Clinical Study Protocol

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: Amendment 7 (19 October 2021)

Certain information within this document has been redacted (i.e., specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

PROTOCOL

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

Sponsor:	Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421 617-349-0200 Takeda Development Centre Asia, Pte. Limited 8 Marina Boulevard #15-01, Marina Bay Financial Centre, Singapore 018981		
Study Number:	Vedolizumab-4013		
IND Number:	Not applicable	**EudraCT Number:**	2016-000678-40
Compound:	Vedolizumab IV		
Date:	19 October 2021	**Amendment Number:**	7

Amendment History:

Date	Amendment Number	Amendment Type	Region
17 March 2016	Initial Protocol	Not applicable	Global
22 April 2016	Amendment 1	Nonsubstantial	South Africa
12 August 2016	Amendment 2	Substantial	Global
10 October 2016	Amendment 3	Nonsubstantial	Global
21 November 2016	Amendment 4	Nonsubstantial	Global
07 February 2017	Amendment 5	Nonsubstantial	Global
25 June 2018	Amendment 6	Nonsubstantial	Global
19 October 2021	Amendment 7	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the medical monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/ Role	United States/Canada Contact	Europe Contact	Asia Contact
Serious adverse event and pregnancy reporting	Fax : +1-224-554-1052 Email: PVSafetyAmericas@tpna.com	Email: eupv@tgrd.com	Email: eupv@tgrd.com
Medical Monitor (for urgent contact with the Medical Monitor please call the hotline)	PPD NA Hotline: +1-800-201-8725 +1-888-483-7729	PPD EMEA/APAC Hotline: +44-1223-374240	PPD EMEA/APAC Hotline: +44-1223-374240
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted]	[redacted]	[redacted]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual subjects in accordance with the requirements of this clinical study protocol and also in accordance with the following:

The ethical principles that have their origin in the Declaration of Helsinki.

International Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.

All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

DocuSigned by:
[redacted], MD
Date
Entyvio and IBD Programs
Global Medical Affairs – Specialty GI

DocuSigned by:
[redacted]; GI Statistics
26-Oct-2021 | 23:13 JST
Date
Statistical and Quantitative Sciences,
Data Sciences Institute

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, the vedolizumab intravenous (IV) (Entyvio) package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the life, dignity, integrity, confidentiality of personal information, rights, safety, privacy, and well-being of study subjects in accordance with the following:

The ethical principles that have their origin in the Declaration of Helsinki.

International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.

All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.

Terms outlined in the Clinical Study Site Agreement.

- Appendix A– Schedule of Study Procedures for Main XAP Study.
- Appendix B– Responsibilities of the Investigator.
- Appendix F– Schedule of Study Procedures for XAP-PK Substudy (*if applicable*).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 7 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment 7.

The primary purpose of this amendment is to provide additional clarifications and include all changes made to the original version of the protocol (dated 17 March 2016). Full details regarding changes made to the text are given in Appendix I. Minor grammatical and editorial changes are included for clarification purposes only. The below table summarizes the main changes in the protocol.

Change in Protocol	**Rationale/Justification**	**Version of amendment (s) in which change was made effective**
Cover Page Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy); and Amendment 3 (Global)
Excluded EU Takeda sponsor company.	[redacted].	Amendment 7 (Global)
Updated corporate addresses of TDC Americas and TDC Asia, Takeda sponsor companies.	To update current corporate addresses of TDC Americas and TDC Asia, Takeda sponsor companies.	
Administrative Information Representatives of Takeda	To update current Takeda representatives	Amendment 7 (Global)
Investigator Agreement Included language per DoH requirement.	To be fully compliant with this DoH requirement.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
2.0 Study Summary Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy); and Amendment 3 (Global)
Excluded EU Takeda sponsor company	[redacted].	Amendment 7 (Global)
2.0 Study Summary Included additional qualifying study	An additional qualifying study MLN0002-3028 was added along with the existing study C13008. Included to clarify the completion of qualifying study for enrolled subjects.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
2.0 Study Summary Details related to subject's population and dose level have been modified for clarity.	Clarification added related to the window period of ±7 days with every dose administered to subject and dosing regimen permitted in the study. Text updated as per the modifications in respective sections within protocol main body text.	Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
3.4 Corporate Identification Included Takeda sponsor companies in the European and Asian regions. Excluded EU Takeda sponsor company	This is a global study. Inadvertently omitted in Initial Protocol version. [redacted].	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy); and Amendment 3 (Global) Amendment 7 (Global)
4.1.2 Vedolizumab IV 4.3 Risk: Benefit Assessment Updated number of subjects received and exposure duration and safety details of vedolizumab till 19 May 2021.	Text updated as per the details in the latest IB.	Amendment 6 (Global); Amendment 7 (Global)
6.1 Study Design Included additional qualifying study and clarified study design text.	An additional qualifying study, MLN0002-3028 has been added along with the existing study C13008 for the main XAP study only.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
6.1 Study Design Included countries name and clarified study design text. Included text related to risk and mitigation approach due to interruption from COVID-19.	Text has been added to clarify the XAP study design related to dosing regimen permitted in the study and timepoint of first dose in the XAP study. Countries for XAP and XAP-PK studies have been clarified to avoid ambiguity for the sites involved in XAP-PK substudy. No subjects will be enrolled in the XAP-PK substudy from countries that are not specifically listed in the protocol. Similarly, no subjects will be rolled-over from the C13008 or MLN0002-3028 studies unless country name is specifically listed in protocol. Due to the interruption from the COVID-19 pandemic, a risk and mitigation approach was finalized and provided in the protocol to maintain subject safety and to ensure data quality and integrity.	Amendment 6 (Global) Amendment 7 (Global)
6.2 Number of Subjects Included additional text related to subject enrollment in XAP study.	Added clarification for the subject participation from the qualifying study to XAP study.	Amendment 6 (Global)
6.3 Duration of Study	Text has been added to clarify the	Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
Included additional text related to study design text and study completion.	duration of the XAP study.	
6.4 Justification for Study Design, Dose, and Endpoints Date was updated	Date updated as per the details in the latest IB.	Amendment 7 (Global)
8.1.3. Dose and Regimen 8.2 Drug Dosing and Dispensing Procedures Included additional text related to dose regimen.	Text has been added to clarify the dose schedule and regimen along with window period of ±7 days with every dose.	Amendment 6 (Global)
8.4 Accountability and Destruction of Sponsor-Supplied Drugs Included additional text related to remote drug reconciliation and destruction	Text has been added to clarify that the drug reconciliation will be completed remotely and destruction can be carried out locally or by a contracted third party as per local regulations.	Amendment 6 (Global)
9.1 Study Procedures Included a statement to cross-refer details of COVID-19.	Text has been added to cross-refer details of COVID-19-related study procedural changes.	Amendment 7 (Global)
9.1.5 Documentation of Concurrent Medical Conditions Included text regarding the recording of ongoing AEs from qualifying study.	Added clarification that "ongoing AEs" from qualifying study, at the time of signing informed consent to participate in this XAP study, will be captured as a concurrent medical condition.	Amendment 6 (Global)
9.1.7 Physical Examination Included text regarding procedures that have been conducted within last 24 hours.	Added clarification that if physical examination has been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
9.1.8 Vital Sign Procedure Included text regarding procedures that have been conducted within last 24 hours.	Added clarification that if vital sign measurements have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
9.1.9 Weight, Height, and BMI Included text regarding procedures that have been conducted within last 24 hours. In addition, BMI calculation details have been added.	Added clarification that if weight and height have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)

Change in Protocol	**Rationale/Justification**	**Version of amendment (s) in which change was made effective**
9.1.11 Contraception & Pregnancy Avoidance Procedure Clarification that spermicides are not commercially available in South Africa. South African subjects will be counselled to use other double-barrier methods.	Clarification to support applicable double-barrier contraception and pregnancy avoidance procedures in South African trial sites.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
9.1.11 Contraception & Pregnancy Avoidance Procedure Included text regarding procedures that have been conducted within last 24 hours. Deleted text related to sperm donation period for male subjects	Added clarification that if pregnancy test result has been recorded within the last 24 hours at screening, the results of that test can be used and the procedure does not need to be redone. This information has already been clarified at the beginning of the sentence.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy) Amendment 7 (Global)
9.1.15 Collection of AEs and SAEs Included text related to the time of collection of AEs and SAEs during the study.	Added clarification that AEs and SAEs will be collected from the time when the subject signs the informed consent to participate in the study through to follow-up visit.	Amendment 6 (Global)
9.3.2 Treatment Period Included text to clarify study treatment and completion period. Included a statement to cross-refer details of COVID-19.	Text has been added to clarify the dose schedule and regimen. Text has been added to cross-refer details of COVID-19-related visit window changes.	Amendment 6 (Global) Amendment 7 (Global)
9.3.6 Follow-up Period Included text to clarify study procedure to be followed at follow-up period.	Added clarification over the follow-up period and procedure to be followed.	Amendment 6 (Global)
9.3.7 COVID-19-Related Protocol Considerations/Mitigations Included a section to clarify procedures/risk mitigation approaches during the COVID-19 pandemic.	Text has been added to update details of COVID-19-related study procedural changes.	Amendment 7 (Global)
10.1.3 Additional Points to Consider for AEs 10.1.5 Severity of AEs 10.2.1.2 AE Reporting 13.1.4 Safety Analysis The term 'severity' of AEs changed to 'intensity' of AEs recorded during the study.	Added to reduce the ambiguity between the terminologies.	Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
Included text related to the time of collection of AEs and SAEs during the study.		
10.1.11 Action Concerning Study Medication Every 8-week changed to Q8W	Editorial change added for consistency and defining dosing schedule technically.	Amendment 6 (Global)
10.2.1.1 AE collection period Included text regarding the collection of ongoing AEs from qualifying study, and AEs during the study and safety follow-up. 13.1.4 Safety Analysis	Added clarification that ongoing AEs from qualifying study at the time of signing informed consent to participate in this study will be captured as a concurrent medical condition and AEs/SAEs will be collected from the time when the subject signs the informed consent to participate in the study, through study till safety follow-up visit.	Amendment 6 (Global)
13.2 Interim Analysis and Criteria for Early Termination	Text has been updated to clarify that interim looks at study data to review safety and treatment persistence of study subjects might be done.	Amendment 7 (Global)
14.2 Protocol Deviations Included a statement to cross-refer details of COVID-19.	Text has been added to cross-refer the details of how to document COVID-19-related protocol deviations.	Amendment 7 (Global)
15.0 Ethical Aspects of the Study Re-emphasized the objective of the global Extended Access Program (XAP).	Clarification to satisfy Declaration of Helsinki requirements.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
15.1 IRB and/or IEC Approval Added clarifications for funding, sponsors, institutional affiliations and potential conflicts of interest.	Clarification to satisfy Declaration of Helsinki requirements.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
15.2 Subject Information, Informed Consent, Subject Authorization Added references to the "assent form" for use if applicable, eg, mentally incapacitated persons or subjects deemed otherwise incapable of providing informed consent.	Clarification to satisfy Declaration of Helsinki requirements.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
16.0 References	Added 2 new references.	Amendment 7 (Global)
Appendix A Schedule of Study Procedures for Main XAP Study Included footnote to the procedures that are not required to be repeated if	To include the timing of the initial study visit for MLN0002-3028 and to clarify that the results of procedures that have been conducted in last 24	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)

Change in Protocol	**Rationale/Justification**	**Version of amendment (s) in which change was made effective**
performed within 24 hours of the screening/enrollment visit and clarified the timing of the initial study visit for additional qualifying study. Included a statement in footnote to cross-refer details of COVID-19.	hours at enrollment visit can be used and the procedure does not need to be redone. Added list of abbreviations and footnote text to cross-refer details of COVID-19-related protocol considerations/mitigations.	Amendment 7 (Global)
Appendix A Schedule of Study Procedures for Main XAP Study Footnotes were shortened to remove repetitive details.	Footnotes have been reduced to remove redundancy. Details of XAP-PK substudy procedures moved to a separate Appendix F	Amendment 6 (Global)
2.0 Summary Included details about XAP-PK substudy. 4.2.1 Rationale for XAP-PK Substudy 5.1.2 Exploratory Objectives for XAP-PK Substudy 5.2.2 Exploratory Endpoints for XAP-PK Substudy 6.1.1 Study Design of the XAP-PK Substudy 6.2 Number of Subjects 6.3 Duration of Study 6.4 Justification for Study Design, Dose, and Endpoints 6.5.1 Criteria for Premature Termination or Suspension of the Study 7.1 Inclusion Criteria 7.6 Criteria for Discontinuation or Withdrawal of a Subject 7.7 Procedures for Discontinuation or Withdrawal of a Subject 9.1.1.1 XAP-PK Substudy Informed Consent Procedure 9.1.9 Weight, Height, and BMI 9.1.16 Partial Mayo Score 9.1.17 Harvey-Bradshaw Index Score 9.1.18 Sample Collection and Analysis 9.3.1 Enrollment Visit 1	Details related to rationale, objectives, endpoints, study design, subjects, inclusion and withdrawal criteria, study procedures, and statistical considerations were added to explain XAP-PK substudy. All these changes are now described separately as XAP-PK substudy in Appendix E and schedule of study procedures for XAP-PK substudy are summarized in Appendix F. For XAP-PK substudy additional clarifications have been included to specify that end of substudy and Week 56 are same ie, end of substudy visit/Week 56. Clarification that End of Sub-study/Week 56 visit should be scheduled in conjunction with a regular infusion visit of the Main study has been added. Mention of predictive models for XAP-PK substudy have been removed as they were added inadvertently	Amendment 2 (Global) and Amendment 6 (moved to separate Appendix) Amendment 5 (Global): Removed MLN0002-3028 from eligibility to participate in the XAP-PK substudy. It was added in error in Amendment 4. Subjects in MLN0002-3028 are not switching from Q4W to Q8W dosing and are therefore an inappropriate population for the substudy. Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
9.3.2 Treatment Period 9.3.6 Follow-up Period 13.1.1 Analysis Sets 13.3 Determination of Sample Size 13.4 XAP-PK Substudy Analysis Appendix E Details Specific to XAP-PK Substudy Appendix F Schedule of Study Procedures for XAP-PK Substudy		
Appendix C Elements of the Subject Informed Consent	To include a statement to cover the requirements for the XAP-PK substudy	Amendment 2 (Global)
Appendix G Partial Mayo Score	Scale copy has been added for reference	Amendment 6 (Global)
Appendix H Harvey-Bradshaw Index	Scale copy has been added for reference	Amendment 6 (Global)

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc. (TDC Americas)
Takeda Development Centre Asia, Pte. Limited, Singapore</td><td colspan="2">Compound:
Vedolizumab IV</td></tr>
<tr><td>Title of Protocol: Entyvio (Vedolizumab IV) Extended Access Program in Ulcerative Colitis and Crohn’s Disease</td><td>IND No.: Not Applicable</td><td>EudraCT No.:
2016-000678-40</td></tr>
<tr><td>Study Number: Vedolizumab-4013</td><td colspan="2">Phase: 3b/4</td></tr>
<tr><td colspan="3">Study Design:
This is a multinational, multicenter, phase 3b/4, open-label extended access program (XAP) study to monitor ongoing safety (eg, adverse events [AEs], serious AEs [SAEs], and AEs of special interest [AESIs]) and provide access to vedolizumab for qualifying subjects who have successfully completed participation in qualifying vedolizumab clinical studies.
Subjects entering the XAP study from C13008 and who are switching from every 4-week (Q4W) to every 8-week (Q8W) dosing at the time of enrollment, will be eligible to enroll in an optional pharmacokinetic (PK) substudy. Details related to rationale for the XAP-PK substudy are provided in Appendix E.</td></tr>
<tr><td colspan="3">Objective
Primary Objectives for the Main XAP 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.</td></tr>
<tr><td colspan="3">Subject Population:
Subjects who have successfully completed participation (having received the final dose of vedolizumab but not yet having completed the safety follow-up period) in qualifying vedolizumab clinical studies and meet the inclusion/exclusion criteria. At this time, qualified studies include C13008 and MLN0002-3028. Additional qualifying studies may be included at a later date as specified within the protocol for the qualifying vedolizumab study. They will not be specifically called out in this protocol, unless the roll-over requires a change to the conduct of the main XAP study.</td></tr>
<tr><td colspan="2">Number of Subjects:
The number of subjects will be determined based upon the qualifying subjects who have received treatment with vedolizumab, completed participation in qualifying vedolizumab clinical studies, meet the inclusion/exclusion criteria, and agree to enroll in the XAP study.</td><td colspan="2">Number of Sites:
The number of countries and number of sites will be determined based upon the number and location of sites with qualifying subjects completing qualifying vedolizumab clinical studies.</td></tr>
<tr><td colspan="2">Dose Level:
300 mg of vedolizumab administered every 8 weeks (±7 days).
The first dose of vedolizumab in this study should occur 8 weeks (±7 days) after the last dose of study medication</td><td colspan="2">Route of Administration:
Intravenous (IV)</td></tr>
</table>

in the qualifying study. If indicated, the time to the first dose of vedolizumab in this study may be extended, but will be performed no later than the safety follow-up visit in the qualifying study. If the subject experiences reduction in efficacy on Q8W dosing, the dosing frequency, based on the investigator's judgment of subject's clinical status and acknowledged by the medical monitor, may be changed to Q4W dosing. It will be at the investigator's discretion when Q8W dosing will be reintroduced again. Subjects entering from a qualifying study in which the subject was on a more frequent dose can 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.	
Duration of Treatment: Subjects will remain in the study until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner.	**Period of Evaluation:** The subject will be evaluated until the time at which they leave the study. The subject is expected to return for a safety follow-up visit 18 weeks after the final study dose.
Main Criteria for Inclusion: Received vedolizumab (excluding comparator or placebo subjects) during participation in a qualifying vedolizumab study. In the opinion of the investigator, the subject is continuing to derive benefit from vedolizumab and 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. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of informed consent throughout the duration of the study and for 18 weeks after last dose. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.	
Main Criteria for Exclusion: For the subject's particular clinical scenario, vedolizumab is currently available to the subject through commercial channels, including reimbursement. Subject has any clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing requirements or poses a risk to the subject being in the study. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter. Subject has received a live vaccine in the last 18 weeks or is in need of a live vaccine during the study or up to 18 weeks after the last study dose.	

