CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761133Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA Resubmission to Complete Response
Application Number(s)	761133
Priority or Standard	Standard, Class 2 Resubmission
Initial Submit Date(s)	March 7, 2019
Initial Received Date(s)	March 7, 2019
Complete Response Action Date (Initial)	December 17, 2019
Resubmission Submit Date(s)	March 26, 2023
Resubmission Received Date(s)	March 27, 2023
Resubmission PDUFA Goal Date	September 27, 2023
Division/Office	Division of Gastroenterology
Review Completion Date	September 27, 2023
Established/Proper Name	Vedolizumab Injection
(Proposed) Trade Name	Entyvio and Entyvio Pen
Pharmacologic Class	Integrin receptor antagonist
Code name	MLN0002SC
Applicant	Takeda Pharmaceuticals, U.S.A., Inc.
Dosage form	• 108 mg/0.68 mL solution in a single-dose prefilled syringe with needle safety device • 108 mg/0.68 mL solution in a single-dose prefilled pen
Applicant proposed Dosing Regimen	In adults with ulcerative colitis, the recommended dosage of subcutaneous maintenance treatment, following at least two intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks. The first subcutaneous maintenance dose should be administered in place of the next scheduled intravenous infusion and every two weeks thereafter.
Applicant Proposed Indication(s)/Population(s)	Same as approved: In adults for the treatment of moderately to severely active ulcerative colitis
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	64766004 Ulcerative colitis (disorder)
Recommendation on Regulatory Action	Approval

Recommended Indication(s)/Population(s) (if applicable)	Same as approved
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	64766004 Ulcerative colitis (disorder)
Recommended Dosing Regimen	*Subcutaneous Injection* • Following the first two intravenous doses administered at Week 0 and Week 2 in adults with ulcerative colitis, Entyvio may be switched to subcutaneous injection at Week 6. • Week 6 and thereafter: Administer 108 mg subcutaneously once every 2 weeks. • Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14. • Entyvio may be switched from intravenous infusion to subcutaneous injection, for patients in clinical response or remission beyond Week 6. To switch patients to Entyvio subcutaneous injection, administer the first subcutaneous dose in place of the next scheduled intravenous infusion and every two weeks thereafter.

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AI	autoinjector
AR	adverse reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	cross-discipline team leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DPV	Division of Pharmacovigilance
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HF	human factors
ICH	International Conference on Harmonisation

IBD	Inflammatory bowel disease
IND	investigational new drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSD	needle safety device
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	periodic benefit-risk evaluation report
PD	pharmacodynamics
PFS	prefilled syringe
PI	prescribing information
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	periodic safety update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
UC	ulcerative colitis

1 Executive Summary

1.1. Product Introduction

Entyvio (vedolizumab) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7. The established pharmacologic class is integrin receptor antagonist.

Entyvio (vedolizumab) for injection (referred to below as vedolizumab IV) was approved in May 2014 for the treatment adults for the treatment of moderately to severely active ulcerative colitis (UC) and the treatment of moderately to severely active Crohn's disease (CD).

In this application, Takeda Pharmaceuticals, U.S.A., Inc. (Applicant) proposes Entyvio (vedolizumab) injection (referred to below as vedolizumab SC), a drug-device combination product with a new dosage form (injectable solution) in two presentations (a single-dose prefilled syringe with needle safety device and a single-dose prefilled pen), a new route of administration (subcutaneous; SC), and new dosage regimen (maintenance treatment following at least two initial intravenous induction doses of Entyvio for injection) for the treatment of adults with moderately to severely active UC.

Entyvio and Entyvio Pen are intended for subcutaneous use under the guidance and supervision of a healthcare professional. Patients or caregivers may self-inject using either the prefilled syringe or prefilled pen after training in subcutaneous injection technique.

There is no proposed change to the currently approved indication in adults for the treatment of moderately to severely active UC.

