up visit in the qualifying study.

Subjects entering from a qualifying study on a more frequent dose (e.g., Q4W) could stay on at the dose provided in the qualifying study, if medically indicated based on the investigator's clinical judgment and acknowledged by the Medical Monitor.

If the subject experienced reduction in efficacy on Q8W dosing, the dosing frequency, based on the investigator's judgement of subject's clinical status and acknowledged by the Medical Monitor, may have been escalated to Q4W dosing. It then was at the investigator's discretion when to reduce back to Q8W again.

4.5.2 Blinding und Unblinding

Not applicable. This is an open-label study.

5 ANALYSIS ENDPOINTS

5.1 Efficacy Endpoints

No direct efficacy endpoints were defined and assessed.

Need for dose escalation, persistence on Q8W dosing regimen and incidence of relapse are analyzed based on drug exposure and safety data using the following endpoints:

- Incidence of relapse (see definition in section 7.1.1)
- Time to relapse
- Incidence of dose escalation (from Q8W to Q4W)
- Time to dose escalation
- Relapse-free persistence on Q8W dosing regimen for ≥ 6 months.

5.2 Pharmacokinetic/Pharmacodynamic Endpoints

Not applicable.

The analysis of data from the XAP PK-substudy is not subject to this SAP.

5.3 Safety Endpoints

Safety assessments were to be made throughout the treatment period at the infusion visits. Any safety information discovered during the routine treatment of a subject should be reported. All adverse events (AEs) that occurred from the time of signing informed consent form (ICF) up to the safety follow-up visit, regardless of their study treatment attribution, were to be recorded on the electronic case report form (eCRF).

Safety evaluations will be based on incidence, intensity, relationship to study treatment and type of AEs, and worsening of CD/UC and inflammatory bowel disease (IBD) hospitalizations. Clinically significant vital signs were to be reported as AEs.

Main safety endpoints are:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Adverse events of special interest (AESIs):
  serious infections including opportunistic infections such as progressive multifocal leukoencephalopathy (PML), malignancies, liver injury, infusion-related hypersensitivity reactions, and injection site reactions
- Adverse events leading to study drug discontinuation.
- Worsening of CD/UC
- AEs leading to IBD-related hospitalizations

5.4 Other Data and Variables Collected

5.4.1 Demographics and Baseline Characteristics, and Prior Therapies

Demographic data (summarized in section 7.5, Table 7.a) and baseline characteristics (summarized in section 7.5, Table 7.b) for enrolled subjects were to be obtained at the enrollment visit (Day 1) and may be complemented with corresponding data from the qualifying study.

Data on baseline disease characteristics such as disease history (date of first vedolizumab administration, study in which vedolizumab was first administered, date of IBD diagnosis, IBD therapy prior the vedolizumab treatment) were not acquired in the XAP-study and will be transferred from the qualifying study.

5.4.2 Dosing Regimen / Drug Exposure

Details on vedolizumab dosing (dosing dates, change in dosing regimens) were to be captured in the eCRF throughout the study.

5.4.3 Protocol Deviations

Significant protocol deviations (see section 7.4) were to be collected in the eCRF throughout the conduct of the study.

5.5 Medical History and Concurrent Medical Conditions

Concurrent medical conditions are significant ongoing conditions or diseases that were present at enrollment (ICF signature). This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities and AEs from the qualifying study that are ongoing at the time of enrollment. Concurrent medical conditions were to be recorded at the enrollment visit.

5.6 Prior and Concomitant Medications

All relevant prior medications for the treatment of UC or CD, including corticosteroids (CS) and immunosuppressants/immunomodulators (IMM), were to be recorded at enrollment. Any concomitant medications were to be recorded from enrollment until study completion/discontinuation.

6 DETERMINATION OF SAMPLE SIZE

The XAP Main study was not sized based on power considerations.

The number of subjects enrolled is determined by the number of eligible subjects who have received vedolizumab treatment in a qualifying study and have completed participation (having received the final dose of vedolizumab but not yet having completed the safety follow-up period) of the qualifying study.

7 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This document provides further details regarding the definition of analysis variables and analysis methodology of the data collected in the XAP Main study. The analysis of the XAP PK-substudy is not subject of this document. This SAP will be prepared and finalized prior to database lock for the XAP Main study. The shells for tables, listings and graphs will be provided in a separate document.

All analyses for the XAP Main study will be descriptive and no formal statistical hypothesis testing will be performed.