Main Criteria for Evaluation and Analyses:

The primary endpoints for the XAP study are:

- Number and percentage of subjects with AEs and SAEs.
- Number and percentage of subjects with AESIs.

Statistical Considerations:

This XAP study is not sized based on power considerations. All analyses will be descriptive. No formal statistical hypothesis testing is to be performed.

Safety evaluations will be based on incidence, intensity and type of AEs, and vital signs. Descriptive statistics will be calculated.

The number and percentage of subjects with treatment-emergent adverse events (TEAEs), defined as any AEs, regardless of relationship to study medication), AESIs (ie, serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy, malignancies, liver injury, infusion-related hypersensitivity reactions and injection site reactions), AEs leading to discontinuation, and SAEs that occur from the time of signing informed consent form and up to the safety follow-up visit will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), high-level term (HLT), and preferred term (PT) overall, by intensity, and by relationship to study medication for each treatment group. Separate summaries will also be generated for TEAEs overall and by intensity.

To summarize the number of subjects with AEs, subjects reporting the same event more than once will have that event counted only once within each SOC, HLT, and PT. All AEs will be presented in separate data listings. Exposure-adjusted AEs will also be presented.

Absolute values and change from baseline in vital sign measurements will be summarized. Vital sign data will be presented in data listings.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities document. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area, and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-ASAs	5-aminosalicylic acid
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVA	anti-vedolizumab antibodies
BMI	body mass index
CD	Crohn's disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
ePIP	electronic Protocol Inquiry Platform
EU	European Union
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HBI	Harvey-Bradshaw Index
hCG	human chorionic gonadotropin
HLT	high-level term
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test

MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
PC	product complaint
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PT	preferred term
PVC	polyvinyl chloride
Q4W	every 4-week
Q8W	every 8-week
SAE	serious adverse event
SC	subcutaneous
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
WBC	white blood cells
WHODRUG	World Health Organization Drug Dictionary
XAP	extended access program

3.4 Corporate Identification

TDC Asia	Takeda Development Centre Asia, Pte. Limited
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Asia and/or TDC Americas, as applicable
Takeda	TDC Asia and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 The Inflammatory Bowel Diseases: Ulcerative Colitis and Crohn's Disease and Current Treatments

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal (GI) tract that includes 2 entities, namely ulcerative colitis (UC) and Crohn's disease (CD).

UC is a relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. The prevalence of UC (in adults and pediatric population) is approximately 200 cases/100,000 of population in the United States (US), 150 cases/100,000 of the population in Western Europe [1-4]. Among first-degree relatives of subjects with UC, the incidence of UC is 30 to 100 times higher than the general population, indicating a significant genetic component to the disease [5].

CD is a relapsing, remitting inflammatory disease that may involve any portion of the length of the GI tract from mouth to anus in a transmural fashion from mucosa to serosa. The prevalence of CD is approximately 125 cases/100,000 of population in the US and approximately 150 cases/100,000 of population in Western Europe [1-4]. Approximately 20% of all cases of CD occur in the pediatric population under the age of 15 years. A male preponderance is reported in pediatric CD, while a female preponderance is seen only among subjects diagnosed during adolescence (13 to19 years) [6].

In both the adult and pediatric populations, clinical manifestations of both diseases include diarrhea (typically bloody in subjects with UC), as well as abdominal pain, fecal urgency, and incontinence. Systemic features such as fever, weight loss, malaise, and fatigue are indicators of more extensive disease. The characteristic pathology of UC is one of chronic inflammation characterized by large numbers of lymphocytes and histiocytes in the diseased mucosa and submucosa with an acute inflammatory infiltrate composed of neutrophils variably present, while CD involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration.

Conventional pharmacological treatments for both UC and CD include the 5-aminosalicylic acids (5-ASAs), corticosteroids, and immunomodulators (thiopurines, such as azathioprine and 6-mercaptopurine), along with methotrexate for CD. In addition, standard practice often involves using these treatments in combination. Tumor necrosis factor-alpha (TNF-α) antagonists approved for treatment of UC and CD in the US, European Union (EU), and in other regions include infliximab (Remicade) [7] administered by intravenous (IV) infusion, adalimumab (Humira) [8] administered by subcutaneous (SC) injection, and golimumab (Simponi) [9] administered by SC injection for the treatment of UC only. In the US, 2 additional treatments are approved for CD: certolizumab (Cimzia) [10], a SC administered TNF-α antagonist, and natalizumab (TYSABRI) [11], a pan α4 integrin antagonist administered by IV infusion. Natalizumab is also approved in the EU with limited reimbursement. Current treatments have

been effective for many subjects with IBD but have numerous limitations for subjects with moderately to severely active disease. 5-aminosalicylates are the main stay of UC pharmacotherapy for induction and maintenance of remission for subjects with mild to moderate disease, but are less effective in severe disease. The National Cooperative Crohn's Disease Study demonstrated a role for sulfasalazine (a 5-ASA–containing molecule) in moderate to severe CD [12]. Despite its use, the benefit is debatable in moderate to severely active UC [13]. Corticosteroids are often required for the one-third of subjects who fail to respond to 5-ASAs. While highly effective for induction of remission, corticosteroids are not recommended for the maintenance of remission in CD because they carry significant undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection [14]. Immunomodulatory agents have relatively slow onset of action, which precludes their use during flares of disease, and the use of these agents has been reported to potentially increase the risk of lymphoma in subjects with IBD [15].

Methotrexate, while ineffective in UC, has a role in the management of refractory CD; however, it also demonstrates a number of dose-limiting toxicities. Antibiotics have marginal efficacy in maintenance of remission in CD. TNF-α antagonists are effective in only a subset of subjects, with roughly two-thirds of subjects in controlled trials not in remission at the end of the first year of therapy [16,17]. The TNF-α antagonists are also associated with a number of serious safety concerns based on their suppression of systemic immunity, including reactivation of tuberculosis (TB); various bacterial, viral, fungal, and opportunistic infections; and malignancies such as hepatosplenic T-cell lymphoma [7,8]. Natalizumab is cautiously prescribed for treatment of CD due to the increased risk of developing rare but often fatal neurodegenerative disorder, progressive multifocal leukoencephalopathy (PML), which is a mechanism-based side effect [11].

Failure of pharmacological therapy leads to colectomy in 9% to 35% of subjects with UC within 5 years. Colectomy is considered to be an important adjunct treatment for refractory UC; however, colectomy with ileal pouch anal anastomosis (the standard surgical therapy) has many limitations and is associated with its own set of complications, including high stool frequency [18], female infertility [19], and a cumulative incidence of pouchitis of 50% at 10 years [20]. The limitations of current therapies for IBD indicate that there is a significant need for safer and more effective therapies.

4.1.2 Vedolizumab IV

Vedolizumab (also called MLN0002) is a humanized immunoglobulin G1 monoclonal antibody directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [21-24]. Vedolizumab binds to the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [25].

Vedolizumab IV (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; or MLN0002 IV) is approved in the US, EU and multiple other countries worldwide for the treatment of adult subjects with moderately to severely active UC or CD who have failed conventional treatment, that include corticosteroids, immunomodulators, or TNF-α antagonists [26,27]. The approved dosing and administration regimen consists of 300 mg vedolizumab infused IV, over approximately 30 minutes, at Weeks 0, 2 and 6, then once every 8 weeks thereafter.

Detailed information regarding the nonclinical pharmacology and toxicology of vedolizumab along with previously conducted clinical studies which have characterized the efficacy, safety, tolerability, pharmacokinetic (PK), pharmacodynamic, and immunogenicity of vedolizumab can be found in the current version of the Investigator's Brochure (IB).

As of 19 May 2021, approximately 6949 subjects (869 healthy subjects, 2782 subjects with UC, and 3022 subjects with CD, 213 subjects undergoing allogeneic-hematopoietic stem cell transplantation or with acute graft-versus-host disease involving the intestinal tract, 51 subjects with pouchitis, and 12 subjects with melanoma) have received at least 1 dose of vedolizumab across completed and ongoing company-sponsored interventional clinical studies (see current version of IB). Vedolizumab exposure in clinical studies has extended for ≥12 months in 2957 subjects, ≥24 months in 1906 subjects, ≥36 months in 1474 subjects, ≥48 months in 965 subjects, ≥60 months in 717 subjects, ≥72 months in 477 subjects, ≥84 months in 308 subjects, ≥96 months in 271 subjects, and ≥108 months in 201 subjects.

Vedolizumab has shown an acceptable safety based on an analysis of safety data from both completed and ongoing studies. The integrated summary of safety for the completed studies, as well as a summary of safety from the ongoing phase 3/3b and 3b/4 programs (based on a data cut off of 19 May 2021), are detailed in the current version of the IB. As of 19 May 2021, a total of 103 subjects who participated in vedolizumab clinical studies have died during the study or up to 2 years following the last dose of study drug. Eight of the 103 subjects were being treated for UC and 14 subjects for CD (Studies C13006, C13007, C13008, C13011, MLN0002-3026, MLN0002SC-3027, MLN0002SC-3031, Vedolizumab-3034, Vedolizumab-4013, and Vedolizumab-4014). The causes of death varied and additional information can be found in the current version of the IB. No cases of PML have been reported to date. Overall, vedolizumab IV was well tolerated in clinical studies.

4.2 Rationale for the Proposed Study

Establishing the safety and tolerability of vedolizumab is a key component of the pivotal development programs in both UC and CD. The benefit-to-risk of vedolizumab is favorable to date (see current version of the IB) and suggests that the drug has the potential to address an important unmet medical need in the treatment of UC and CD. Vedolizumab efficacy has been established in the registrational trials.

The primary aim of the currently planned study is to monitor ongoing safety in subjects with UC and CD and to provide access to vedolizumab for qualifying subjects who have received

vedolizumab during participation in a qualifying vedolizumab study and who, in the opinion of the investigator, are continuing to derive benefit from vedolizumab and for whom continued treatment with vedolizumab is desired because there is no other commercial product available or the subject may be expected to develop worsening of disease if they were to modify treatment.

The study will facilitate collection of additional safety information on important clinical events for a larger subject population. Qualifying subjects will be provided access to vedolizumab from the end of the qualifying vedolizumab study until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner.

Subjects entering the extended access program (XAP) study from C13008 and who are switching from every 4-week (Q4W) to every 8-week (Q8W) dosing at the time of enrollment, will be eligible to enroll in an optional XAP-PK substudy. Details related to rationale for the XAP-PK substudy are provided in Appendix E.

4.3 Risk: Benefit Assessment

An integrated safety analysis was conducted using data from completed vedolizumab clinical studies with a cut-off of 14 March 2013. This analysis of 237 healthy subjects and 2216 subjects with UC or CD demonstrated an acceptable safety for vedolizumab. The safety profile of vedolizumab through 19 May 2021 remains consistent with this integrated analysis and no new safety signals have been identified. Thus, vedolizumab has a favorable risk to benefit to date. The risks (identified and potential) have been assessed in the clinical and nonclinical studies and are detailed in the current version of IB. The benefits will be continued access to vedolizumab for qualified subjects who have completed participation in qualifying vedolizumab clinical studies until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objective

5.1.1 Primary Objectives for the Main XAP Study

- To monitor ongoing safety in subjects with UC and 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.

Details related to exploratory objectives for the XAP-PK substudy are provided in Appendix E.

5.2 Endpoints

5.2.1 Primary Endpoints for the Main XAP Study

- Number and percentage of subjects with adverse events (AEs) and serious AEs (SAEs).
- Number and percentage of subjects with adverse events of special interest (AESIs).

Details related to exploratory endpoints for the XAP-PK substudy are provided in Appendix E.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design of the Main XAP Study

This is a multinational, multicenter, phase 3b/4, open-label XAP study to monitor ongoing safety (eg, AEs, SAEs, and AESIs) and provide access to vedolizumab for qualifying subjects who have successfully completed participation in qualifying vedolizumab clinical studies. At this time, qualified studies include C13008 and MLN0002-3028. Additional qualifying studies may be included at a later date as specified within the protocol for the qualifying vedolizumab study. They will not be specifically called out in this protocol, unless the roll-over requires a change to the conduct of the main XAP study. The XAP study will start in a staggered manner depending on the start-up timelines of the countries where the XAP will be conducted. Eligible subjects will be enrolled into the study upon the approval of local sites.

In this XAP study, subjects will have an enrollment visit at which they will be consented. This visit should be in conjunction with the final visit of the qualifying study. Baseline data for the subject (eg, medical history, disease history, demographics, and prior therapies) will be obtained at the enrollment visit. In addition to the enrollment visit, the subject will have vedolizumab dosing visits every 8 weeks (±7 days). The first dose of vedolizumab in this study should occur 8 weeks (±7 days) after the last dose of study medication in the qualifying study. If indicated, the time to the first dose of vedolizumab in this study may be extended, but will be performed no later than the safety follow-up visit in the qualifying study.

If the subject experiences reduction in efficacy on Q8W dosing, the dosing frequency, based on the investigator's judgment of subject's clinical status and acknowledged by the medical monitor, may be changed to Q4W dosing. It will be at the investigator's discretion when Q8W dosing will be reintroduced again.

Subjects entering from a qualifying study in which the subject was on a more frequent dose can 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.

Subjects will remain in the XAP study until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner. If vedolizumab is available to the subject through commercial channels, including reimbursement, for Q8W dosing but the subject has not been stable on that regimen for the previous 6 months, the subject will only exit the XAP study if vedolizumab will be available to the subject through commercial channels at the previous, more frequent dosing regimen. If it will not be commercially available at the previous dosing regimen, the subject will remain in the XAP study until they are stable for 6 months and can move to commercially available Q8W dosing of vedolizumab.

Within 60 days of the subject having access to vedolizumab through commercial channels, including reimbursement, for the subject's clinical scenario, the subject should have the final

study infusion visit. Subjects will return 18 weeks after their final study infusion for a safety follow-up visit.

Safety assessments will be made throughout the treatment period at the infusion visits. Physicians will follow the local standard of care guidelines for disease monitoring. Any safety information discovered during the routine treatment of a subject should be reported. All SAEs and AEs regardless of study medication attribution will be recorded on the electronic case report form (eCRF) and analyzed.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International Council for Harmonisation [ICH] guidelines).

A schedule of assessments is listed in Appendix A.

The MLN0002-3028 parent protocol is applicable only in sites from Czech Republic, Hungary, Italy, and Poland.

In the event a subject is unable to report to the site for required study visits or procedures in a timely manner (ie, within permitted visit windows), due to the coronavirus disease 2019 (COVID-19) pandemic, alternative procedural considerations or mitigation approaches may be followed to maintain subject safety and to ensure data quality and integrity (Section 9.3.7).

Subjects entering the XAP study from C13008 and who are switching from Q4W to Q8W dosing at the time of enrollment, will be eligible to enroll in an optional XAP-PK substudy applicable only sites in Australia, Czech Republic, Hungary, New Zealand, Korea (South), Poland, and Russia. Details related to study design of the XAP-PK substudy are provided in Appendix E.

6.2 Number of Subjects

The number of subjects will be determined based upon the qualifying subjects who have received treatment with vedolizumab, completed participation (having received the final dose of vedolizumab but not yet having completed the safety follow-up period) in qualifying vedolizumab clinical studies, meet the inclusion/exclusion criteria, and agree to enroll in the XAP study.