The Applicant's proposed dosage regimen is maintenance treatment, following at least two intravenous infusions, consisting of 108 mg administered by subcutaneous injection once every 2 weeks. The first subcutaneous maintenance dose should be administered in place of the next scheduled intravenous infusion and every two weeks thereafter.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of Entyvio injection and Entyvio Pen injection for subcutaneous use for the indication of treatment of adults with moderately to severely active UC based on a single, adequate and well-controlled study. Study SC-3027 was a 52-week trial with a 6-week open-label induction phase and a 46-week randomized, double-blind, double-dummy treatment phase for subjects who demonstrated clinical response to intravenous Entyvio as induction treatment. A clinically

meaningful and statistically significant benefit was demonstrated for the primary endpoint and two key secondary endpoints in the trial.

The recommended dosage regimen, as found in labeling, is:

Subcutaneous Injection

- Following the first two Entyvio intravenous doses administered at Week 0 and Week 2, Entyvio may be switched to subcutaneous injection at Week 6.
- Week 6 and thereafter: Administer 108 mg subcutaneously once every 2 weeks.
- Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14.
- Entyvio may be switched from intravenous infusion to subcutaneous injection, for patients in clinical response or remission beyond Week 6. To switch patients to Entyvio subcutaneous injection, administer the first subcutaneous dose in place of the next scheduled intravenous infusion and every two weeks thereafter.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Entyvio (vedolizumab) injection and Entyvio Pen (vedolizumab) injection for subcutaneous use (BLA 761133) has demonstrated safety and effectiveness in adults for the treatment of moderately to severely active UC. In this application, the Applicant proposes two presentations of Entyvio injection (vedolizumab SC) as a drug-device combination product (a single-dose prefilled syringe with needle safety device and a single-dose prefilled pen with autoinjector). The recommended dosage regimen is for subcutaneous administration following intravenous induction treatment with Entyvio (vedolizumab) for injection. BLA 761133, submitted March 7, 2019, received a Complete Response action on December 17, 2019, citing major review issues with the device and formulation (b) (4) In the BLA 761133 resubmission, received March 27, 2023, the Applicant made changes to the device (b) (4) that adequately resolved the deficiency related to needle clogging. The Applicant also adequately addressed the other remaining product quality and device deficiencies from the December 17, 2019, CR letter. There are no remaining deficiencies, and the regulatory recommendation is for approval.

Moderately to severely active UC is a serious chronic disease associated with morbidity and mortality when inadequately treated. Although multiple therapies are approved for this indication not all patients will respond, have continued response to any given treatment, and may require frequent healthcare visits. Entyvio for injection, an integrin receptor antagonist, has been approved for the treatment of moderately to severely active UC in adults since 2014 (BLA 125476) and is administered as an intravenous infusion for both induction and maintenance treatment. A subcutaneous formulation of Entyvio for use as a maintenance treatment, following induction with intravenous Entyvio, provides an alternative route of administration for long-term maintenance therapy. Patients or caregivers may self-inject subcutaneous Entyvio using either the prefilled syringe or prefilled pen after training in subcutaneous injection technique. Intravenous infusion by a healthcare provider in an infusion center may not be convenient as long-term therapy for some patients while availability of a subcutaneous product allows convenience for self-administration or administration by a caregiver at home.

The effectiveness of Entyvio injection and Entyvio Pen injection for subcutaneous use was established in the original BLA 761133 submission based on evidence from Study SC-3027 that demonstrated efficacy of vedolizumab SC in achieving clinical remission at Week 52 in subjects with moderate to severely active UC who had achieved clinical response following induction with intravenous Entyvio. This single adequate and well-controlled trial (SC-3027) was supported by confirmatory evidence from existing adequate and well-controlled clinical investigations of Entyvio administered intravenously for both induction and maintenance therapy for the treatment of moderately to severely active UC. Efficacy of the intravenous form of Entyvio (vedolizumab) was previously demonstrated in two adequate and well-controlled trials used to support approval of