Unless specified otherwise, for continuous data, the number of subjects with non-missing observations, mean, standard deviation (SD), median, minimum, and maximum will be presented. Minimum and maximum values will be presented using the same number of decimal places as the recorded data; means and medians will be presented to 1 more decimal place than the recorded data; the SD will be presented to 2 more decimal places than the recorded data, with possible exceptions made for derived data. If applicable, confidence intervals (CIs) for a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

For categorical data, the number (and %) of subjects falling into each category and the number of missing observations be presented. In summary tables for categorical data for which categories are pre-defined on the electronic case report form (eCRF), all categories will be presented as specified, even if the subject count within a category is zero. For other categorical data (e.g., AEs), only categories with at least one subject will be presented. If not otherwise mentioned, percentages will be calculated based on the number of 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 study data collected for the purpose of the XAP Main study will be listed for all enrolled subjects (data collected only for the purpose of the PK substudy will not be listed).

All statistical analyses will be conducted using SAS® Version 9.4.

7.1.1 Study Definitions

An enrolled subject is defined as a subject participating in a qualifying study, who was considered eligible for rolling over to XAP study and who consented (i.e., signed the ICF) to participate in the XAP study.

A subject is considered to have regularly completed the XAP study once the subject transitioned to commercially available and reimbursed product.

T0 is defined as the date of the first vedolizumab dose within the XAP = date of last vedolizumab dose in the qualifying study. If not mentioned otherwise, T0 is the reference time point for calculations of duration (e.g. time to event) in the XAP study (see also 7.1.2).

For all variables, unless defined otherwise in below sections, the baseline value for a subject is the value obtained at the enrollment visit; if not reported at enrollment to the XAP study the information might be transferred over from the qualifying study.

Definition of "efficacy-related" endpoints

A relapse is defined as occurrence of any of the following events (after enrollment to the XAP study):

(1) vedolizumab dose escalation (from Q8W to Q4W)

(2) premature study drug or study withdrawal due to loss of response to study treatment (i.e., reason for discontinuation reported on the CRF as "no longer an adequate benefit")

(3) AE worsening of UC/CD (AE with preferred term "Colitis ulcerative", "Crohn's disease" or "Proctitis") fulfilling any of the criteria below

a) AE of mild or moderate intensity and associated commencement or dose increase of CS, IMM, anti-TNFs or other biologic co-medication
(i.e., start or dose increase of co-medication at/after AE onset date and before AE end date)

b) AE (of any severity) with associated dose increase of study drug (i.e., study drug action taken = dose increased)

c) AE (of any severity) leading to premature discontinuation of study or study drug

d) AE of severe intensity

e) AE is a serious AE (SAE).

Consequently, the date of relapse is defined as the date or onset/start of the first event considered relapse and the time to relapse is defined as the time from the last vedolizumab administration in the qualifying study (T0, see section 7.1.2) to the date of relapse:

Time to relapse (days) = date of relapse – T0 + 1.

If only condition (3a) is fulfilled, then the date of relapse is the date of onset of worsening (AE), even if the commencement or dose increase of associated co-medication is later.

Time to dose escalation is defined as

Time to dose escalation (days) = date of first dose on Q4W regimen – T0 + 1.

Relapse-free persistence on Q8W dosing regimen (for subjects who were enrolled/started the XAP study on Q8W dosing regimen):

The duration on Q8W dosing regimen without relapse (from T0) will be derived as

Duration on Q8W without relapse (days) =
MIN (date of relapse, date of XAP study completion) – T0 + 1.

A subject with a duration on Q8W dosing regimen without relapse of ≥ 180 days (6 months) will be considered as 'relapse-free persistent on Q8W'. Subjects who completed the study regularly before Day 180 will be censored appropriately.

IBD related hospitalization (AEs leading to IBD related hospitalization)

An IBD related adverse event (AE) for which any of the two CRF flags for prolonged hospitalization or in-patient hospitalizations is ticked is considered as AE leading to IBD related hospitalization. IBD related AEs requiring hospitalization will be identified in context of the data review.

Concomitant medications of interest

In general, concomitant medication of interest listed below will be identified via ATC code and route of administration as described below. The subset of IBD-related concomitant medications, i.e. given to treat the diseases under study CD and UC, will be identified in context of the data review also considering the indication/reason for use.