Details related to number of subjects for the XAP-PK substudy are provided in Appendix E.

6.3 Duration of Study

Subjects will remain in the XAP study until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner. If vedolizumab is available to the subject through commercial channels, including reimbursement, for Q8W dosing but the subject has not been stable on that regimen for the previous 6 months, the subject will only exit the XAP study if vedolizumab will be available to the subject through commercial channels at the previous, more frequent dosing regimen. If it will not be commercially available at the previous dosing regimen, the subject will

remain in the XAP study until they are stable for 6 months and can move to commercially available Q8W dosing of vedolizumab. Subjects will return 18 weeks after their final study infusion for a safety follow-up visit. Subjects will be considered to have completed the XAP study once transitioned to commercially available and reimbursed product.

If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit. Details related to duration of study of the XAP-PK substudy are provided in Appendix E.

6.4 Justification for Study Design, Dose, and Endpoints

The benefit-to-risk of vedolizumab is favorable to date (as summarized in the IB, Edition 25 [Dated 14 July 2021]) in the treatment of UC and CD. The proposed vedolizumab IV dose (300 mg every 8 weeks) is consistent with pivotal study data and the approved label information [26]. In subjects with moderately to severely active CD or UC, vedolizumab IV 300 mg administered as an IV infusion at Weeks 0 and 2 (induction) followed by every 8 weeks or every 4 weeks administration from Week 6 through Week 52 (maintenance) demonstrated statistically significant differences in efficacy compared with placebo for both the induction phase and maintenance phase and demonstrated an acceptable safety.

The current XAP study will 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. Safety will be monitored through the collection of AEs, SAEs, and AESIs during this study.

Details related to justification for study design, dose, and endpoints of the XAP-PK substudy are provided in Appendix E.

6.5 Premature Termination or Suspension of Study or Investigational Site

6.5.1 Criteria for Premature Termination or Suspension of the Study

The XAP study will be completed when the last subject completes the study unless one or more of the following criteria are satisfied that may require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of vedolizumab indicates a change in the known risk/benefit for vedolizumab, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the study objective or subject safety.
- Prior to the product becoming commercially available, another access program becomes available in the country of residence that will provide access to subjects outside of the study.

- The study is terminated at a site.
- The study is terminated by the sponsor.

Details related to criteria for premature termination or suspension of the XAP-PK substudy are provided in Appendix E.

6.5.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement or the site is unable to ensure adequate performance of the study.

6.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria need to be confirmed prior to entry into the treatment period.

7.1 Inclusion Criteria

Any subject who meets the inclusion criteria for the qualifying vedolizumab clinical studies and meets any of the following criteria will qualify for entry into the study:

1. Received vedolizumab (excluding comparator or placebo subjects) during participation in a qualifying vedolizumab study.
2. In the opinion of the investigator, the subject is continuing to derive benefit from vedolizumab and 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.
3. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.
4. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.11, Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities are defined in Section 9.1.12, Pregnancy.

Details related to additional inclusion criteria of the XAP-PK substudy are provided in Appendix E.

7.2 Exclusion Criteria

Any subject who meets any of the exclusion following criteria will not qualify for entry into the study:

1. For the subject's particular clinical scenario, vedolizumab is currently available to the subject through commercial channels, including reimbursement.
2. Subject has any clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing requirements or poses a risk to the subject being in the study.
3. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.

4. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
5. Subject has received a live vaccine in the last 18 weeks or is in need of a live vaccine during the study or up to 18 weeks after the last study dose.

7.3 Concomitant Procedures and Medications

During the course of this study, physicians are expected to follow their subjects according to acceptable medical practice with regards to disease monitoring and treatment. All medications that are administered and all procedures that are performed during the study must be recorded in the subject's eCRF and in the source documents. Concomitant medications for medical conditions other than UC or CD are permitted as clinically indicated, subject to specific protocol requirements outlined in Section 7.3.1 for excluded medications. Subjects should be up to date on TB testing per local requirements.

7.3.1 Excluded Medications

The following medications are excluded from the study:

- Either approved or investigational biological agents for the treatment of non-IBD conditions, other than localized injections (eg, intra-ocular injections for wet macular degeneration).
- All live vaccines during study treatment and for at least 18 weeks after the last dose of study medication.

7.4 Diet, Fluid, Activity Control

There are no restrictions on diet or fluid during the study.

The requirements for the contraception for female subjects of childbearing potential and male subjects who are nonsterilized are detailed in the contraception and pregnancy avoidance procedures (Section 9.1.11).

7.5 Management of Clinical Events

7.5.1 AEs of Special Interest

AESI (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

7.5.2 Infusion-Related Hypersensitivity Reactions

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence,

such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication prior to any study medication infusion. Corticosteroids, if given as premedication, should be limited to the day of infusion.

Subjects will be monitored for acute infusion-related hypersensitivity reactions during infusion and for at least 1 hour after the completion of each administration of vedolizumab. Epinephrine and parenteral diphenhydramine must be readily available for immediate use in case an infusion-related reaction occurs. Site personnel must be able to detect and treat infusion-related reactions.

Subjects should be instructed to report the development of rash, hives, pruritus, flushing, urticaria, etc. that may represent an infusion-related reaction to vedolizumab. If any signs or symptoms of infusion-related reactions are observed during the infusion, administration of vedolizumab must be immediately discontinued and the subject treated as medically appropriate. In the case of a mild reaction, vedolizumab infusion may be reinitiated (with appropriate premedication) at the discretion of the investigator. Subjects with a severe or serious infusion-related reaction (eg, stridor, angioedema, life-threatening change in vital signs) must be withdrawn from the study.

In all cases of infusion-related reactions, the medical monitor must be informed as soon as is practical. The disposition of subjects with less severe infusion-related reactions should be discussed with the medical monitor. All cases of infusion-related reactions that do not meet SAE definitions as specified in Section 10.1.4 will be collected as AEs. The intensity, relationship to study medication, action taken and outcome for all cases of infusion-related reactions, regardless of seriousness, will be recorded on the AE eCRF.

7.5.3 Serious Infection

Subjects will be monitored for signs and symptoms of serious infection during the study. Subjects with signs and symptoms suggestive of infection, including GI infections, opportunistic infections (such as PML) will be treated as clinically indicated; interventions may include antibiotic treatment, if appropriate, and/or discontinuation of concomitant immunomodulatory medications. Blood, sputum, urine, and/or stool cultures will be obtained as appropriate for detection and diagnosis of infection per local guidelines. Withholding or terminating vedolizumab administration may be considered as described in Section 7.6. Failure to respond to standard therapies for infection will be recorded as part of AE collection.

7.5.4 Malignancy

All cases of malignancies that are detected during the study will be reported as AEs or SAEs as defined in Section 10.1. Local medical practices will apply. Monitoring for colorectal mucosal dysplasia and cancer will be performed per local guidelines.

7.5.5 Liver Injury

Liver injury is defined in Section 10.2.3.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study, or study medication should be recorded in the eCRF using the following categories. For baseline/enrollment failure subjects, see Section 9.1.13.

1. AE. The subject has experienced an AE that requires the subject to discontinue vedolizumab or the subject elects to discontinue vedolizumab.
2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic or for infusion visits.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
5. Clinical study. The subject consents to participation in another clinical study.
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.
8. The investigator or subject feels there is no longer an adequate benefit being derived from vedolizumab, or
9. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue their participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, subjects should return 18 weeks after their final study infusion for a safety follow-up visit.

Details related to procedures for discontinuation or withdrawal of a subject in the XAP-PK substudy are provided in Appendix E.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV

The study sites will be supplied by the sponsor with the following medication in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study medication will be provided in a glass vial as a lyophilized solid for reconstitution using 4.8 mL of sterile water for injection and dilution in 250 mL of sterile 0.9% sodium chloride. Each vial will be packaged in an appropriately labeled single vial carton. Both the primary and secondary label information will fulfill all requirements specified by local governing regulations.

Additional reference information and administration instructions can be found in the Pharmacy Manual.

8.1.1.2 Other Protocol-Specified Materials

The following supplies will also be required for study treatment administration and are to be provided by the clinical study site:

Bottled sterile water for injection (for vedolizumab reconstitution).

250 mL 0.9% sodium chloride for injection in polyvinyl chloride (PVC) IV bag(s) or 250 mL 0.9% sodium chloride in alternative IV bags or bottles listed in the Pharmacy Manual.

PVC infusion line or alternative infusion line listed in the Pharmacy Manual.

8.1.2 Storage

Study medication must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or its designee for destruction. Study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed.

Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF to 46ºF). A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Subjects will receive a 300 mg dose of vedolizumab by IV infusion over approximately 30 minutes at every 8 weeks (±7 days) until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject

withdrawal, whichever is sooner. Longer infusion times of up to 60 minutes may be used based on study observations. All subjects will be observed at the clinical site for at least 1 hour after the completion of each dose in a room where appropriate treatment for infusion-related reactions is available. The subject should be considered clinically stable by the investigator or designee prior to discharge. The first dose of vedolizumab in this study should occur 8 weeks (±7 days) after the last dose of study medication in the qualifying study. If indicated, the time to the first dose of vedolizumab in this study may be extended, but will be performed no later than the safety follow-up visit in the qualifying study.

If the subject experiences reduction in efficacy on Q8W dosing, the dosing frequency, based on the investigator's judgment of subject's clinical status and acknowledged by the medical monitor, may be changed to Q4W dosing. It will be at the investigator's discretion when Q8W dosing will be reintroduced again.

Subjects entering from a qualifying study in which the subject was on a more frequent dose can 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.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study medication, to or by a study subject, at a dose above that is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on an AE eCRF according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Drug Dosing and Dispensing Procedures

Subjects will be assigned to receive their treatment every 8 weeks (±7 days) unless the medical monitor provides approval for the subject to enter the study at the dosing regimen in their qualifying study. The investigator or designee will access the interactive voice/web response system (IVRS/IWRS) at enrollment visit to obtain the study-specific subject identification (ID) number (subject number). Study medication will be prepared according to the procedures outlined in the Pharmacy Manual.

During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at enrollment visit. The Medication ID Number of the study medication to be dispensed will then be provided by the IVRS/IWRS. If

sponsor-supplied drug is lost or damaged, the site can request a replacement from IVRS/IWRS (Refer to IVRS/IWRS Manual provided separately). The Medication ID Number will be entered into the eCRF. At subsequent infusion visits, the investigator or designee will again contact the IVRS/IWRS to request additional study medication for a subject. The Medication ID Number of the study medication to be dispensed will be provided by the IVRS/IWRS. The Medication ID Number will be entered into the eCRF.

Subjects will be assigned to receive the next available Medication ID Number allocated to each study site. The Medication ID Number will be entered into the eCRF.

8.3 Blinding and Unblinding

This is an open-label study; there is no blinding.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or its designee.

The investigator or designee must ensure that the sponsor-supplied drug (vedolizumab IV) is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or its designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form/by recording in IVRS/IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Monitoring expiration dates (monitored via IVRS/IWRS).
- Verifying that the log is completed for the Medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IVRS/IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (vedolizumab IV) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of the investigator, site identifier and number, description of sponsor-supplied drugs, expiry or re-test date and amount dispensed, including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject (by subject identifier) to whom sponsor-supplied drug is dispensed.

The investigator's designated site staff administering the study medication infusion must complete an individual subject accountability log to document if infusion was complete or if incomplete and study medication was returned to the pharmacy, including the date and amount returned to the pharmacy, including the initials, seal, or signature of the person administering the infusion.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform remote sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. If required by local regulations and the process is reviewed and approved by sponsor, destruction can be performed locally or by a contracted third party (for details refer to Section 6 of Pharmacy Manual). The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or its designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A. The subjects enrolling in this study will have participated in a qualifying vedolizumab study and will receive a dosing regimen as detailed in Section 6.1 and Section 8.1.3. Details of COVID-19-related study procedural changes are provided in Section 9.3.7.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2 and Appendix C.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed. During the consent process, subjects will be made aware of the known and potential risks of vedolizumab IV treatment, infusion visits, and what to report to their health care professional in case of AEs. All subjects will be given an opportunity to ask questions.

A unique subject ID number (subject number) will be assigned to each subject at the time that informed consent is obtained through the IWRS/IVRS system; this subject number will be used throughout the study.

Details related to the informed consent procedure of the XAP-PK substudy are provided in Appendix E.

9.1.2 Alert Card

An alert card specifically for this study that denotes key study information will be distributed at the enrollment visit and 18-week safety follow-up visit.

9.1.3 Assessment for Continued Eligibility

At each visit, the investigator should assess the subject for continued eligibility (see Section 7.6) and determine if vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario.

9.1.4 Demographics, Medical History, and Prior Therapies

Demographics information, medical history, and prior therapies will be obtained for all subjects at the enrollment visit.

For this XAP study, medical history refers to any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent for the XAP study, and may include resolved AEs from the qualifying study. AEs that resolved during the qualifying study but were significant, that is, represented a new diagnosis (eg, myocardial infarction) and/or

resulted in unplanned surgery or procedure (eg, coronary artery bypass graft surgery) or met any of the seriousness criteria should be recorded into the medical history. All moderate, severe, and serious AEs which resolved during the qualifying study will be captured into the medical history of the XAP study.

Where possible, all prior medications for the treatment of UC or CD, including date of diagnosis, with the reason for discontinuation, are to be collected for all subjects at the enrollment visit.

Ongoing conditions are considered concurrent medical conditions (see Section 9.1.5).

9.1.5 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. Concurrent medical conditions include clinically significant laboratory, ECG, or physical examination abnormalities. This will be obtained for all subjects at the enrollment visit. The condition (ie, diagnosis) should be described. AEs from the qualifying study which are ongoing at the time of signing informed consent to participate in this XAP study will be captured as concurrent medical conditions.

9.1.6 Disease History

The disease (UC or CD) history information will be confirmed for all subjects at the enrollment visit.

9.1.7 Physical Examination Procedure

A symptom-directed physical examination will be performed at baseline. Any clinically significant findings on the physical examination will be recorded as AEs. If a physical examination has been conducted in the previous 24 hours, the results of that examination can be used, but clinically significant results will be captured and considered as concurrent medical conditions.

9.1.8 Vital Sign Procedure

Vital signs, including body temperature, respiratory rate, supine blood pressure (resting more than 5 minutes), and pulse (beats per minute), will be obtained at every visit. At infusion visits, vital sign measurements will be recorded prior to dosing. At the enrollment visit, if vital sign measurements have been conducted in the previous 24 hours, the results of those measurements can be used.

9.1.9 Weight, Height, and Body Mass Index

A subject should have weight measured at each visit while wearing indoor clothing and with shoes off. At infusion visits, weight will be recorded prior to dosing. Height will be measured only at enrollment. At the enrollment visit, if height and/or weight have been recorded in the previous 24 hours, the results of those measurements can be used. The Takeda standard for

collecting height is centimeters without decimal places and for weight it is kilograms with 1 decimal place.

The body mass index (BMI) should be derived as follows:

Metric: BMI = weight (kg) / [height (m^2)]

The values should be reported to 1 decimal place by rounding.

Details related to weight, height, and BMI for the XAP-PK substudy are provided in Appendix E.

9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over-the-counter. Concomitant medication is not provided by Takeda. The information on concomitant medications will be collected for all subjects at the enrollment visit. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medications, including vitamin supplements, over-the-counter products, and oral herbal preparations, must be recorded in the eCRF.

Subjects must be instructed to consult the investigator before taking any medications, including over-the-counter products.

Any medications that are ongoing at the time of enrollment into the current study will be reviewed at each visit and recorded in the eCRF.

9.1.11 Contraception and Pregnancy Avoidance Procedure

For male subjects:

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly; or vaginal ring plus male condom). (Protocol Amendment No. 1: the use of spermicides does not apply for South Africa. See footnotes below.) In addition, they must be advised not to donate sperm during this period.

For female subjects of childbearing potential:

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal

(eg, defined as at least 1 year since last regular menses with a follicle-stimulating hormone >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

Barrier Methods (Each Time the Subject has Intercourse):	**Intrauterine Devices:**	**Hormonal Contraceptives:**
Male condom PLUS spermicide.	Copper T PLUS condom or spermicide.	Implants.
Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.	Progesterone T PLUS condom or spermicide.	Hormone shot/injection.
Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.		Combined pill.
		Minipill.
		Patch.
		Vaginal ring PLUS male condom and spermicide.

Protocol Amendment No. 1 (South Africa): The use of spermicides does not apply for South Africa since these products have been removed from the list of Health Authority–approved medications and are therefore not commercially available. South African subjects will be counselled to use one of the alternative double-barrier methods specified above, and this will also be specified in the country-specific informed consent form.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed via dipstick test only for women of childbearing potential before dosing at each infusion visit and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures (Appendix A). In addition to a negative urine hCG pregnancy test at screening, female subjects also must have a negative urine hCG pregnancy test prior to receiving each IV dosing. If at screening, a subject has had a pregnancy test in the last 24 hours, the results of that test can be used and the test does not need to be readministered.

9.1.12 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and vedolizumab should be immediately discontinued. In addition, any pregnancies in the partner of a male subject

during the study or for 18 weeks after the last dose of study medication should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of study medication (after enrollment visit) or within18 weeks of the last dose of study medication, a pregnancy notification form should be completed and the pregnancy should be reported immediately to the contact listed in Section 1.0.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All pregnancies in subjects will be followed up to final outcome, using the pregnancy notification form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.13 Documentation of Baseline/Enrollment Failure

Investigators must account for all subjects who sign an informed consent.

If the subject is found to be not eligible at the enrollment visit, the investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of baseline/enrollment failure.

The primary reason for baseline/enrollment failure is recorded in the eCRF using the following categories:

- AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Other, specify.

Subject numbers assigned to subjects who fail baseline/enrollment should not be reused.

9.1.14 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria specified in Section 7.1 and Section 7.2, respectively, are eligible for entrance into the treatment period.

If the subject is found to be not eligible for the treatment period, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.15 Collection of AEs and SAEs

AEs and SAEs will be collected from the time the subject signs the informed consent to participate in the study through to the final safety follow-up visit.

SAEs that occur after the end of study and are considered to be related to vedolizumab will be collected and forwarded to Takeda Pharmacovigilance (see Section 10.2). Definitions, documentation, and reporting of SAEs are described in detail in Section 10.0.

Details related to sample collection and analysis and collection of serum for PK sampling for the XAP-PK substudy are provided in Appendix E.

Details related to partial Mayo score and Harvey-Bradshaw Index Score for the XAP-PK substudy are provided in Appendix G and Appendix H, respectively.

9.2 Monitoring Subject Treatment Compliance

A vedolizumab dispensing log, including records of drug received from the sponsor and volume of vedolizumab dispensed to each subject intravenously, will be maintained by the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.3.1 Enrollment Visit 1

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria, the subject should be enrolled using the IVRS/IWRS as described in Section 8.2. See Section 9.1.13 for procedures for documenting baseline/enrollment failures.

Procedures to be completed at the enrollment visit for the XAP study can be found in the Schedule of Study Procedures (Appendix A). Subjects will be given infusion instructions for the first dose of study medication as described in Section 8.1.3.

Details related to enrollment visit 1 for the XAP-PK substudy are provided in Appendix E and study procedures for XAP-PK substudy are provided in Appendix F.

9.3.2 Treatment Period

Subjects entering the XAP study will receive Q8W dosing.

The first dose of vedolizumab in this study should occur 8 weeks (±7 days) after the last dose of study medication in the qualifying study. Further details related to dosing and regimen have been provided in Section 8.1.3.

Subjects entering from a qualifying study in which the subject was on a more frequent dose can 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.

The subjects will visit an infusion center for their infusion as per the dosing regimen. Procedures to be completed at infusion visits can be found in the Schedule of Study Procedures

(Appendix A). AEs will be collected at each visit. Details of COVID-19-related visit window changes are provided in Section 9.3.7.

Subjects will continue in the XAP study until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner. Subjects will return 18 weeks after their final study infusion for a safety follow-up visit.

Details related to treatment period for the XAP-PK substudy are provided in Appendix E.

9.3.3 Final Infusion Visit

Within 60 days of the subject having access to vedolizumab through commercial channels, including reimbursement, for the subject's clinical scenario, the subject should have the final study infusion visit.

9.3.4 Routine or Unscheduled Office Visits

During the course of the study, subjects will continue to be treated by their physician. Any AEs discovered during routine or unscheduled office visits must be reported.

The visit details will be captured in the eCRF.

9.3.5 Post Study Care

Subjects will remain in the study until vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario or until subject withdrawal, whichever is sooner. There will be a follow-up safety visit for the subjects 18 weeks after the subject's final study dose. 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 the availability of vedolizumab or they withdrew from the study for other reasons). Procedures to be completed at the safety follow-up visit can be found in the Schedule of Study Procedures (Appendix A).

9.3.6 Follow-up Period

Procedures to be completed during the follow-up period in the main XAP study can be found in the Schedule of Study Procedures (Appendix A).

Details related to follow-up period for the XAP-PK substudy are provided in Appendix E.

9.3.7 COVID-19-Related Protocol Considerations/Mitigations

On a temporary basis, in order to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic, subjects who may be impacted should contact the principal investigator to determine the best course of action. Depending on the impact, in some cases it may be possible to arrange for alternative solutions as permitted by local regulations [28,29]. Any decision on procedural changes should

be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical monitor, while maintaining subject safety and confidentiality as the priority.

Missing data, remote visits, changes to assessment approaches, and altered visit windows during the COVID-19 public health emergency may affect the study results. Thus, it is important to identify all protocol deviations and altered data collection (ie, remote data collection or missing data points) or assessment methods. It is crucial that any deviations related to COVID-19 be clearly identified as such in the eCRF.

The following procedural changes may be considered:

- Scheduling of study visits: If modifications to the study visits schedule are necessary, the investigator must submit notification via the PPD electronic Protocol Inquiry Platform (ePIP) system for medical monitor's review. Each modification will be evaluated on a case-by-case basis to assess safety concerns/risk to the subject, as well as study impact. The medical monitor's review will be documented within the ePIP system. The investigator's clinical expertise and discretion as it pertains to the health and wellbeing of the subject, as well as familiarity with local conditions, will ultimately determine the best course of action for the subject, including whether the subject can safely remain in the study to complete the study procedures per protocol.
  - The acceptable windows for study visits and study drug dosing may be expanded as follows:
    i) Q4W regimen: from every 4 weeks (±7 days) to every 4 weeks (±10 days).
    ii) Q8W regimen: from every 8 weeks (±7 days) to every 8 weeks (±14 days).
- If a subject is unable to physically report to the site for required study visits (to complete any of the study procedures in whole or in part), remote visits/checks (if appropriate) may be performed by the investigator via phone contacts and missing procedures will be captured as protocol deviations. Two or more consecutive missed infusion visits/checks, or a missed safety follow-up visit, will be considered as significant deviations. In the event of 2 consecutive missed infusion visits, the subject's further study participation will be based on the investigator's opinion that the subject would derive benefit from vedolizumab if continued in the study and there were no safety concerns. The investigator must submit notification via the PPD ePIP system for medical monitor's approval before the subject could restart study medication. All collected data will be recorded in the subject's medical record and captured within the eCRF, as applicable. As a check on subject's safety and wellbeing, at minimum, sites will attempt to collect the following data per the protocol:
  - Assessment for continued eligibility (Section 9.1.3).
  - Documentation of concomitant medications (Section 9.1.10).
  - Confirm contraception and pregnancy avoidance procedures (Section 9.1.11) and pregnancy reporting responsibilities (Section 9.1.12).

  - Collection of AEs, SAEs, and AESIs (Section 9.1.15 and Section 7.5.1). (Note: If a subject has a known infection of COVID-19 and was deemed serious (based on the SAE criteria [Section 10.1.4]), then the event will be recorded as an AESI. If the subject is asymptomatic or having mild symptoms, then the event will be recorded only as an AE.)

- In the event a subject misses the site visit(s), the following scenarios may be considered while rescheduling missed visits:
  - If a subject misses 1 site visit: The subject should be brought back within the acceptable window and as close to their originally planned dose regimen as possible.
  - If a subject misses ≥2 site visits: The subject should be brought back as soon as possible and their originally planned dose regimen will resume from that point forward.
    - In all cases, the investigator's judgment and knowledge about the subject's individual scenario will be relied upon. The investigator must submit notification via the PPD ePIP system for medical monitor's review once the visit date has been rescheduled.
- If sites are unable to adhere to the planned infusion schedule, subjects may be transferred to investigational sites away from risk zones to complete required visits, provided that the mitigation plan has been reviewed in advance by Takeda and the following criteria are met:
  - Study drug accountability, preparation, handling, and administration is performed, and documented, in accordance with the study protocol and approved Pharmacy Manual.
  - All study related activities are conducted only by qualified study staff who have been trained on the protocol and have been delegated by the investigator to perform specific study tasks.
  - Any deviations are documented and reported to PPD (and captured within the eCRF, as appropriate), as well as notified to the regulatory authorities as locally applicable.
  - All relevant data are reported in the subject's medical record and captured within the eCRF.

Note: Reversal of COVID-19-related allowances may be permitted in countries where measures are in place to maintain subject safety and to ensure study integrity and within the timelines specified per country regulations.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.2 Product Complaint

A product complaint (PC) is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product and/or device (eg, prefilled syringe).

An investigator who is made aware of or identifies a potential PC should immediately report the event to Takeda in accordance with the contact list provided to the site. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from a Takeda representative.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions of underlying disease should not be considered AEs.)

- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be

recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays, etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an ongoing AE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators

should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires subject HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

AE: adverse event.

AEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Section 10.2.2 and Section 10.3).

10.1.5 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.9 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE; eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.
- Dosing Frequency – the dosing frequency could be increased to qualifying study dosing regimen as agreed between the medical monitor and investigator on clinical justification, such as AEs, including flares or if the subject loses efficacy on Q8W dosing. The dosing

frequency will be decreased to every 8 weeks for subjects who were on prior study dosing regimen other than Q8W dosing in the qualifying studies or for subjects whose dosing frequency was changed to qualifying study dosing due to AEs, including flares as per investigator's discretion.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/ symptoms, or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

AEs from the qualifying study which are ongoing at the time of signing informed consent to participate in this study will not be collected as AEs in this study but will be captured as concurrent medical conditions (see Section 9.1.5).

Collection of AEs will commence from the time that the subject signs the informed consent to participate in the study. Routine collection of AEs will continue until the final safety follow-up visit.

10.2.1.2 AE Reporting

At each infusion visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious ongoing AE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious ongoing AEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to study drug. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time (if available).
3. Intensity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for ongoing AEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for ongoing AEs).
7. Outcome of event.
8. Seriousness.

10.2.1.3 Special Interest AE Reporting

If an AESI, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria in Section 7.5, it should be recorded in a special interest AE eCRF or SAE form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

The special interest AEs have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor/the clinical contract research organization (CRO) within 24 hours.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

A Takeda SAE eCRF or SAE form must be completed in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject ID number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE eCRF should be completed within 24 hours of first onset or notification of the event. However, as a back-up, if required, the SAE form should be completed and reported to Takeda Pharmacovigilance or designee within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal LFT

If a subject is noted to have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevated >3 × upper limit of normal (ULN) on 2 consecutive occasions during routine blood collection by the attending physician, the abnormality should be recorded as an AE. In addition, if LFT increases, eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. In addition, if LFT increases, eCRF must be completed and transmitted with the Takeda SAE form.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately to the sponsor (within 24 hours of receipt). Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or its designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, adjudication committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary (WHODRUG).

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor or delegated CRO will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

The eCRFs will be remotely reviewed for completeness and acceptability by study monitors periodically. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media, such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable,

thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents as follows:

1. The day on which marketing approval of the study medication is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued).
2. The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A 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.

13.1.1 Analysis Sets

The full analysis set (FAS) will include all enrolled subjects who receive at least 1 dose of study medication and will be used for the safety analyses.

Details related to analysis set for the XAP-PK substudy are provided in Appendix E.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. For continuous variables, summary statistics (nonmissing values, mean, median, standard deviation, minimum, and maximum) will be generated. For categorical variables, the counts and percentages of each possible value will be generated.

Medical history and concurrent medical conditions will be summarized by system organ class (SOC) and preferred term (PT). Medication history and concomitant medications will be summarized by PT.

13.1.3 Efficacy Analysis

No efficacy analyses are planned for this XAP study.

13.1.4 Safety Analysis

Safety analysis will be summarized using the FAS.

All analyses will be descriptive, and no formal statistical hypothesis testing is to be performed.

Safety evaluations will be based on incidence, intensity and type of AEs, and vital signs. Descriptive statistics will be calculated.

The number and percentage of subjects with treatment-emergent adverse events (TEAEs, defined as any AEs, regardless of relationship to study medication), AESIs (ie, serious infections, including opportunistic infections, such as PML, malignancies, liver injury, infusion-related hypersensitivity reactions, and injection site reactions), AEs leading to discontinuation, and SAEs that occur from the time of signing informed consent form and up to the safety follow-up visit will be summarized by MedDRA SOC, high-level term (HLT), and PT overall, by intensity,

and by relationship to study medication. Separate summaries will also be generated for TEAEs overall and by intensity.

To summarize the number of subjects with AEs, subjects reporting the same event more than once will have that event counted only once within each SOC, HLT, and PT. All AEs will be presented in separate data listings. Exposure-adjusted AEs will also be presented.

Absolute values and change from baseline in vital sign measurements will be summarized. Vital sign data will be presented in data listings.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for this XAP study.

However, interim looks at study data to review safety and treatment persistence of study subjects might be done.

13.3 Determination of Sample Size

The main XAP study is not sized based on power considerations. The number of subjects will be determined as discussed in Section 6.2.

Details related to substudy analysis for the XAP-PK substudy are provided in Appendix E.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring

The study site will be monitored remotely by the CRO periodically during the study to ensure that all aspects of the protocol are followed and will include an electronic data capture system, which has a set of automatic data checks with data queries for programmed data collection. There will be monitoring of study site by telephone to ensure that the study drug supplies have been provided and protocol instructions are well understood and applied.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or its designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or its designee for any significant deviation from the protocol.

Details of how to document COVID-19-related protocol deviations are provided in Section 9.3.7.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or its designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. The primary objective of the study is to monitor ongoing safety in subjects with UC and 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. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align their conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or its designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding their abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or its designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or its designee before commencement of the study (ie, before shipment of the sponsor-supplied study drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or

IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor. The study is being funded by Takeda. Payments for the conduct of the study that will be made to each study site and/or investigator will be specified in the Clinical Study Site Agreement.

All investigators and sub-investigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and sub-investigator before the study starts at their study site; in addition, any potential conflicts of interest that are not covered by this financial disclosure form should be disclosed separately to the sponsor prior to the start of the study at their site.

All institutional affiliations of the investigator and sub-investigator should be declared on their curriculum vitae, which must be provided to the sponsor prior to the start of the study.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), assent form (if applicable, eg, mentally incapacitated persons), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The ICF will detail the requirements of the subject and the fact that they are free to withdraw at any time without giving a reason and without prejudice to their further medical care. For a potential research subject who is deemed incapable of giving informed consent, but is able to give assent to decisions about participation in research, the principal investigator will be required to seek that assent in addition to the consent of the legally acceptable representative.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF, the assent form (if applicable), and the subject authorization form (if applicable). The ICF, subject authorization form (if applicable), assent form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), assent form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), assent form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the

event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent or assent to decisions about participation in research for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF, assent form (if applicable), and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF, assent form (if applicable), and subject authorization form (if applicable) at the time of consent and prior to the subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), assent form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), assent form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and its designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its medical monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires

the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator's name, address, and phone number to the callers requesting trial information. Once subjects receive investigator's contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or its designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, they should contact the sponsor or its designee.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures for Main XAP Study

	XAP Procedures [a]		
	Enrollment Visit (Final Visit of Qualifying Study)	**Infusion Visit [b]**	**Safety Follow-up Visit [c]** (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 [d]	–
Demographics/medical and prior therapies/concurrent medical conditions	X	–	–
UC/CD history	X	–	–
Physical examination [e]	X [f]	–	–
Vital signs [g]	X [f]	X	X
Weight and BMI [g]	X [f]	X	X
Height	X [f]	–	–
Concomitant medications [h]	X	X	X
Pregnancy testing [i]	X [f]	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 [j]	X	X	X

AE: adverse event; AESI: adverse event of special interest; BMI: body mass index; CD: Crohn's disease; COVID-19: coronavirus disease 2019; hCG: human chorionic gonadotropin; IBD: inflammatory bowel disease; ID: identification; IV: intravenous; IVRS: interactive voice response system; IWRS: interactive web response system; PML: progressive multifocal leukoencephalopathy; SAE: serious adverse event; UC: ulcerative colitis; XAP: extended access program.

[a] At the time of this protocol amendment, the COVID-19 pandemic continues to affect the way clinical studies are being conducted such that alternative measures are being implemented to maintain subject safety and to ensure data quality and integrity. A detailed description of COVID-19-related protocol considerations/mitigations is provided in Section 9.3.7.

[b] 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). A detailed description is provided in Section 6.1.

[c] 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).