- IBD-related oral corticosteroids (CS) will be primarily identified by ATC 4th level (chemical subgroup) codes A07EA, C05AA, H02AB, H02 with the following exceptions:
  - CS not considered CD/UC-related treatment according to the reported indication/reason for use.
  - CS with route of administration reported as nasal, by inhalation, rectal, per rectum (or similar)
- Immunosuppressants (IMM) will be identified by ATC 4th level codes: L01BB ("PURINE ANALOGUES"), L04AD ("CALCINEURIN INHIBITORS"), L04AX ("OTHER IMMUNOSUPPRESSANTS").
- Tumor necrosis factor-alpha antagonist (anti-TNF) treatment will be identified by the ATC 4th level subgroup "TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS", ATC code L04AB.
- Other biologics for IBD treatment will be identified by the ATC 4th level codes, ATC code L04AA ("SELECTIVE IMMUNOSUPPRESSANTS", incl. e.g. vedolizumab) and L04AC ("INTERLEUKIN INHIBITORS").

7.1.2 Definition of Study Days

The following study days and reference time points are defined:

- Day 1 is defined as the day of enrollment (signature of ICF).
- Other study days of study assessments are defined relative to the Day 1. The schedule of study assessments is listed in Table 9.a.

- T0 is the day of last vedolizumab administration in the qualifying study; for some patients this might be before Day 1.
  All time-to-event and duration variables will use T0 as reference date for start of treatment in the XAP study.

7.1.3 Cut-off Date

In this SAP the term "cut-off date" refers to

- "end of study" for the end-of-study-analysis
- the actual data cut-off date for the Interim Look described in section 7.13

and is to be interpreted as applicable to the context.

7.1.4 Covariates and Subgroups/Subpopulations

The data analysis will be grouped/stratified by disease type, qualifying study and dosing regimen according to the classifications described below.

Disease type:

- Ulcerative colitis (UC)
- Crohn's disease (CD)

Qualifying study:

- MLN0002-3028 (CD only)
- C13008

Dosing regimen (see Figure 7.a):

- Q4W/Q4W: subject was on Q4W dosing regimen in qualifying study and remained on Q4W dosing regimen in the XAP study through end of study/cut-off date (qualifying study C13008 only)
- Q4W/Q8W: subject was on Q4W dosing regimen in qualifying study, switched to Q8W dosing regimen at enrollment to XAP study (i.e., reduced dosing frequency) and remained on Q8W through end of study/cut-off date (qualifying study C13008 only)
- Q4W/Q8W/Q4W: subject was on Q4W dosing regimen in qualifying study, switched to Q8W dosing regimen at enrollment to XAP study (i.e., reduced dosing frequency) and then escalated to Q4W in course of the XAP study (qualifying study C13008 only)
- Q8W/Q4W: subject was on Q8W dosing regimen in qualifying study and escalated to Q4W dosing regimen at enrollment to XAP study (qualifying study MLN0002-3028 only)
- Q8W/Q8W: subject was on Q8W dosing regimen in qualifying study and remained on Q8W dosing regimen in the XAP study through end of study/cut-off date

- Other (other dosing regimen combinations not listed above and multiple changes of dosing regimens within the XAP study)

where the first dosing regimen refers to the last regimen in the qualifying study at T0, the second (and third, if applicable) to the dosing regimens applied in the XAP study.

Subjects who discontinued the XAP study after the last dosing in the qualifying study (i.e., T0) but before the next planned dosing in the XAP study will be assigned to the dosing regimen intended at enrollment to the XAP study.

Figure 7.a: Dosing Regimen Subgroups by Qualifying Study

Qualifying Study (QS)	C13008				MLN0002-3028		
Last dosing regimen in QS	Q4W				Q8W		
Dosing regimen in XAP	Q8W*	Q4W*	Q8W*/Q4W	Other/ multiple changes#	Q8W*	Q8W*/Q4W	Other/ multiple changes#
Label meaning	Q8W maintained	Q4W maintained	Dose escalation to Q4W	Other/ multiple changes	Q8W maintained	Dose escalation to Q4W	Other/ multiple changes
Label in TLFs	Dose Reduction to Q8W	Dose Maintenance on Q4W	Dose Escalation to Q4W	Other/ multiple Dose Changes	Dose Maintenance on Q8W	Dose Escalation to Q4W	Other/ multiple Dose Change

*dosing regimen at start of XAP
#column only to be presented if any subject falls into this dosing regimen category

Further stratification variables are described below.

Concomitant medication:

Furthermore, subgroups are defined as below by concomitant use of IBD-related corticosteroids (CS) and immunosuppressants/immunomodulators (IMM) at the time of enrollment (Day 1).