[d] At each visit, the investigator should assess the subject for continued eligibility (see Section 7.6) and determine if vedolizumab is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario.

[e] A symptom-directed physical examination will be performed at baseline. Any clinically significant findings on the physical examination will be recorded as AEs.

[f] 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.

[g] Should occur prior to dosing at infusion visits.

[h] 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 as detailed in Section 9.1.10.

[i] 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.
[j] 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. AEs from the qualifying study which are ongoing at the time of signing informed consent to participate in this study will not be as AEs collected in this study but will be captured as concurrent medical conditions.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572) that must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s).
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the medical monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may

discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from screening throughout the duration of the study. Regular pregnancy tests will be

performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. Male subjects must use adequate contraception (as defined in the informed consent) from screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.
27. For the XAP-PK substudy, a statement that results of the XAP-PK substudy will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Details Specific to XAP-PK Substudy

I. STUDY SUMMARY of XAP-PK SUBSTUDY

Name of Sponsor(s): Takeda Development Center Americas, Inc. USA Takeda Development Centre Europe Ltd., UK Takeda Development Centre Asia, Pte Ltd., Singapore	**Compound:** Vedolizumab IV	
Title of Protocol: Entyvio (Vedolizumab IV) Extended Access Program in Ulcerative Colitis and Crohn's Disease	**IND No.:** Not Applicable	**EudraCT No.:** 2016-000678-40
Study Number: Vedolizumab-4013	**Phase:** 3b/4	

Study Design:

Subjects entering the XAP from the C13008 clinical study will undergo a decrease in dosing frequency from every 4 week (Q4W) dosing to an every 8 week (Q8W) dosing regimen. Subjects making the transition between the 2 studies and moving to Q8W dosing may consent to take part in a pharmacokinetic (PK) substudy (XAP-PK). The XAP-PK substudy will assess the PK of vedolizumab (serum vedolizumab concentration and anti-vedolizumab antibodies [AVAs]) in subjects who move from Q4W dosing to Q8W dosing. Trough PK samples will be drawn immediately before the last dose in the C13008 study (T0), and in addition, before the first Q8W dose at Week 8 (T+1) and the second Q8W dose (T+2) at Week 16 (see Appendix F) to quantify PK at the new steady state for Q8W dosing. Should the subject lose clinical response to vedolizumab over time after the transition to Q8W dosing, further trough blood samples will be drawn for PK immediately prior to first dose after decision to return to Q4W dosing (T'0) and in addition before the next 2 doses (T'+1, T'+2), to quantify PK at the new steady state for Q4W dosing. The XAP-PK substudy will also assess the proportion of subjects who move from Q4W dosing to Q8W dosing and remain on Q8W dosing through to Week 56/End of Substudy Visit. Vedolizumab PK will also be described based on trough concentrations by baseline subject factors influencing variability in subjects who remain on Q8W dosing, as well as those who return to Q4W dosing, either regaining response or not.

Objectives:

XAP-PK Substudy Exploratory Objectives:

To assess drug concentration during changes in dosing regimens in subjects who stay on Q8W dosing through Week 56/End of Substudy Visit, subjects who return to Q4W dosing and regain clinical response, and subjects who return to Q4W dosing and do not regain clinical response.

To understand the effects of AVAs on a subject's ability to maintain or regain clinical response during changes in dosing regimens in subjects who stay on Q8W dosing through Week 56/End of Substudy Visit, subjects who return to Q4W dosing and regain clinical response, and subjects who return to Q4W dosing and do not regain clinical response.

To understand the proportion of subjects who maintain clinical response during a change in dosing regimen from Q4W dosing to Q8W dosing in subjects who stay on Q8W dosing through Week 56/End of Substudy Visit.

To describe vedolizumab PK based on trough concentrations by baseline subject characteristics influencing variability.

To assess predose serum drug concentration and AVA in relation to efficacy and safety.

Number of Subjects:

Subjects who consent and qualify for the XAP study and are transitioning off the C13008 study will be offered

the opportunity to participate in the XAP-PK substudy (applicable for countries in which the XAP-PK substudy is available). No statistical assumption was used to estimate the sample size for the XAP-PK substudy. The number will be based on the number of subjects who consent and qualify for the XAP-PK substudy.

Period of Evaluation:

In the XAP-PK substudy, the subjects will be followed until Week 56 or a decision is made to change the subjects' dosing regimen, the subject stops vedolizumab, or the subject withdraws from the study, whichever comes first. If at Week 56, the subject is still awaiting a T'+1 and/or a T'+2 sample, the subject will be followed until the T'+2 sample is collected and T' +2 will become the End of Substudy Visit and no additional samples will be collected.

The End of Substudy/Week 56 visit should be scheduled in conjunction with a regular infusion visit of the Main XAP study (may or may not be exactly at Week 56 of the substudy but at the infusion visit closest to Week 56 from T0).

If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit.

Trough PK draws for the initial Q4W dosing to Q8W dosing transition occur prior to dosing at T0, T+1, and T+2:

T0 = Week 0 – Last Q4W dose in C13008
T+1 = Week 8 – 1st Q8W dose
T+2 = Week 16 – 2nd Q8W dose

Trough PK draws for change in dosing regimen from Q8W to Q4W dosing occur predose at T'0, T'+,1 and T'+2:

T'0 = First dose after decision to return to Q4W dosing
T'+1 = 1st Q4W dose (4 weeks after T'0)
T'+2 = 2nd Q4W dose (8 weeks after T'0)

Main Criteria for Inclusion:

Additional XAP-PK Substudy Inclusion Criteria:

Received vedolizumab during participation in the C13008 study.

The subject will start the main XAP study on Q8W dosing.

The subject or, when applicable, the subject's legally acceptable representative, has signed and dated a written informed consent form for the procedures related to the XAP-PK substudy.

Main Criteria for Evaluation and Analyses:

XAP-PK Substudy Exploratory Endpoints:

- Summary statistics of predose serum drug concentration between T0 (immediately prior to last dose in C13008) and T+2 (Week 16: immediately prior to second Q8W dose) for those who remain on Q8W dosing through Week 56/End of Substudy Visit.
- Summary statistics of predose serum drug concentration between T'0 (immediately prior to first dose after decision to return to Q4W dosing) and T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and regain clinical response through Week 56/End of Substudy Visit.
- Summary statistics of predose serum drug concentration between T'0 (immediately prior to first dose after decision to return to Q4W dosing) and T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and do not regain clinical response through Week 56/End of Substudy Visit.

- Summary statistics of predose serum drug concentration at available on-treatment time points and at time at which decision is made to stop vedolizumab for subjects who stop taking vedolizumab prior to Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at T0 (immediately prior to last dose in C13008), T+1 (Week 8), and at T+2 (Week 16: immediately prior to second Q8W dose) for those who remain on Q8W dosing through Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at T'0 (immediately prior to first dose after decision to return to Q4W dosing), T'+1 (4 weeks after T'0 and immediately prior to first Q4W dose), and at T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and regain clinical response through Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at T'0 (immediately prior to first dose after decision to return to Q4W dosing), T'+1 (4 weeks after T0 and immediately prior to first Q4W dose), and at T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and do not regain clinical response through Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at available on-treatment time points and at time at which decision is made to stop vedolizumab for subjects who stop taking vedolizumab prior to Week 56/End of Substudy Visit.
- Proportion of subjects who, after moving to Q8W dosing from Q4W dosing, remain on Q8W dosing through Week 56/End of Substudy Visit.
- Describe vedolizumab PK based on trough concentrations by baseline subject characteristics influencing variability.
- Summary statistics of predose serum drug concentration and AVA status in relation to efficacy and safety.

Statistical Considerations:

XAP-PK Substudy:

This XAP-PK substudy is not sized based on power considerations. As for the main study, all analyses will be descriptive and no formal statistical hypothesis testing is to be performed. Predose serum concentrations of vedolizumab and maximum AVA titer will be summarized descriptively by collection time points. All proportion-based endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion. Partial Mayo score, Harvey-Bradshaw Index score, C-reactive protein assessment, albumin levels, and white blood cells will be also summarized descriptively by collection time points.

RATIONALE FOR THE XAP-PK SUBSTUDY

Subjects entering the extended access program (XAP) from the C13008 clinical study will undergo a decrease in dosing frequency from every 4 week (Q4W) dosing to every 8 week (Q8W) dosing. Subjects making the transition between the 2 studies and moving to Q8W dosing may consent to take part in a pharmacokinetic (PK) substudy (XAP-PK).

The XAP-PK substudy will assess the PK of vedolizumab (serum vedolizumab concentration and anti-vedolizumab antibodies [AVAs]) in subjects who move from Q4W dosing to Q8W dosing. Trough PK samples will be drawn immediately before the last dose in the C13008 study (T0), and in addition before the first Q8W dose at Week 8 (T+1) and the second Q8W dose (T+2) at Week 16 (see Appendix F) to quantify PK at the new steady state for Q8W dosing. Should the subject lose clinical response to vedolizumab over time after the transition to Q8W

dosing, further trough blood samples will be drawn for PK (T0) immediately prior to first dose after decision to return to Q4W dosing (T'0) and in addition before the next 2 doses (T'+1, T'+2), to quantify PK at the new steady state for Q4W dosing. Vedolizumab PK will also be described based on trough concentrations by baseline subject factors influencing variability in subjects who remain on Q8W dosing, as well as those who return to Q4W dosing, either regaining response or not.

The XAP-PK substudy will also assess the proportion of subjects who move from Q4W dosing to Q8W dosing and remain on Q8W dosing through to Week 56/End of Substudy Visit. During the development program, information regarding the outcome of switching subjects from Q4W dosing to Q8W dosing after they achieved clinical remission was not available. This information is considered critical for the understanding of PK-efficacy relationship of vedolizumab.

EXPLORATORY OBJECTIVES FOR XAP-PK SUBSTUDY

- To assess drug concentration during changes in dosing regimens in subjects who stay on Q8W dosing through Week 56/End of Substudy Visit, subjects who return to Q4W dosing and regain clinical response, and subjects who return to Q4W dosing and do not regain clinical response.
- To understand the effects of AVAs on a subject's ability to maintain or regain clinical response during changes in dosing regimens in subjects who stay on Q8W dosing through Week 56/End of Substudy Visit, subjects who return to Q4W dosing and regain clinical response, and subjects who return to Q4W dosing and do not regain clinical response.
- To understand the proportion of subjects who maintain clinical response during a change in dosing regimen from Q4W dosing to Q8W dosing in subjects who stay on Q8W dosing through Week 56/End of Substudy Visit.
- To describe vedolizumab PK based on trough concentrations by baseline subject characteristics influencing variability.
- To assess predose serum drug concentration and AVA in relation to efficacy and safety.

EXPLORATORY ENDPOINTS FOR XAP-PK SUBSTUDY

- Summary statistics of predose serum drug concentration between T0 (immediately prior to last dose in C13008) and T+2 (Week 16: immediately prior to second Q8W dose) for those who remain on Q8W dosing through Week 56/End of Substudy Visit.
- Summary statistics of predose serum drug concentration between T'0 (immediately prior to first dose after decision to return to Q4W dosing) and T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and regain clinical response through Week 56/End of Substudy Visit.
- Summary statistics of predose serum drug concentration between T'0 (immediately prior to first dose after decision to return to Q4W dosing) and T'+2 (8 weeks after T'0 and

immediately prior to the second Q4W dose) for those who return to Q4W dosing and do not regain clinical response through Week 56/End of Substudy Visit.

- Summary statistics of predose serum drug concentration at available on-treatment time points and at time at which decision is made to stop vedolizumab for subjects who stop taking vedolizumab prior to Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at T0 (immediately prior to last dose in C13008), T+1 (Week 8), and at T+2 (Week 16: immediately prior to second Q8W dose) for those who remain on Q8W dosing through Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at T'0 (immediately prior to first dose after decision to return to Q4W dosing), T'+1 (4 weeks after T'0 and immediately prior to first Q4W dose), and at T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and regain clinical response through Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at T'0 (immediately prior to first dose after decision to return to Q4W dosing), T'+1 (4 weeks after T'0 and immediately prior to first Q4W dose), and at T'+2 (8 weeks after T'0 and immediately prior to the second Q4W dose) for those who return to Q4W dosing and do not regain clinical response through Week 56/End of Substudy Visit.
- The maximum AVA titer and proportion of subjects with each AVA status at available on-treatment time points and at time at which decision is made to stop vedolizumab for subjects who stop taking vedolizumab prior to Week 56/End of Substudy Visit.
- Proportion of subjects who, after moving to Q8W dosing from Q4W dosing, remain on Q8W dosing through Week 56/End of Substudy Visit.
- Describe vedolizumab PK based on trough concentrations by baseline subject characteristics influencing variability.
- Summary statistics of predose serum drug concentration and AVA status in relation to efficacy and safety.

STUDY DESIGN AND DESCRIPTION OF XAP-PK SUBSTUDY

i. Study Design of the XAP-PK Substudy

Subjects entering the XAP from the C13008 clinical study will undergo a decrease in dosing frequency from Q4W dosing to an Q8W dosing regimen. Subjects making the transition between the 2 studies and moving to Q8W dosing may consent to take part in a PK substudy (XAP-PK). The XAP-PK substudy will assess the PK of vedolizumab (serum vedolizumab concentration and AVAs) in subjects who move from Q4W dosing to Q8W dosing. Trough PK samples will be drawn immediately before the last dose in the C13008 study (T0), and in addition, before the first

Q8W dose at Week 8 (T+1) and the second Q8W dose (T+2) at Week 16 (see Appendix F) and at Week 56/End of Substudy to quantify PK at the new steady state for Q8W dosing. Should the subject lose clinical response to vedolizumab over time after the transition to Q8W dosing, further trough blood samples will be drawn for PK immediately prior to first dose after decision to return to Q4W dosing (T'0) and in addition before the next 2 doses (T'+1, T'+2), to quantify PK at the new steady state for Q4W dosing. The XAP-PK substudy will also assess the proportion of subjects who move from Q4W dosing to Q8W dosing and remain on Q8W dosing through to Week 56/End of Substudy. Vedolizumab PK will also be described based on trough concentrations by baseline subject factors influencing variability in subjects who remain on Q8W dosing, as well as those who return to Q4W dosing, either regaining response or not consenting subjects who meet the eligibility criteria will have blood drawn and assessments taken (body mass index [BMI], partial Mayo score; Appendix G, Harvey-Bradshaw Index [HBI] score; Appendix H) prior to the final C13008 study dose (Day 1). Subjects remaining on Q8W dosing at Week 8 will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score) prior to their first Q8W dose (T+1). Subjects remaining on Q8W dosing through Week 16 will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score) prior to their second Q8W dose (T+2) (see below for details).

If at any time during the 56 weeks of the XAP-PK substudy, the subject changes dosing regimens from Q8W dosing to Q4W dosing, the subject will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score) immediately prior to the first dose after the decision to return to Q4W (T'0). Four weeks later at the first dose of the new dosing schedule (T'+1), the subject will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score) prior to the dose. If they remain on the new dosing schedule, they will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score) immediately prior to the second dose of the new dosing schedule (T'+2).

At any time during the course of the XAP-PK substudy (56 weeks), if a subject stops taking vedolizumab, the subject, at the time the decision is made, will have an end of substudy visit. At the end of the substudy visit, the subject will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score). Additionally, every effort should be made to conduct an end of substudy visit on subjects who withdraw from the study.

Subjects who remain on vedolizumab at Week 56 will have an end of substudy visit at which they will have their blood drawn and assessments completed (BMI, partial Mayo score, HBI score), or if, by Week 56, the subject has had a T'0 draw due to a dose change and is awaiting a T'+1 and/or a T'+2 draw, the subject's last visit will be the visit at which the T'+2 draw is completed, a decision is made to change the subject's dosing regimen, the subject stops vedolizumab, or the subject withdraws from the study, whichever comes first.

If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit.

The XAP-PK substudy will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International Council for Harmonisation [ICH] guidelines).

A schedule of assessments is listed in Appendix F.

ii. Number of Subjects in XAP-PK Substudy

Subjects who consent and qualify for the XAP study and are transitioning off the C13008 study will be offered the opportunity to participate in the XAP-PK substudy (applicable for countries in which the XAP-PK substudy is available). No statistical assumption was used to estimate the sample size for the XAP-PK substudy. The number will be based on the number of subjects who consent and qualify for the XAP-PK substudy.

iii. Duration of Study of XAP-PK Substudy

In the XAP-PK substudy, the subjects will be followed until Week 56 or a decision is made to change the subjects' dosing regimen, the subject stops vedolizumab, or the subject withdraws from the study, whichever comes first. If at Week 56, the subject is still awaiting a T'+1 and/or a T'+2 sample, the subject will be followed until the T'+2 sample is collected.