- Subjects with concomitant use of CS (CS+/IMM-);
- Subjects with concomitant use of IMM (CS-/IMM+);
- Subjects with concomitant use of CS and IMM (CS+/IMM+);
- Subjects without concomitant use of CS or IMM (CS-/IMM-).

Prior anti-TNF exposure:

Further subgroups are formed based on the prior anti-TNF exposure status (prior to first vedolizumab administration):

- anti-TNF experienced (with a history of anti-TNF exposure)
- anti-TNF naïve (without a history of anti-TNF exposure)

7.1.5 Conventions for Missing IBD Diagnosis Dates

Partial initial IBD diagnosis date will be imputed as the earliest possible date for the missing field, e.g., first day of the month, first month of the year.

7.1.6 Conventions for Missing Adverse Event Dates

In general, missing dates for onset and stop of adverse events will be treated as missing and no imputation of (partially) missing dates will be applied.

Only for the purpose of calculation of time to relapse (based on AEs), partial AE onset dates will be imputed by the 1st of the month (if month and year present) or 1-January of the year (if only year present).

7.1.7 Conventions for Missing Concomitant Medication Dates

In general, missing date for start/stop of medications will be treated as missing and no partial date imputation will be applied, unless otherwise specified.

Only for the purpose of calculation of time to relapse (based on use of relevant concomitant medication), partial medication start dates will be imputed by the 1st of the month (if month and year present) or 1-January of the year (if only year present). The same imputation rule may be applied when needed to identify if a medication was started/stop prior or after T0.

7.1.8 Other Missing Data Handling Conventions

In general, other missing data will not be imputed. Where applicable, further missing data handling rules are described in the respective sections.

7.2 Analysis Sets

The following analysis set(s) will be used for analysis and presentation of the study data:

- The full analysis set (FAS) consists of all subjects enrolled in the XAP study, who received at least 1 dose of vedolizumab treatment, including the dose given at T0 (last dose in qualifying study).

Per definition, each subject enrolled is already on vedolizumab treatment and therefore belongs to the FAS.

The subpopulation to be used for analysis at the interim look is described in section 7.13.

7.3 Disposition of Subjects

Subject disposition will be summarized once by disease type (and total) and by qualifying study (and total) and once by disease type, by qualifying study and by dosing regimen, showing:

- Number of subjects enrolled
- Number of subjects who received at least one vedolizumab dose after T0
- Number of subjects enrolled who did not receive vedolizumab after T0
- Number (and %) of subjects ongoing in a dosing regimen subgroup at cut-off date (only for interim look)
- Number (and %) of subjects who completed study regularly (i.e., switched to commercial product, see definition in section 7.1.1)
- Number (and %) of subjects who discontinued prematurely:
  total and by reason for discontinuation (e.g. due to loss of response ["no longer adequate benefit" or disease worsening], due to an AE, due to a significant protocol deviation, lost to follow-up, voluntary withdrawal, pregnancy and other primary reasons).

Percentages will be based on the number of subjects enrolled for each subgroup. Percentages in the summary of reason for discontinuation will be based on the total number of subjects who discontinued prematurely.

7.4 Significant Protocol Deviations

Significant protocol deviations were to be collected on the eCRF throughout the conduct of the study. Significant protocol deviations will be tabulated by disease type and by qualifying study using the following categories:

- Entry Criteria
- Concomitant Medication
- Procedures Not Performed Per Protocol (related to primary endpoint or safety)
- Study Medication
  (e.g., missing two consecutive study medication dosing visits is considered significant protocol deviation)
- Withdrawal Criteria

Significant protocol deviations will be identified by data review as relevant for the XAP Main study or for the XAP PK substudy. Significant protocol deviations will be summarized overall (i.e., relevant for Main study or PK substudy); additionally, separate summaries of significant protocol deviations relevant for the XAP Main study and significant protocol deviations relevant for the XAP PK substudy will be provided. All significant protocol deviations will be listed with those considered only relevant for the XAP PK substudy identified.

In addition, significant COVID-related protocol deviations (identified by the term 'COVID' in the deviation term) and non-significant COVID-related protocol deviations captured in CTMS will be summarized separately.

7.5 Demographic and Other Baseline Characteristics

Demographic data (see Table 7.a) and baseline disease characteristics (see Table 7.b) will be summarized descriptively based on FAS population by disease type (CD, UC) and by qualifying study and total. Demographic and baseline characteristics will also be summarized by dosing regimen and total for CD subjects and UC subjects in separate tables, with only summaries applicable to the specific disease type included.

Table 7.a: Summary of Demographic Data

Characteristic	Summarized as	Categories and measurement units
Age	Continuous	years
Age group	Categorical	<65, and >=65 years <35 and >=35 years
Gender	Categorical	Female/male
Race	Categorical	As defined in eCRF. (subjects who have more than one race category reported on the CRF, are only included in the category "multiracial")
Weight	Continuous	kg
Height	Continuous	cm
Body Mass Index (BMI)	Continuous	kg/m^2
BMI categories	Categorical	Underweight: BMI<18.5 Normal: BMI ≥18.5 to <25.0 Overweight: BMI ≥25.0 to <30.0 Obese: BMI ≥30.0

Table 7.b: Summary of Subjects' Baseline Disease Characteristics

Characteristic	Summarized as	Categories and measurement units	Comments
Disease type	Count	CD, UC	
First vedolizumab study	Count (%)	C13004 C13006 C13007 C13011 De-novo patients in C13008 MLN0002-3028	First vedolizumab study number can be extracted from the subject ID in the qualifying study.
Years since IBD diagnosis at first vedolizumab dose	Continuous	Years	To be taken from qualifying study
Years since IBD diagnosis at XAP enrollment	Continuous	Years	At XAP enrollment

Characteristic	Summarized as	Categories and measurement units	Comments
Years since first vedolizumab dose s at XAP enrollment	Continuous	Years	Years since start of vedolizumab therapy in prior studies at XAP enrollmentt
Prior Anti-TNF exposure status at start of vedolizumab therapy	Categorical	anti-TNF experienced anti-TNF naïve	To be taken from qualifying study
Anti-TNF therapy failure status	Categorial	Yes, No	To be taken from qualifying study
Any acute CD/UC exacerbation within the past 12 months	Categorial	Yes, No	At XAP enrollment
Any hospitalization for CD/UC within the past 12 months	Categorial	Yes, No	At XAP enrollment
Prior surgery for CD/UC	Categorial	Yes, No	At XAP enrollment
History of extraintestinal manifestations	Categorial	Yes, No	At XAP enrollment
Duration of CS exposure (weeks) in past 12 months	Continuous	Weeks	At XAP enrollment
Concomitant use of CS/IMM use at XAP enrollment	Categorical	CS+/IMM-; CS+/IMM+; CS-/IMM+; CS-/IMM-	At XAP enrollment. See definition for CS and IMM in section 7.7.
CD-specific characteristics			
Clinical Remission CD*	Categorical	Yes, No	At XAP enrollment (status at end of qualifying study)
Corticosteroid-free remission CD*	Categorical	Yes, No	At XAP enrollment (status at end of qualifying study)
HBI score (CD subjects)	Continuous	Points	For baseline of XAP this should be the last available assessment in the qualifying study prior to enrollment into XAP (value to be transferred from C13008; not available for MLN0002-3028)
UC-specific characteristic			
Clinical Remission UC*	Categorical	Yes, No	At XAP enrollment (status at end of qualifying study)
Corticosteroid-free remission UC*	Categorical	Yes, No	At XAP enrollment (status at end of qualifying study)
Partial Mayo score (UC subjects)	Continuous	Points	For baseline of XAP this should be the last available assessment in study C13008 prior to enrollment into XAP (value to be transferred from C13008)
History of fistulizing disease	Categorial	Yes, No	At XAP enrollment

* Endpoints clinical remission and corticosteroid-free remission to be shown combined for CD and UC.
For CD, clinical remission is defined as HBI score ≤ 4 (C13008) or total CDAI score ≤ 150 (MLN0002-3028); for UC, clinical remission is defined as partial Mayo score ≤ 2.

7.6 Medical History and Concurrent Medical Conditions

Concurrent medical conditions are medical conditions that have been started before enrollment into the XAP study and were still going on/after the date of enrollment. Adverse events (AE) from the qualifying study which are ongoing at the time of enrollment into the XAP study were not to be collected as AEs in this study but instead were to be captured as concurrent medical condition.

Medical history and concurrent medical conditions will be coded using the MedDRA (Version 19 or higher) coding system. Medical history and concurrent medical conditions will be summarized by disease type, and by qualifying study and total.

The number and percentage of subjects with any significant medical history and concurrent medical conditions will be summarized for system organ class (SOC), and preferred term (PT). The table will be sorted in alphabetic order by SOC and in decreasing frequency based on the total number of reports by PT in each SOC. The percentages will be calculated based on the FAS population for each subgroup. If a subject reported multiple events with the same PT or same within SOC, the subjects will be counted only once per PT and SOC, respectively.