The End of Substudy/Week 56 visit should be scheduled in conjunction with a regular infusion visit of the Main XAP study (may or may not be exactly at Week 56 of the substudy but at the infusion visit closest to Week 56 from T0).

If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit.

iv. Justification for Study Design, Dose, and Endpoints of XAP-PK Substudy

The XAP-PK substudy will evaluate the effect of decreasing the dosing frequency on the serum drug concentrations of vedolizumab, AVA titers, and maintenance of clinical response in subjects with UC or CD. The study will assess relationship between serum drug concentrations by subject characteristics influencing variability (BMI, disease type [UC or CD], C-reactive protein [CRP], white blood cell count [WBC], and albumin).

During the XAP-PK substudy, relevant information will be collected to help the characterization of the PK-efficacy relationship and factors that can potentially affect this relationship. Data from the pivotal vedolizumab GEMINI studies showed that median vedolizumab trough concentrations for subjects at steady state were around 10 µg/mL for Q8W dosing and 31 µg/mL for Q4W dosing. This substudy aims to identify if changing the dose frequency from every 4 weeks to every 8 weeks will have an impact on efficacy, and what factors might have an impact on clearance and clinical response

PREMATURE TERMINATION OR SUSPENSION OF STUDY OR INVESTIGATIONAL SITE OF XAP-PK SUBSTUDY

i. Criteria for Premature Termination or Suspension of XAP-PK Substudy

The XAP-PK substudy will be completed when the last subject completes the end of substudy visit. If one or more of the following criteria are satisfied, it may require temporary suspension or early termination the study:

- New information or other evaluation regarding the safety or efficacy of vedolizumab indicates a change in the known risk/benefit for vedolizumab, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the study objective or subject safety.
- Prior to the product becoming commercially available, another access program becomes available in the country of residence that will provide access to subjects outside of the study.
- The study is terminated at a site.
- The study is terminated by the sponsor.

SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS FOR XAP-PK SUBSTUDY

i. Additional Inclusion Criteria of XAP-PK Substudy

1. Received vedolizumab during participation in the C13008 study.
2. The subject will start the main XAP study on Q8W dosing.
3. The subject or, when applicable, the subject's legally acceptable representative, has signed and dated a written ICF for the procedures related to the XAP-PK substudy.

ii. Procedures for Discontinuation or Withdrawal of a Subject of XAP-PK Substudy

Subjects in the XAP-PK substudy may discontinue study participation at any time during the substudy when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the substudy. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, every effort should be made to conduct an end of substudy visit for subjects who are discontinued or who withdraw their participation.

STUDY PROCEDURES FOR XAP-PK SUBSTUDY

i. XAP-PK Substudy Informed Consent Procedure

A separate ICF pertaining to collection of blood for analysis, the storage of samples, and the assessments conducted must be obtained prior to performing any procedures related to the XAP-PK substudy. The provision of consent to collect and analyze the samples is independent of consent to the other aspects of the main XAP study. The signed ICF for the XAP-PK substudy will be taken at the enrollment visit along with the informed consent procedures for the XAP study.

ii. Weight, Height, and BMI Measurement in XAP-PK Substudy

Subjects in the XAP-PK substudy will have height measured at enrollment visit and weight measured at each of the visits for the calculation of BMI. The BMI should be derived as follows:

Metric: BMI = weight (kg) / [height (m^2)]

The values should be reported to 1 decimal place by rounding.

iii. Partial Mayo Score in XAP-PK Substudy

For subjects in the XAP-PK substudy with a diagnosis of UC, the partial Mayo score will be evaluated at the enrollment visit, at time points in which blood is drawn as is specified in Appendix G, and at the end of substudy visit. The partial Mayo score will be evaluated prior to the blood draw.

iv. Harvey-Bradshaw Index Score in XAP-PK Substudy

For subjects in the XAP-PK substudy with a diagnosis of CD, the HBI score will be evaluated at the enrollment visit, at time points in which blood is drawn as is specified in Appendix H and at the end of substudy visit. The data used to derive the HBI score (ie, clinical symptoms and physical examination findings) will be obtained prior to the blood draw.

v. Sample Collection and Analysis in XAP-PK Substudy

Subjects in the XAP-PK substudy will have samples taken at the enrollment visit (the last dosing visit of the C13008 study, prior to dosing), and in addition before the first Q8W dose at Week 8 and the second Q8W dose at Week 16. If, at any time during the XAP-PK substudy, the subject changes to Q4W dosing, the subject will have their blood drawn immediately prior to first dose after the decision to return to Q4W dosing (T'0). If they remain on the new dosing schedule for 2 doses, they will have samples taken immediately prior to the next 2 doses (T'+1 and T'+2). At Week 56 and if, at any time during the course of the XAP-PK substudy, a subject stops taking vedolizumab or withdraws from the study, an end of substudy visit should be conducted that includes sample collection. If the subject has had a T'0 draw due to a dose change prior to Week

56 and is awaiting a T'+1 or T'+2 draw, the subject's end of substudy visit will be the visit at which the T'+2 draw is completed.

Trough PK draws for the initial Q4W dosing to Q8W dosing transition occur prior to dosing at T0, T+1, and T+2:

T0 = Week 0 – Last Q4W dose in C13008

T+1 = Week 8 – 1st Q8W dose

T+2 = Week 16 – 2nd Q8W dose

Trough PK draws for change in dosing regimen from Q8W to Q4W dosing occur predose at T'0, T'+1, and T'+2:

T'0 = First dose after decision to return to Q4W dosing

T'+1 = 1st Q4W dose (4 weeks after T'0)

T'+2 = 2nd Q4W dose (8 weeks after T'0)

vi. Collection of Serum for Pharmacokinetic Sampling in XAP-PK Substudy

Bioanalytical methods:

Trough serum concentrations of vedolizumab will be measured by a validated sandwich enzyme-linked immunosorbent assay.

C-reactive protein assessment, albumin levels, and WBC:

Levels of CRP and albumin and WBC counts will be measured at all XAP-PK substudy visits specified in Appendix F. The samples for CRP and albumin level assessments and WBC will be obtained from the same blood draw done for the PK assessments.

Anti-vedolizumab antibodies:

Blood specimens for the assessment of AVAs will be collected as shown in the Schedule of Study Procedures (Appendix F). A sample will be assessed for neutralizing AVAs, if AVAs are detected.

Serum titers of AVA will be determined using a validated assay. Neutralizing AVAs will be determined using a validated assay. Please refer to the Study Manual for information on sample collection and preparation.

SCHEDULE OF OBSERVATIONS AND PROCEDURES OF XAP-PK SUBSTUDY

i. Enrollment Visit 1 in XAP-PK Substudy

Procedures to be completed at the enrollment visit for the XAP-PK substudy can be found in the Schedule of Study Procedures (Appendix F).

ii. Treatment Period in XAP-PK Substudy

Subjects in the XAP-PK substudy will visit the site/infusion center for blood draws and other assessments as detailed in Appendix F. Procedures to be completed at XAP-PK substudy visits can be found in the Schedule of Study Procedures (Appendix F).

If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit.

iii. Follow-up Period in XAP-PK Substudy

Procedures to be completed during the follow-up period can be found in the Schedule of Study Procedures (Appendix F).

In the XAP-PK substudy, the subjects will be followed until Week 56, or a decision is made to change the subjects' dosing regimen, the subject stops vedolizumab, or the subject withdraws from the study, whichever comes first. If at Week 56, the subject is still awaiting a T'+1 and/or a T'+2 sample, the subject will be followed until the T'+2 sample is collected.

The end of substudy/Week 56 visit should be scheduled in conjunction with a regular infusion visit of the Main XAP study (may or may not be exactly at Week 56 of the substudy but at the infusion visit closest to Week 56 from T0).

If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit.

STATISTICAL METHODS IN XAP-PK SUBSTUDY

i. Statistical and Analytical Plans in XAP-PK Substudy

Analysis set

The FAS-PK is the FAS within the XAP-PK substudy.

ii. Determination of Sample Size in XAP-PK Substudy

The XAP-PK substudy is not sized based on power considerations. The number of subjects will be determined as discussed earlier in Section ii.

iii. XAP-PK Substudy Analysis

Predose serum concentrations of vedolizumab and maximum AVA titer will be summarized descriptively by collection time points, and by whether the subject:

- Remains on Q8W dosing through Week 56/End of Substudy Visit.

- Returns to Q4W dosing and regains clinical response through Week 56/End of Substudy Visit.
- Returns to Q4W dosing and does not regain clinical response through Week 56/End of Substudy Visit.
- Stops taking vedolizumab prior to Week 56/End of Substudy Visit.

For all dichotomous endpoints, corresponding rates and 95% confidence intervals will be reported using the same analysis groups described above. All proportion-based endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion.

Partial Mayo score, HBI score, CRP assessment, albumin levels, and WBC will be also summarized descriptively by collection time points.

Appendix F Schedule of Study Procedures for XAP-PK Substudy

	XAP-PK Procedures		
	Enrollment Visit (Final Visit of Qualifying Study)	**XAP-PK Blood Draw Visit (b)**	**Week 56/End of Substudy visit (c)**
Visit Number:	**1**	–	–
Informed consent	X(d)	–	–
Assess inclusion/exclusion criteria	X(e)	–	–
Partial Mayo score (a)	X	X	X
HBI score (a)	X	X	X
C-reactive protein (a) (f)	X	X	X
Albumin (a) (f)	X	X	X
WBC (a) (f)	X	X	X
Trough vedolizumab concentration (a) (g)	X	X	X
AVA (a) (g)	X	X	X

(a) Should occur prior to dosing at infusion visits.
(b) During the course of the substudy, samples will be drawn at the following times:

1. Trough PK draws for the initial Q4W dosing to Q8W dosing transition occur prior to dosing at T0, T+1, and T+2:
   T0 = Week 0 – Last Q4W dose in C13008
   T+1 = Week 8 – 1st Q8W dose
   T+2 = Week 16 – 2nd Q8W dose
2. Trough PK draws for change in dosing regimen from Q8W to Q4W dosing occur predose at T'0, T'+1, and T'+2:
   T'0 = First dose after decision to return to Q4W
   T'+1 = 1st Q4W dose (4 weeks after T'0)
   T'+2 = 2nd Q4W dose (8 weeks after T'0)

(c) The XAP-PK end of substudy visit will be at the infusion visit closest to Week 56 unless:

1. The subject stops vedolizumab prior to Week 56 in which case the last end of substudy visit should coincide with the time at which it was decided to stop vedolizumab.
2. At Week 56, the subject has had a T'0 draw due to a dose change and is awaiting a T'+1 or T'+2 draw. In which case, the subject's end of substudy visit will be the visit at which the T'+2 draw is completed, the time point at which the subject stops vedolizumab, the time at which a decision is made to change the dosing regimen, or the subject withdraws from the study, whichever comes first.
3. If a subject exits the XAP study prior to Week 56 because they are moving on to commercially available and reimbursed product, the subject will also exit the XAP-PK substudy. The end of substudy visit will be conducted at the time of the final XAP dosing visit.

(d) The subjects interested in participating in the XAP-PK substudy will sign an additional informed consent at the XAP enrollment visit (last visit of C13008).

(e) Subjects consenting to the XAP-PK substudy will need to meet additional inclusion criteria as detailed in Appendix E.

(f) Obtained from the same blood draw sample done for the PK assessments (trough vedolizumab concentration).

(g) See laboratory manual for blood draw volume.

Appendix G Partial Mayo Score

Partial Mayo Scoring System for the Assessment of Ulcerative Colitis Activity [a]

Category
Stool frequency [b] 0 = Normal no. of stools for this patient 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Sub score, 0 to 3
Rectal bleeding [c] 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes Sub score, 0 to 3
Physician's global assessment [d] 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Sub score, 0 to 3

[a] Partial Mayo score ranges from 0–9 with higher scores indicating more severe disease.
[b] Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
[c] The daily bleeding score represents the most severe bleeding of the day.
[d] The physician's global assessment acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317(26):1625-9.

Appendix H Harvey-Bradshaw Index

Harvey-Bradshaw Scoring System for the Assessment of Crohn's Disease Activity

Category	Total
General Wellbeing 0 = Very Well 1 = Slightly Below Par 2 = Poor 3 = Very Poor 4 = Terrible	☐
Abdominal Pain 0 = None 1 = Mild 2 = Moderate 3 = Severe	☐
Number of Liquid Stools Per Day	☐
Abdominal Mass 0 = None 1 = Dubious 2 = Definite 3 = Definite and Tender	☐

Category	**Total**
Complications ***(score 1 per item)***	☐
☐ Arthralgia/Arthritis	
☐ Uveitis/Iritis	
☐ Erythema nodosum	
☐ Apthous ulcers	
☐ Pyoderma gangrenosum	
☐ Anal fissure	
☐ Draining fistula (eg, perianal, enterocutaneous, rectovaginal)	
☐ Perianal Abscess	
Final Score (add totals)	☐

Adapted from: Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1(8167):514.

Appendix I Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment 7. Italicized text represents the existing text from original protocol (dated 17 March 2016) that is being replaced or moved. Bold text represents the addition of the text. Minor grammatical changes (if any) are not shown.

Page 1, Sponsor

Existing Text

Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015
United States of America

Takeda Development Centre Europe Limited
61 Aldwych, London WC2B 4AE
United Kingdom

Takeda Development Centre Asia, Pte Limited
21 Biopolis Road, Nucleos North Tower, Level 4
Singapore 138567

Revised Text

Takeda Development Center Americas, Inc. **(TDC Americas)**
95 Hayden Avenue
Lexington, MA 02421
617-349-0200

Takeda Development Centre Asia, Pte**.** Limited
8 Marina Boulevard #15-01, Marina Bay
Financial Centre, Singapore 018981

Rationale for Amendment

[redacted].

To update current corporate addresses of TDC Americas and TDC Asia, Takeda sponsor companies.

Page 3, Approval

Existing Text

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD
[redacted]
Global Medical Affairs – Specialty GI

[redacted],
Global Statistics and Statistical Programming

[redacted], *MD*
[redacted], *Pharmacovigilance*

Revised Text

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD
[redacted]
Entyvio and IBD Programs
Global Medical Affairs – Specialty GI

[redacted]
GI Statistics
Statistical and Quantitative Sciences, Data Sciences Institute

Rationale for Amendment

Details of Takeda representatives were updated.

Page 17, Section 2.0

Existing Text

Name of Sponsor(s):
Takeda Development Center Americas, Inc. USA
Takeda Development Centre Europe Ltd., UK
Takeda Development Centre Asia, Pte Ltd., Singapore

Revised Text

Name of Sponsor(s):

Takeda Development Center Americas, Inc. **(TDC Americas)**

Takeda Development Centre Asia, Pte**. Limited,** Singapore

Rationale for Amendment

[redacted].

Page 22, Section 3.4

Existing Text

TDC Asia	Takeda Development Center Asia, Pte Ltd.
TDC Europe	*Takeda Development Centre Europe Ltd.*
TDC Americas	Takeda Development Center Americas, Inc.
TDC	*TDC Asia, TDC Europe and/or TDC Americas, as applicable*
Takeda	*TDC Asia, TDC Europe and/or TDC Americas, as applicable*

Revised Text

TDC Asia	Takeda Development **Centre** Asia, Pte**. Limited**
TDC Americas	Takeda Development Center Americas, Inc.
TDC	**TDC Asia and/or TDC Americas, as applicable**
Takeda	**TDC Asia and/or TDC Americas, as applicable**

Rationale for Amendment

[redacted].

Page 25, Section 4.1.2

Existing Text

As of *19 Nov 2016*, approximately *4200* subjects (*309 healthy subjects, 1811 subjects with UC, and 2138 subjects with CD, 3 subjects undergoing allogeneic-hematopoietic stem cell transplantation, 1 subject with pouchitis, and 2 subjects with melanoma*) have received at least 1 dose of vedolizumab across completed and ongoing company-sponsored interventional clinical studies (see current version of IB). Vedolizumab exposure in clinical studies has extended for ≥12 months in *1832* subjects, ≥24 months in *1379* subjects, ≥36 months in *1169* subjects, ≥48 months in *862* subjects, ≥60 months in *645* subjects, ≥72 months in *308* subjects, ≥84 months in *32* subjects, and ≥96 months in *22* subjects.

Vedolizumab has shown an acceptable safety based on an analysis of safety data from both completed and ongoing studies. The integrated summary of safety for the completed studies, as well as a summary of safety from the ongoing *phase 3 programs* (based on a data cut off of

19 Nov 2016), are detailed in the current version of the IB. As of *19 Nov 2016*, a total of *30* subjects who participated in vedolizumab clinical studies have died during the study or up to 2 years following the last dose of study drug (*Studies C13004, C13006, C13007, C13008, CCT-101, and Vedolizumab-1015*). The causes of death varied and additional information can be found in the current version of the IB. No cases of PML have been reported to date. Overall, vedolizumab IV was well tolerated in clinical studies.

Revised Text

As of **19 May 2021**, approximately **6949** subjects (**869** healthy subjects, **2782** subjects with UC, and **3022** subjects with CD, **213** subjects undergoing allogeneic-hematopoietic stem cell transplantation **or with acute graft-versus-host disease involving the intestinal tract**, **51 subjects with pouchitis,** and **1**2 subjects with melanoma) have received at least 1 dose of vedolizumab across completed and ongoing company-sponsored interventional clinical studies (see current version of IB). Vedolizumab exposure in clinical studies has extended for ≥12 months in **2957** subjects, ≥24 months in **1906** subjects, ≥36 months in **1474** subjects, ≥48 months in **965** subjects, ≥60 months in **717** subjects, ≥72 months in **477** subjects, ≥84 months in **308** subjects, ≥96 months in **271** subjects, **and ≥108 months in 201 subjects**.

Vedolizumab has shown an acceptable safety based on an analysis of safety data from both completed and ongoing studies. The integrated summary of safety for the completed studies, as well as a summary of safety from the ongoing phase 3/**3b and 3b/4** programs (based on a data cut off of 19 **May 2021**), are detailed in the current version of the IB. As of 19 **May 2021**, a total of **103** subjects who participated in vedolizumab clinical studies have died during the study or up to 2 years following the last dose of study drug. **Eight of the 103 subjects were being treated for UC and 14 subjects for CD** (Studies C13006, C13007, C13008, **C13011, MLN0002-3026, MLN0002SC-3027, MLN0002SC-3031**, **Vedolizumab-3034, Vedolizumab-4013, and Vedolizumab-4014**). The causes of death varied and additional information can be found in the current version of the IB. No cases of PML have been reported to date. Overall, vedolizumab IV was well tolerated in clinical studies.

Rationale for Amendment

Text updated as per the details in the latest IB. This change has been incorporated in Amendment 7.

Page 26, Section 4.3

Existing Text

An integrated safety analysis was conducted using data from completed *and unblinded* clinical studies *as of* 14 March 2013. This analysis of 237 healthy subjects and 2216 subjects with UC or CD demonstrated an acceptable safety for vedolizumab. The safety of vedolizumab through *19 November 2016* remains consistent with this integrated analysis and no new safety signals have been identified. Thus, vedolizumab has a favorable risk to benefit to date.

Revised Text

An integrated safety analysis was conducted using data from completed **vedolizumab** clinical studies **with a cut-off of** 14 March 2013. This analysis of 237 healthy subjects and 2216 subjects with UC or CD demonstrated an acceptable safety for vedolizumab. The safety **profile** of vedolizumab through 19 **May 2021** remains consistent with this integrated analysis and no new safety signals have been identified. Thus, vedolizumab has a favorable risk to benefit to date.

Rationale for Amendment

Text updated as per the details in the latest IB. This change has been incorporated in Amendment 7.

Page 29, Section 6.1

Existing Text

6.1 Study Design

Remain same

Revised Text

In the event a subject is unable to visit the site for required study visits in a timely manner (ie, within permitted visit windows), due to the coronavirus disease 2019 (COVID-19) pandemic, alternative procedural considerations or mitigation approaches may be followed to maintain subject safety and to ensure data quality and integrity (Section 9.3.7).

Rationale for Amendment

Due to the interruption from the COVID-19 pandemic, a risk and mitigation approach was finalized and provided in the protocol to maintain subject safety and to ensure data quality and integrity.

Page 30, Section 6.4

Existing Text

The benefit-to-risk of vedolizumab is favorable to date (as summarized in the IB, Edition *19* [Dated *Feb 2017*]) in the treatment of UC and CD. The proposed vedolizumab IV dose (300 mg every 8 weeks) is consistent with pivotal study data and the approved label information [26].

Revised Text

The benefit-to-risk of vedolizumab is favorable to date (as summarized in the IB, Edition **25** [Dated **14 July 2021**]) in the treatment of UC and CD. The proposed vedolizumab IV dose (300 mg every 8 weeks) is consistent with pivotal study data and the approved label information [26].

Rationale for Amendment

Date has been updated as per the latest IB.

Page 40, Section 9.1

Existing Text

Remain same

Revised Text

Details of COVID-19-related study procedural changes are provided in Section 9.3.7.

Rationale for Amendment

Text has been added to cross-refer details of COVID-19-related study procedural changes.

Page 42, Section 9.1.11

Existing Text

For male subjects:

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly; or vaginal ring plus male condom). (Protocol Amendment No. 1: the use of spermicides does not apply for South Africa. See footnotes below.) In addition, they must be advised not to donate sperm during this period *from signing of informed consent to 18 weeks after the last dose of study medication*.

Revised Text

For male subjects:

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, nonsterilized male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly; or vaginal ring plus male condom). (Protocol Amendment No. 1: the use of spermicides does not apply for South Africa. See footnotes below.) In addition, they must be advised not to donate sperm during this period**.

Rationale for Amendment

Deleted text related to sperm donation period for male subjects. This information has already been clarified at the beginning of the sentence.

Page 46, Section 9.3.2

Existing Text

Remain same

Revised Text

Details of COVID-19-related visit window changes are provided in Section 9.3.7.

Rationale for Amendment

Text has been added to cross-refer details of COVID-19-related visit window changes.

Page 46 through 48, Section 9.3.7

Existing Text

None (a new section was added in revised text)

Revised Text

9.3.7 COVID-19-Related Protocol Considerations/Mitigations

On a temporary basis, in order to maintain subject safety, confidentiality, and study integrity in the context of healthcare delivery challenges presented by the COVID-19 pandemic, subjects who may be impacted should contact and the principal investigator to determine the best course of action. Depending on the impact, in some cases it may be possible to arrange for alternative solutions as permitted by local regulations [28,29]. Any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical monitor, while maintaining subject safety and confidentiality as the priority.

Missing data, remote visits, changes to assessment approaches, and altered visit windows during the COVID-19 public health emergency may affect the study results. Thus, it is important to identify all protocol deviations and altered data collection (ie, remote data collection or missing data points) or assessment methods. It is crucial that any deviations related to COVID-19 be clearly identified as such in the eCRF.

The following procedural changes may be considered:

- **Scheduling of study visits: If modifications to the study visits schedule are necessary, the investigator must submit notification via the PPD electronic Protocol Inquiry Platform (ePIP) system for medical monitor's review. Each modification will be evaluated on a case-by-case basis to assess safety concerns/risk to the subject, as well as study impact. The medical monitor's review will be documented within the ePIP system. The investigator's clinical expertise and discretion as it pertains to the health and wellbeing of the subject, as well as familiarity with local conditions, will ultimately**

determine the best course of action for the subject, including whether the subject can safely remain in the study to complete the study procedures per protocol.

- **The acceptable windows for study visits and study drug dosing may be expanded as follows:**
  - **i) Q4W regimen: from every 4 weeks (±7 days) to every 4 weeks (±10 days).**
  - **ii) Q8W regimen: from every 8 weeks (±7 days) to every 8 weeks (±14 days).**

- **If a subject is unable to physically report to the site for required study visits (to complete any of the study procedures in whole or in part), remote visits/checks (if appropriate) may be performed by the investigator via phone contacts and missing procedures will be captured as protocol deviations. Two or more consecutive missed infusion visits/checks, or a missed safety follow-up visit, will be considered as significant deviations. In the event of 2 consecutive missed infusion visits, the subject's further study participation will be based on the investigator's opinion that the subject would derive benefit from vedolizumab if continued in the study and there were no safety concerns. The investigator must submit notification via the PPD ePIP system for medical monitor's approval before the subject could restart study medication. All collected data will be recorded in the subject's medical record and captured within the eCRF, as applicable. As a check on subject's safety and wellbeing, at minimum, sites will attempt to collect the following data per the protocol:**
  - **Assessment for continued eligibility (Section 9.1.3).**
  - **Documentation of concomitant medications (Section 9.1.10).**
  - **Confirm contraception and pregnancy avoidance procedures (Section 9.1.11) and pregnancy reporting responsibilities (Section 9.1.12).**
  - **Collection of AEs, SAEs, and AESIs (Section 9.1.15 and Section 7.5.1). (Note: If a subject has a known infection of COVID-19 and was deemed serious (based on the SAE criteria [Section 10.1.4]), then the event will be recorded as an AESI. If the subject is asymptomatic or having mild symptoms, then the event will be recorded only as an AE.)**

- **In the event a subject misses the site visit(s), the following scenarios may be considered while rescheduling missed visits:**
  - **If a subject misses 1 site visit: The subject should be brought back within the acceptable window and as close to their originally planned dose regimen as possible.**
  - **If a subject misses ≥2 site visits: The subject should be brought back as soon as possible and their originally planned dose regimen will resume from that point forward.**
    - **In all cases, the investigator's judgment and knowledge about the subject's individual scenario will be relied upon. The investigator must submit notification**

via the PPD ePIP system for medical monitor's review once the visit date has been rescheduled.

- **If sites are unable to adhere to the planned infusion schedule, subjects may be transferred to investigational sites away from risk zones to complete required visits, provided that the mitigation plan has been reviewed <u>in advance</u> by Takeda and the following criteria are met:**
  - **Study drug accountability, preparation, handling, and administration is performed, and documented, in accordance with the study protocol and approved Pharmacy Manual.**
  - **All study related activities are conducted only by qualified study staff who have been trained on the protocol and have been delegated by the investigator to perform specific study tasks.**
  - **Any deviations are documented and reported to PPD (and captured within the eCRF, as appropriate), as well as notified to the regulatory authorities as locally applicable.**
  - **All relevant data are reported in the subject's medical record and captured within the eCRF.**

Note: Reversal of COVID-19-related allowances may be permitted in countries where measures are in place to maintain subject safety and to ensure study integrity and within the timelines specified per country regulations.

<u>Rationale for Amendment</u>

Text has been added to update details of COVID-19-related study procedural changes.

<u>Page 62, Section 13.2</u>

<u>Existing Text</u>

No interim analysis is planned.

<u>Revised Text</u>

No interim analysis is planned **for this XAP study**.

However, interim looks at study data to review safety and treatment persistence of study subjects might be done.

<u>Rationale for Amendment</u>

Text has been updated to clarify that interim looks at study data to review safety and treatment persistence of study subjects might be done.

Page 63, Section 14.2

Existing Text

Remain same

Revised Text

Details of how to document COVID-19-related protocol deviations are provided in Section 9.3.7.

Rationale for Amendment

Text has been added to cross-refer details of COVID-19-related protocol deviations.

Page 71, Section 16

Existing Text

Remain same

Revised Text

28. European Commission, EMA, and Head of Medicines Agencies. Guidance on the management of clinical trials during the covid-19 (coronavirus) pandemic. Updated 4 February 2021. Accessed 13 September 2021. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

29. US FDA. Conduct of clinical trials of medical products during the covid-19 public health emergency: Guidance for industry, investigators, and institutional review boards. Updated 30 August 2021. Accessed 13 September 2021. Available at: https://www.fda.gov/media/136238/download.

Rationale for Amendment

Added 2 new references.

Page 72 and 73, Appendix A

Existing Text

Appendix A Schedule of Study Procedures

	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). A detailed description is provided in Section 6.1.
(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 (see Section 7.6) 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 as detailed in Section 9.1.10.
(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. AEs from the qualifying study which are ongoing at the time of signing informed consent to participate in this study will not be as AEs collected in this study but will be captured as concurrent medical conditions.
(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.

Revised Text

Appendix A Schedule of Study Procedures for Main XAP Study

	XAP Procedures [a]		
	Enrollment Visit (Final Visit of Qualifying Study)	**Infusion Visit** [b]	**Safety Follow-up Visit** [c] (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 [d]	–
Demographics/medical and prior therapies/concurrent medical conditions	X	–	–
UC/CD history	X	–	–
Physical examination [e]	X [f]	–	–
Vital signs [g]	X [f]	X	X
Weight and BMI [g]	X [f]	X	X
Height	X [f]	–	–
Concomitant medications [h]	X	X	X
Pregnancy testing [i]	X [f]	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 [j]	X	X	X

AE: adverse event; AESI: adverse event of special interest; BMI: body mass index; CD: Crohn's disease; COVID-19: coronavirus disease 2019; hCG: human chorionic gonadotropin; IBD: inflammatory bowel disease; ID: identification; IV: intravenous; IVRS: interactive voice response system; IWRS: interactive web response system; PML: progressive multifocal leukoencephalopathy; SAE: serious adverse event; UC: ulcerative colitis; XAP: extended access program.

[a] **At the time of this protocol amendment, the COVID-19 pandemic continues to affect the way clinical studies are being conducted such that alternative measures are being implemented to maintain subject safety and to ensure data quality and integrity. A detailed description of COVID-19-related protocol considerations/mitigations is provided in Section 9.3.7.**

[b] 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). A detailed description is provided in Section 6.1.

[c] 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).

[d] At each visit, the investigator should assess the subject for continued eligibility (see Section 7.6) and determine if vedolizumab

is available to the subject through commercial channels, including reimbursement, for the subject's clinical scenario.
[e] A symptom-directed physical examination will be performed at baseline. Any clinically significant findings on the physical examination will be recorded as AEs.
[f] **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.**
[g] Should occur prior to dosing at infusion visits.
[h] 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 as detailed in Section 9.1.10.
[i] 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.
[j] 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. AEs from the qualifying study which are ongoing at the time of signing informed consent to participate in this study will not be as AEs collected in this study but will be captured as concurrent medical conditions.

Rationale for Amendment

Added list of abbreviations and footnote text to cross-refer details of COVID-19-related protocol considerations/mitigations.

1.3 Protocol Amendment 6 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment 6.

The primary purpose of this amendment is to provide additional clarifications and include all changes made to the original version of the protocol (dated 17 March 2016). Full details regarding changes made to the text are given in Appendix I. Minor grammatical and editorial changes are included for clarification purposes only. The below table summarizes the main changes in the protocol.