7.7 Prior and Concomitant Medications

Medication history and concomitant medications will be coded using the WHODrug dictionary. Medications that were started prior to T0 are considered prior medications (medication history); medications ongoing or started at or after T0 are considered concomitant medications.

Concomitant medications will be summarized by ATC therapeutic classification (defined as ATC Level 4 in WHODrug) and preferred medication name, by disease type, by qualifying study and in total. The tables will be sorted in alphabetic order by ATC Level 4 and in decreasing frequency based on the total number of reports by preferred medication name. The percentages will be calculated based on the FAS population for each subgroup.

IBD-related concomitant medications are defined in section 7.1.1

7.8 Study Drug Exposure

Study drug exposure will be summarized descriptively for the FAS population.

Duration of exposure

Duration of exposure in XAP study will be calculated as

duration of exposure in XAP study (days)
= date of last dose in XAP study – date of first dose in XAP study (T0) + 1 +126

while adding days between last dosing visit and safety follow-up visit up to 126 days accounts for 5 times the half live of vedolizumab, first dose refers to the last vedolizumab dose in the qualifying study (T0), and last dose refers to the last vedolizumab dose in the XAP study (for interim look: before cut-off date).

The total duration of exposure from first vedolizumab dose will be calculated similarly as

total duration of vedolizumab exposure (days)
= date of last dose in XAP study – date of first dose + 1 +126,

where first dose refers to the first vedolizumab dose at treatment initiation in the qualifying study or its preceding study. Additionally, the total duration of exposure will be calculated in years by dividing the total duration of exposure in days by 365.25.

Drug exposure information will be summarized descriptively once by disease type, and qualifying study and once by disease type, qualifying study, dose regimen for:

- Duration of vedolizumab treatment in XAP (years),
as time from first dose in XAP (T0) to last dose in XAP
- Number of doses administered in XAP
- Duration of vedolizumab exposure in XAP (days), see definition above
- Total vedolizumab treatment duration (years),
as time from first vedolizumab dose in qualifying study to last dose in XAP
- Total vedolizumab exposure (years)
- Total vedolizumab exposure (days)

Adherence to Treatment Regimen (doses received, compliance and treatment gaps)

Adherence to the treatment regimen within the XAP will be evaluated by means of number of doses received per year, treatment compliance rates and incidence and number of treatment gaps.

The number of doses received per year of study participation will be summarized by disease type and dosing regimen.

Treatment compliance will be reported in terms of the rate (percentage) of number of planned doses administered; compliance rates will be determined and summarized for the following *intervals*:

- Total XAP duration (from T0 to last dose)
- Per year of subject's participation in the XAP
- (individual) XAP participation before the COVID pandemic and during the COVID pandemic (country-specific COVID pandemic onset dates will be applied for this calculation).

For each subject and *interval*, the number of planned doses within the *interval* will be determined and the compliance rate will be derived as

Compliance rate [*interval*] (%) =
(no. of doses administered [*interval*] / no. of doses planned [*interval*]) * 100

For each *interval* the compliance rate will be summarized (by disease type and dosing regimen) using descriptive statistics and showing number (and %) of subjects falling into the compliance categories <50%, 50-<80%, 80-120%, > 120%.

Treatment gaps are defined as periods without vedolizumab treatment of > 16 weeks (i.e., > 112 days), which is equivalent to 2 missed doses per Q8W regimen. The incidence of treatment gaps will be summarized (by disease type and dosing regimen) by frequency tables, showing

- Number (%) of subjects without and with at least 1 treatment gap
- Number (%) of subjects by number of treatment gaps within XAP
  (here the percentage will be derived using the number of subjects with at least 1 treatment gap as denominator)

7.9 Efficacy Analysis

Need for dose escalation, persistence on Q8W dosing regimen and incidence of relapse will be analyzed for subjects who were on Q8W dosing regimen at XAP enrollment (or switched to Q8W at XAP enrollment).

Summary tables will be provided by disease type (and total) and by qualifying study, showing:

- Number (and %) of subjects experiencing a relapse (see definition in section 7.1.1)
- Descriptive statistics for time to a relapse from T0 (see definition in section 7.1.1)
- Number (and %) of subjects with relapse-free persistence on Q8W for at least 6 months (see definition in section 7.1.1)
- Number (and %) of subjects requiring dose escalation from Q8W to Q4W
- Descriptive statistics for time to dose escalation from T0 (see definition in section 7.1.1)

Furthermore, for Kaplan-Meier curves will be provided for time to relapse and time to dose escalation (by disease type and qualifying study). Subjects who completed the study regularly or dropped out prior to experiencing the respective event will be censored appropriately at their last date within the study (date of study completion or date of premature discontinuation, whatever applies).