Change in Protocol	**Rationale/Justification**	**Version of amendment (s) in which change was made effective**
Cover Page Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy); and Amendment 3 (Global)
Investigator Agreement Included language per DoH requirement.	To be fully compliant with this DoH requirement.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
Section 2.0 Summary Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy); and Amendment 3 (Global)
Section 2.0 Summary Included additional qualifying study	An additional qualifying study MLN0002-3028 was added along with the existing study C13008. Included to clarify the completion of qualifying study for enrolled subjects.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
Section 2.0 Summary Details related to subject's population and dose level have been modified for clarity.	Clarification added related to the window period of ±7 days with every dose administered to subject and dosing regimen permitted in the study. Text updated as per the modifications in respective sections within protocol main body text.	Amendment 6 (Global)
3.4 Corporate Identification Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy); and Amendment 3 (Global)
4.1.2 Vedolizumab IV 4.3 Risk: Benefit Assessment Updated number of subject received	Text updated as per details in the current version of the IB.	Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
and exposure duration details to vedolizumab till 19 Nov 2016.		
6.1 Study Design Included additional qualifying study and clarified study design text.	An additional qualifying study, MLN0002-3028 has been added along with the existing study C13008 for the main XAP study only.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
6.1 Study Design Included countries name and clarified study design text.	Text has been added to clarify the XAP study design related to dosing regimen permitted in the study and timepoint of first dose in the XAP study. Countries for XAP and XAP-PK studies have been clarified to avoid ambiguity for the sites involved in XAP-PK substudy. No subjects will be enrolled in the XAP-PK substudy from countries that are not specifically listed in the protocol. Similarly, no subjects will be rolled-over from the C13008 or MLN0002-3028 studies unless country name is specifically listed in protocol.	Amendment 6 (Global)
6.2 Number of Subjects Included additional text related to subject enrollment in XAP study.	Added clarification for the subject participation from the qualifying study to XAP study.	Amendment 6 (Global)
6.3 Duration of Study Included additional text related to study design text and study completion.	Text has been added to clarify the duration of the XAP study.	Amendment 6 (Global)
6.4 Justification for Study Design, Dose and Endpoints	Text updated as per details in the current version of the IB.	Amendment 6 (Global)
8.1.3. Dose and Regimen 8.2 Drug Dosing and Dispensing Procedures Included additional text related to dose regimen.	Text has been added to clarify the dose schedule and regimen along with window period of ±7 days with every dose.	Amendment 6 (Global)
8.4 Accountability and Destruction of Sponsor-Supplied Drugs Included additional text related to remote drug reconciliation and destruction	Text has been added to clarify that the drug reconciliation will be completed remotely and destruction can be carried out locally or by a contracted third party as per local regulations.	Amendment 6 (Global)
9.1.5 Documentation of Concurrent Medical Conditions Included text regarding the recording of ongoing AEs from qualifying study.	Added clarification that “ongoing AEs” from qualifying study, at the time of signing informed consent to participate in this XAP study, will be captured as a concurrent medical condition.	Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
9.1.7 Physical Examination Included text regarding procedures that have been conducted within last 24 hours.	Added clarification that if physical examination has been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
9.1.8 Vital Sign Procedure Included text regarding procedures that have been conducted within last 24 hours.	Added clarification that if vital sign measurements have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
9.1.9 Weight, Height, and BMI Included text regarding procedures that have been conducted within last 24 hours. In addition, BMI calculation details have been added.	Added clarification that if weight and height have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
9.1.11 Contraception & Pregnancy Avoidance Procedure Clarification that spermicides are not commercially available in South Africa. South African subjects will be counseled to use other double-barrier methods.	Clarification to support applicable double-barrier contraception and pregnancy avoidance procedures in South African trial sites.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
9.1.11 Contraception & Pregnancy Avoidance Procedure Included text regarding procedures that have been conducted within last 24 hours.	Added clarification that if pregnancy test result has been recorded within the last 24 hours at screening, the results of that test can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
9.1.15 Collection of AEs and SAEs Included text related to the time of collection of AEs and SAEs during the study.	Added clarification that AEs and SAEs will be collected from the time when the subject signs the informed consent to participate in the study through to follow-up visit.	Amendment 6 (Global)
9.3.2 Treatment Period Included text to clarify study treatment and completion period.	Text has been added to clarify the dose schedule and regimen.	Amendment 6 (Global)
9.3.6 Follow-up Period Included text to clarify study procedure to be followed at follow-up period.	Added clarification over the follow-up period and procedure to be followed.	Amendment 6 (Global)
10.1.3 Additional Points to Consider for AEs 10.1.5 Severity of AEs 10.2.1.2 AE Reporting	Added to reduce the ambiguity between the terminologies.	Amendment 6 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
13.1.4 Safety Analysis The term 'severity" of AEs changed to 'intensity' of AEs recorded during the study. Included text related to the time of collection of AEs and SAEs during the study.		
10.1.11 Action Concerning Study Medication Every 8-week changed to Q8W	Editorial change added for consistency and defining dosing schedule technically.	Amendment 6 (Global)
10.2.1.1 AE collection period Included text regarding the collection of ongoing AEs from qualifying study, and AEs during the study and safety follow-up. 13.1.4 Safety Analysis	Added clarification that ongoing AEs from qualifying study at the time of signing informed consent to participate in this study will be captured as a concurrent medical condition and AEs/SAEs will be collected from the time when the subject signs the informed consent to participate in the study, through study till safety follow-up visit.	Amendment 6 (Global)
15.0 Ethical Aspects of the Study Re-emphasized the objective of the global Extended Access Program (XAP).	Clarification to satisfy Declaration of Helsinki requirements.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
15.1 IRB and/or IEC Approval Added clarifications for funding, sponsors, institutional affiliations and potential conflicts of interest.	Clarification to satisfy Declaration of Helsinki requirements.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
15.2 Subject Information, Informed Consent, Subject Authorization Added references to the "assent form" for use if applicable, eg, mentally incapacitated persons or subjects deemed otherwise incapable of providing informed consent.	Clarification to satisfy Declaration of Helsinki requirements.	Amendment 1 (Local- South Africa only); Amendment 2 (Global – sites participating in XAP-PK substudy)
Appendix A Schedule of Study Procedures for Main XAP Study Included footnote to the procedures that are not required to be repeated if performed within 24 hours of the screening/enrollment visit and clarified the timing of the initial study visit for additional qualifying study.	To include the timing of the initial study visit for MLN0002-3028 and to clarify that the results of procedures that have been conducted in last 24 hours at enrollment visit can be used and the procedure does not need to be redone.	Amendment 3 (Global) and Amendment 4 (Global – sites participating in XAP-PK substudy)
Appendix A Schedule of Study Procedures for Main XAP Study	Footnotes have been reduced to remove redundancy.	Amendment 6 (Global)

Change in Protocol	**Rationale/Justification**	**Version of amendment (s) in which change was made effective**
Footnotes were shortened to remove repetitive details.	Details of XAP-PK substudy procedures moved to a separate Appendix F	
2.0 Summary Included details about XAP-PK substudy. 4.2.1 Rationale for XAP-PK Substudy 5.1.2 Exploratory Objectives for XAP-PK Substudy 5.2.2 Exploratory Endpoints for XAP-PK Substudy 6.1.1 Study Design of the XAP-PK Substudy 6.2 Number of Subjects 6.3 Duration of Study 6.4 Justification for Study Design, Dose, and Endpoints 6.5.1 Criteria for Premature Termination or Suspension of the Study 7.1 Inclusion Criteria 7.6 Criteria for Discontinuation or Withdrawal of a Subject 7.7 Procedures for Discontinuation or Withdrawal of a Subject 9.1.1.1 XAP-PK Substudy Informed Consent Procedure 9.1.9 Weight, Height, and BMI 9.1.16 Partial Mayo Score 9.1.17 Harvey-Bradshaw Index Score 9.1.18 Sample Collection and Analysis 9.3.1 Enrollment Visit 1 9.3.2 Treatment Period 9.3.6 Follow-up Period 13.1.1 Analysis Sets 13.3 Determination of Sample Size 13.4 XAP-PK Substudy Analysis Appendix E Details Specific to XAP-PK Substudy Appendix F Schedule of Study Procedures for XAP-PK Substudy	Details related to rationale, objectives, endpoints, study design, subjects, inclusion and withdrawal criteria, study procedures, and statistical considerations were added to explain XAP-PK substudy. All these changes are now described separately as XAP-PK substudy in Appendix E and schedule of study procedures for XAP-PK substudy are summarized in Appendix F. For XAP-PK substudy additional clarifications have been included to specify that end of substudy and Week 56 are same i.e. end of substudy visit/Week 56. Clarification that End of Sub-study/Week 56 visit should be scheduled in conjunction with a regular infusion visit of the Main study has been added. Mention of predictive models for XAP-PK substudy have been removed as they were added inadvertently	Amendment 2 (Global) and Amendment 6 (moved to separate Appendix) Amendment 5 (Global): Removed MLN0002-3028 from eligibility to participate in the XAP-PK substudy. It was added in error in Amendment 4. Subjects in MLN0002-3028 are not switching from Q4W to Q8W dosing and are therefore an inappropriate population for the substudy. Amendment 6 (Global)
Appendix C Elements of the Subject	To include a statement to cover the	Amendment 2 (Global)

Change in Protocol	Rationale/Justification	Version of amendment (s) in which change was made effective
Informed Consent	requirements for the XAP-PK substudy	
Appendix G Partial Mayo Score	Scale copy has been added for reference	Amendment 6 (Global)
Appendix H Harvey Bradshaw Index	Scale copy has been added for reference	Amendment 6 (Global)

1.3 Protocol Amendment 5 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment 5.

The primary purpose of this amendment is to remove MLN0002-3028 as a study eligible for the XAP-PK substudy. Full details regarding changes made to the text are given in Appendix E. Minor grammatical and editorial changes are included for clarification purposes only.

Change in Protocol	**Rationale/Justification**
Section 2.0 Summary Removed MLN0002-3028 as a qualifying study for the XAP-PK substudy.	MLN0002-3028 was included in the previous version in error. Subjects in MLN0002-3028 are not switching from once every 4 weeks (Q4W) to once every 8 weeks (Q8W dosing and are therefore an inappropriate population for the extended access program-pharmacokinetic (XAP-PK) substudy.
Section 4.2.1 Rationale for the XAP-PK Substudy Section 5.2.2 Exploratory Endpoints for XAP-PK Substudy Section 6.1.1Study Design of the XAP Substudy Section 6.2 Number of Subjects Section 7.1 Inclusion Criteria Section 9.1.18 Sample Collection and Analysis Removed reference to the inclusion of MLN0002-3028 in the XAP-PK substudy.	MLN0002-3028 was included in the previous version in error. Subjects in MLN0002-3028 are not switching from Q4W to Q8W dosing and are therefore an inappropriate population for the XAP-PK substudy.
Appendix A Schedule of Study Procedures Removed reference to the inclusion of MLN0002-3028 in the XAP-PK substudy in a footnote to the procedures table.	MLN0002-3028 was included in the previous version in error. Subjects in MLN0002-3028 are not switching from Q4W to Q8W dosing and are therefore an inappropriate population for the XAP-PK substudy.

1.3 Protocol Amendment 4 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment 4.

The primary purpose of this amendment is to add an additional qualifying study, MLN0002-3028, and to clarify the timing of the initial study visit for this additional study. Full details regarding changes made to the text are given in Appendix E. Minor grammatical and editorial changes are included for clarification purposes only.

Change in Protocol	**Rationale/Justification**
Section 2.0 Summary Included additional qualifying study	An additional qualifying study MLN0002-3028 was added along with the existing study C13008
Section 4.2.1 Rationale for the XAP-PK Substudy Section 5.2.2 Exploratory Endpoints for XAP-PK Substudy Section 6.2 Number of Subjects Section 7.1 Inclusion Criteria Section 9.1.18 Sample Collection and Analysis Included additional qualifying study	An additional qualifying study MLN0002-3028 was added along with the existing study C13008
Section 6.1 Study Design Section 6.1.1 Study Design of the XAP-PK Substudy Included additional qualifying study and clarified study design text	Text has been clarified for study design related to the XAP study and an additional qualifying study, MLN0002-3028, has been added along with the existing study C13008
Section 9.1.7 Physical Examination Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if physical examination has been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone
Section 9.1.8 Vital Sign Procedure Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if vital sign measurements have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone

Change in Protocol	**Rationale/Justification**
Section 9.1.9 Weight, Height, and BMI Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if weight and height have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone
Section 9.1.11 Contraception and Pregnancy Avoidance Procedure Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if pregnancy test result has been recorded within the last 24 hours at screening, the results of that test can be used and the procedure does not need to be redone
Section 10.2 to Section 12.2	Subsections rearranged as per original protocol for better readability
Appendix A Schedule of Study Procedures Included footnote to the procedures that are not required to be repeated if performed within 24 hours of the screening/enrollment visit and clarified the timing of the initial study visit for additional qualifying study.	To include the timing of the initial study visit for MLN0002-3028 and to clarify that the results of procedures that have been conducted in the last 24 hours at enrollment visit can be used and the procedure does not need to be redone.

1.3 Protocol Amendment 3 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment 3.

The primary purpose of this amendment is to add an additional qualifying study, MLN0002-3028 and to clarify the timing of the initial study visit for this additional study. Full details regarding changes made to the text are given in Appendix E. Minor grammatical and editorial changes are included for clarification purposes only.

Change in Protocol	Rationale/Justification
Cover Page Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.
2.0 Summary Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.
2.0 Summary Included additional qualifying study	An additional qualifying study MLN0002-3028 was added along with the existing study C13008
3.4 Corporate Identification Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.
6.1 Study Design Included additional qualifying study and clarified study design text	Text has been clarified for study design related to the XAP study and an additional qualifying study, MLN0002-3028 has been added along with the existing study C13008.
9.1.7 Physical Examination Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if physical examination has been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone
9.1.8 Vital Sign Procedure Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if vital sign measurements have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone
9.1.9 Weight and Height Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if weight and height have been conducted within the last 24 hours at the enrollment visit, the results of that test can be used and the procedure does not need to be redone

Change in Protocol	**Rationale/Justification**
9.1.11 Contraception and Pregnancy Avoidance Procedure Included text regarding procedures that have been conducted within last 24 hours	Added clarification that if pregnancy test result has been recorded within the last 24 hours at screening, the results of that test can be used and the procedure does not need to be redone
Appendix A Schedule of Study Procedures Included footnote to the procedures that are not required to be repeated if performed within 24 hours of the screening/enrollment visit and clarified the timing of the initial study visit for additional qualifying study	To include the timing of the initial study visit for MLN0002-3028 and to clarify that the results of procedures that have been conducted in last 24 hours at enrollment visit can be used and the procedure does not need to be redone.

1.3 Protocol Amendment 2 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment 2.

The primary purpose of this amendment is to add a pharmacokinetic (PK) substudy to the extended access program (XAP-PK). The protocol has also been updated to provide clarifications that satisfy all elements of the Declaration of Helsinki for use in the Vedolizumab-4013 study. Clarification is also outlined for the provision of study drug after the trial. Full details regarding changes made to the text are given in Appendix E. Minor grammatical and editorial changes are included for clarification purposes only.

Change in Protocol	**Rationale/Justification**
Cover Page Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.
Investigator Agreement Included language per Declaration of Helsinki requirement.	To be fully compliant with the Declaration of Helsinki requirement.
2.0 Summary Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.
2.0 Summary Included details about XAP-PK substudy.	Details related to study design, objectives, subjects, endpoints, and statistical considerations added to explain the procedures for substudy.
3.4 Corporate Identification Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in initial protocol version.

Change in Protocol	Rationale/Justification
4.2.1 Rationale for XAP-PK Substudy 5.1.2 Exploratory Objectives for XAP-PK Substudy 5.2.2 Exploratory Endpoints for XAP-PK Substudy 6.1.1 Study Design of the XAP-PK Substudy 6.2 Number of Subjects 6.3 Duration of Study 6.4 Justification for Study Design, Dose, and Endpoints 6.5.1 Criteria for Premature Termination or Suspension of the Study 7.1 Inclusion Criteria 7.6 Criteria for Discontinuation or Withdrawal of a Subject 7.7 Procedures for Discontinuation or Withdrawal of a Subject 9.1.1.1 XAP-PK Substudy Informed Consent Procedure 9.1.9 Weight, Height, and BMI 9.1.16 Partial Mayo Score 9.1.17 Harvey-Bradshaw Index Score 9.1.18 Sample Collection and Analysis 9.3.1 Enrollment Visit 1 9.3.2 Treatment Period 9.3.6 Follow-up Period 13.1.1 Analysis Sets 13.3 Determination of Sample Size 13.4 XAP-PK Substudy Analysis 13.5 Predictive Models	Details related to rationale, objectives, endpoints, study design, subjects, inclusion and withdrawal criteria, study procedures, and statistical considerations were added to explain XAP-PK substudy.

Change in Protocol	**Rationale/Justification**
9.1.11 Contraception and Pregnancy Avoidance Procedure Clarification that spermicides are not commercially available in South Africa. South African subjects will be counseled to use other double-barrier methods.	Clarification to support applicable double-barrier contraception and pregnancy avoidance procedures in South African trial sites.
15.0 Ethical Aspects of the Study Re-emphasized the objective of the global extended access program (XAP).	Clarification to satisfy Declaration of Helsinki requirements.
15.1 IRB and/or IEC Approval Added clarifications for funding, sponsors, potential conflicts of interest, and institutional affiliations.	Clarification to satisfy Declaration of Helsinki requirements.
15.2 Subject Information, Informed Consent, Subject Authorization Added references to the "assent form" for use if applicable, eg, mentally incapacitated persons or subjects deemed otherwise incapable of providing informed consent.	Clarification to satisfy Declaration of Helsinki requirements.
Appendix A Schedule of Study Procedures (Main XAP Study and XAP-PK Substudy) Included assessments for XAP-PK substudy.	To include the XAP-PK substudy procedures.
Appendix C Elements of the Subject Informed Consent	To include a statement to cover the requirements for the XAP-PK substudy.

1.3 Protocol Amendment 1 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 1.

The primary purpose of this amendment is to update the protocol to provide clarifications which satisfy all elements of the Declaration of Helsinki for use in the Vedolizumab-4013 study in the Republic of South Africa. Clarification is also outlined for the provision of study drug post-trial. Full details on changes of text are given in Appendix E.

Change in Protocol	Rationale/Justification
Cover Page Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.
Investigator Agreement Included language per DoH requirement.	To be fully compliant with this DoH requirement.
2.0 Summary Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.
3.4 Corporate Identification Included Takeda sponsor companies in the European and Asian regions.	This is a global study. Inadvertently omitted in Initial Protocol version.
9.1.11 Contraception & Pregnancy Avoidance Procedure Clarification that spermicides are not commercially available in South Africa. South African subjects will be counseled to use other double-barrier methods.	Clarification to support applicable double-barrier contraception and pregnancy avoidance procedures in South African trial sites.
15.0 Ethical Aspects of the Study Re-emphasized the objective of the global Extended Access Programme (XAP)	Clarification to satisfy Declaration of Helsinki requirements.
15.1 IRB and/or IEC Approval Added clarifications for funding, sponsors, institutional affiliations and potential conflicts of interest.	Clarification to satisfy Declaration of Helsinki requirements.

Change in Protocol	Rationale/Justification
15.2 Subject Information, Informed Consent, Subject Authorisation Added references to the "assent form" for use if applicable, eg, mentally incapacitated persons or subjects deemed otherwise incapable of providing informed consent.	Clarification to satisfy Declaration of Helsinki requirements.