In addition, a listing will be provided showing the events considered for the incidence of relapse (as per relapse definition in section 7.1.1) with corresponding onset/start dates.

7.10 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

The analysis of data from the XAP PK-substudy is not subject to this SAP.

7.11 Other Outcomes

Not applicable.

7.12 Safety Analysis

The safety analysis for the XAP study will be performed based on the FAS population.

7.12.1 Adverse Events

AEs and SAEs are collected from the time of enrollment into the XAP study through the end of study visit (or early discontinuation, if applicable). Adverse Events of Special Interest (AESIs) are flagged on the AE-page of the CRF.

AEs from the qualifying study which are ongoing at the time of enrollment into the XAP study (signing ICF) were not to be collected as AEs in this study but were to be captured as concurrent medical condition.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA Version 19 or higher).

An overview of AEs will be provided showing the number of AEs and the number and percentage of subjects with

- AEs
  - Overall
  - By relationship
  - By severity
- AESIs (i.e., serious infections including opportunistic infections such as PML, malignancies, liver injury, infusion-related hypersensitivity reactions, and injection site reactions, see section 5.3).
  - Overall
  - By relationship
  - By severity
- AEs leading to study drug discontinuation
  - Overall
  - By relationship
  - By severity
- SAEs
  - Overall
  - By relationship
  - By severity
- AEs leading to IBD-related hospitalizations
  - Overall
  - By relationship
  - By severity
- Deaths

This overview will be stratified as shown below (with appropriate total columns included):

- by disease type, qualifying study
- by disease type, qualifying study and dosing regimen
- by concomitant CS/IMM use, disease type, qualifying study and dosing regimen
- by prior anti-TNF exposure status, disease type, qualifying study and dosing regimen

AEs (number and percentage of subjects with event, number of events) will be summarized by MedDRA system organ class (SOC), high-level term (HLT), and preferred term (PT) will be summarized as follows

- AEs by disease type, qualifying study and dosing regimen
- AEs by maximum intensity, disease type, qualifying study and dosing regimen
- AEs of severe intensity, by disease type, qualifying study and dosing regimen
- Drug-related AEs by disease type, qualifying study and dosing regimen

Similar summaries will be generated for AESIs, AEs leading to study drug discontinuation, SAEs, AEs leading to IBD-related hospitalizations, AEs leading to death (only overall incidence).

In addition, separate summary table (overall incidence by disease type, qualifying study and dosing regimen) will be provided for COVID infections (reported as an AE) and COVID vaccination related AEs.

The above tables will be sorted by SOC and HLT in alphabetic order and by preferred term (PT) in decreasing frequency. Subjects reporting the same event more than once will be counted only once within each SOC, HLT, and PT.

Furthermore, summary statistics of the number and length of stay of IBD-related hospitalizations will be presented separately (by disease type, qualifying study and dosing regimen).

7.12.2 Clinical Laboratory Evaluations

Not applicable.

7.12.3 Vital Signs

Vital sign data will be presented in data listings.

Any clinically significant worsening in vital signs compare to baseline will be reported as an AE and analyzed in context of the analysis described in section 7.12.1.

7.12.4 Other Observations Related to Safety

Not applicable.

7.13 Interim Look

An interim look is planned after 2 years based on subjects rolled over from study C13008. The cut-off date for this interim look is defined as 2 years after the last vedolizumab dose in the qualifying study (C13008) or 31-JUL-2019 whichever comes first. It is anticipated that only a small number of patients will not have completed 2 years after the last vedolizumab dose in the qualifying study by 31-JUL-2019.

The analysis population for this interim look consists of all subjects from the FAS (see section 7.2), who were rolled over from study C13008 and having had their last vedolizumab dose in the qualifying study at least 2 years prior to the cut-off date. This includes subjects who prematurely discontinued the XAP Main study or completed the study due to access to commercially available vedolizumab within the first 2 years.

In general, the summaries planned to be provided upon completion of the XAP Main study (as defined in this SAP) will have to be provided for the interim look. For the interim look, where applicable, all references to "end of study" or "last visit" will be interpreted as (or replaced by) the cut-off date. For consistency of summaries, for each subject only the data from the last vedolizumab dose in the qualifying study up to 2 years will considered, even if the subject's duration of participation in the XAP study at 31-JUL-2019 is extending 2 years.

For the interim look, summaries of the following data will be provided as described in the corresponding sections (with necessary adaptations):

- Patient disposition (see section 7.3)
- Significant protocol deviations (see section 7.4)
- Demographic and baseline characteristics (see section 7.5)
- Concurrent medical conditions (see section 7.6)
- Concomitant medications (see section 7.7)
- Study drug exposure (see section 7.8)
- Adverse events (see section 7.12)

7.14 Changes in the Statistical Analysis Plan from Protocol

The following changes in the statistical methods from the protocol have been identified:

- It was originally planned to also summarize the incidence of IDB surgeries as safety endpoint. IBD surgeries were not recorded/not documented uniformly in the eCRF and therefore cannot be reliably analyzed.

Changes in the SAP V2.0 (Amendment 1) from SAP V1.0:

- Definition of relapse refined (section 7.1.1)
- Definition of IBD related hospitalization (AEs leading to IBD related hospitalization) added (section 7.1.1)

- Definitions of IBD-related concomitant medication (CS, IMM, anti-TNF, other biologics) updated (section 7.1.1)
- Summaries for COVID-related events added (protocol deviations [section 7.4], treatment adherence prior/during COVID [section 7.8], COVID-related adverse events [section 7.12.1])
- Summaries for adherence to treatment regimen (treatment compliance) added (section 7.8)

8 REFERENCES

Study Vedolizumab-4013: Entyvio (Vedolizumab IV) Extended Access Program in Ulcerative Colitis and Crohn's Disease; Study Protocol incl. Amendment 7, 02 September 2021.

9 APPENDIX

Table 9.a: Schedule of Study Procedures for XAP Main Study

	XAP Procedures		
	Enrollment Visit (Final Visit of Qualifying Study)	**Infusion Visit (a)**	**Safety Follow-up Visit (b)** (Final Study Infusion +18 Weeks)
Visit Number	**1**	**2 onwards**	**-**
Informed consent	X	-	
Alert card	X	-	X
Assess inclusion/exclusion criteria	X	-	-
Assessment for continued eligibility	-	X(c)	-
Demographics/medical and prior therapies/concurrent medical conditions	X	-	-
UC/CD history	X	-	-
Physical examination (d)	X(i)	-	-
Vital signs (e)	X(i)	X	X
Weight and BMI (e)	X(i)	X	X
Height	X(i)	-	-
Concomitant medications (f)	X	X	X
Pregnancy testing (g)	X(i)	X	X
Pregnancy avoidance	X	X	-
Call IVRS/IWRS for Subject ID/Medication ID/subject status	X	X	X
Administer vedolizumab	-	X	-
AE/SAE assessment (h)	X	X	X

(a) The first infusion visit should be no more than 8 weeks (± 7 days) after the last dose in the subject's qualifying study. Infusion visits should occur every 8 weeks (± 7 days).
(b) Subjects will return 18 weeks after their final study infusion visit for a safety follow-up visit. Subjects should return for the follow-up visit regardless of whether they remain on vedolizumab after the study (ie, they left the study due to commercial availability of vedolizumab, or they withdrew from the study for other reasons).
(c) At each visit, the investigator should assess the subject for continued eligibility and determine if vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario.
(d) A symptom-directed physical examination will be performed at Baseline. Any clinically significant findings on the physical examination will be recorded as AEs.
(e) Should occur prior to dosing at infusion visits.
(f) Concomitant medication is any drug given in addition to the study medication. The information will be collected for all subjects at the enrollment visit and subsequent visits:
(g) Urine pregnancy test will be performed via dipstick test for all female subjects of childbearing potential prior to dose of vedolizumab at infusion visits. In addition to a negative urine hCG pregnancy test at Screening, female subjects must also have a negative urine hCG pregnancy test prior to receiving each IV dose. Subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm/ova donation as part of the study procedures.
(h) This will include collection of AEs, SAEs, and AESIs and will include collection of additional safety information on important clinical events (eg, PML-related AEs, IBD-related hospitalizations, malignancies, hypersensitivity, hepatic events, and serious infections). AE assessment includes review of the subject' s alert card. Adverse events from the qualifying study which are ongoing at the time of signing informed consent to participate in this study will not be collected in this study but will be captured in the concurrent medical condition.
(i) At screening, if the procedure has been conducted within the last 24 hours, the results of that test can be used and the procedure does not need to be redone.