BLA 125476 for the treatment of UC in May 2014. In Study SC-3027, all patients received vedolizumab as an intravenous infusion at Weeks 0 and 2. Those patients who achieved a clinical response at Week 6 were randomized to one of three arms: vedolizumab SC, vedolizumab IV, or placebo. The study was powered for comparison of the vedolizumab SC arm to placebo, with the vedolizumab IV arm included only for descriptive comparison. The study demonstrated efficacy of the vedolizumab SC regimen for the primary endpoint of the proportion of patients who demonstrated clinical remission at Week 52, defined as complete Mayo score ≤2 and no individual subscore >1 point. Efficacy was also demonstrated for the first two ranked secondary endpoints of proportion of patients with improvement of endoscopic appearance of the mucosa at Week 52 and clinical response at both Weeks 6 and 52.

The safety of vedolizumab SC was demonstrated by Study SC-3027 and supported by data from an open-label, long-term extension study (SC-3030) of up to 200 weeks. The safety profile of vedolizumab SC was generally comparable to that of the approved intravenous formulation (based on the studies which supported approval of Entyvio for injection for the treatment of adults with moderately to severely active UC), except for injection site reactions. Injection site reaction were reported in 9% of subjects in Study SC-3027 and included erythema, rash, swelling, bruising, and hematoma at the site. None of these injection site reactions were classified serious, severe, or led to discontinuation of treatment. There was no apparent increase in immunogenicity with vedolizumab administered as a subcutaneous injection compared to an intravenous infusion in the clinical trials.

The overall benefit-risk assessment provides substantial evidence of effectiveness as well as safety for the approval of Entyvio injection and Entyvio Pen injection for subcutaneous use for the maintenance treatment of adults with moderately to severely active UC. Labeling will communicate the risks specific to subcutaneous injection. No new safety concerns are anticipated with the subcutaneous formulation post-approval. A shelf-life of 18 months is adequate to prevent needle clogging. The Applicant will conduct two postmarketing studies required under the pediatric research equity act (PREA) for pediatric patients aged 2 to less than 18 years of age.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	See original Unireview, Section 4.6.
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	See original Unireview, Section 8.1.
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

See original Unireview for BLA 761133 dated December 17, 2019, for a discussion of ulcerative colitis, which is a type of chronic inflammatory bowel disease of the colonic mucosa.

2.2. Analysis of Current Treatment Options

See original Unireview (Table 1) for approved treatment options for adult patients with moderately to severely active UC through December 17, 2019. Included in Table 1 below is a list of additional treatment options approved between December 17, 2019, and March 27, 2023, for adult patients with moderately to severely active UC.

Table 1. Additional Treatment Options for UC Approved Between December 17, 2019 and March 27, 2023

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
Rinvoq (upadacitinib) [Janus kinase inhibitor]	For the treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers	2022	Extended-release tablets Induction: 45 mg once daily for 8 weeks. Maintenance: 15 mg once daily. 30 mg once daily may be considered for patients with refractory, severe, or extensive disease.	<u>BOXED WARNING</u> **WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), and THROMBOSIS** ***See full prescribing information for complete boxed warning.*** • **Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with RINVOQ if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative, latent TB test.** • **Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase (JAK) inhibitor vs. tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients.** • **Malignancies have occurred in patients treated with RINVOQ. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients.** • **Higher rate of MACE (defined as cardiovascular death, myocardial**	<u>Limitations of Use</u> RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with other potent immunosuppressants such as azathioprine and cyclosporine.

				infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. • **Thrombosis has occurred in patients treated with RINVOQ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers.**	
Zeposia (ozanimod) [sphingosine 1-phosphate receptor modulator]	For the treatment of moderately to severely active ulcerative colitis in adults	2021	Capsules: after an initial 7-day titration, the recommended dosage is 0.92 mg taken orally once daily starting on Day 8. <u>Dose Titration Regimen</u> Days 1 through 4: 0.23 mg once daily. Days 5 through 7: 0.46 mg once daily. Day 8 and thereafter: 0.92 mg once daily.	NO BOXED WARNING **WARNINGS AND PRECAUTIONS** • Infections: ZEPOSIA may increase the risk of infections. Obtain a complete blood count (CBC) before initiation of treatment. Monitor for infection during treatment and for 3 months after discontinuation. Do not start ZEPOSIA in patients with active infections. • Bradyarrhythmia and Atrioventricular Conduction Delays: ZEPOSIA may result in transient decrease in heart rate; titration is required for treatment initiation. Check an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting ZEPOSIA. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate. • Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating ZEPOSIA. • Fetal Risk: Women of childbearing potential should use effective contraception during treatment and for 3 months after stopping ZEPOSIA. • Increased Blood Pressure (BP): Monitor BP during treatment.	

				• Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated. • Macular Edema: A prompt ophthalmic evaluation is recommended if there is any change in vision while taking ZEPOSIA. Diabetes mellitus and uveitis increase the risk of macular edema; patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation.	

Source: Reviewer's table adapted from current Prescribing Information May 2023.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Regulatory Actions
Entyvio (vedolizumab) for injection, for intravenous use was approved May 2014 under BLA 125476 () in adults for the treatment of:

- Moderately to severely active ulcerative colitis (UC)
- Moderately to severely active Crohn's disease (CD)

The current application is resubmission of BLA 761133, for Entyvio injection and Entyvio Pen injection, a new liquid formulation for subcutaneous use, which received a Complete Response action on December 17, 2019, with deficiencies related to:

- Product quality (b) (4) corrective and preventative action (CAPA), purchasing controls, and cap removal force),
- Human factors (design and labeling of the prefilled syringe/pen), and
- (b) (4) manufacturing facility inspection.

There were additional non-approvability issues related to product quality, microbiology, and clinical pharmacology (if major changes were to be made to the formulation or device).

See Unireview for BLA 761133 and Complete Response letter, both dated December 17, 2019, for a detailed description of the deficiencies identified in the original review of BLA 761133.

The following is a summary of regulatory actions under BLA 125476 since that time:

Table 2. Summary of Regulatory Actions Under BLA 125476 Since December 17, 2019

Date	Summary of Action	Regulatory Outcome
March 31, 2020	Approval of two labeling supplements	updated the prescribing information (PI): • To streamline the Indications and Usage section; and • add safety information on progressive multifocal leukoencephalopathy (PML) in the Warnings and Precautions section and anaphylaxis to the Adverse Reactions, Postmarketing section

June 24, 2020	Fulfillment of PMR 2719-6 (submitted 11/1/2018) An open-label trial to determine the long-term safety of Entyvio (vedolizumab) in patients with UC and CD. Safety evaluations include but are not limited to the occurrence of serious infections including progressive multifocal leukoencephalopathy (PML) and malignancies	Issued Fulfillment of Postmarketing Requirement letter
October 20, 2020	Fulfillment of PMR 2719-8 (submitted 4/9/2020) A milk-only lactation study in lactating women receiving vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk using a validated assay	Issued Fulfillment of Postmarketing Requirement letter
December 16, 2020	Fulfillment of PMC 2719-9 (submitted 3/31/2017) A study to reanalyze banked immunogenicity serum samples from UC trial C13006 and CD trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference	Issued Fulfillment of Postmarketing Requirement letter
August 17, 2021	Labeling supplement	Updated the PI: • to revise the immunogenicity results from studies C13006 and C13007 using an updated assay method in Sections 6.2 Immunogenicity and 12.3 Clinical Pharmacology (PMR 2819-9) • add “acute pancreatitis” to Section 6.3 Postmarketing

		Experience • add the results of a milk-only lactation study (PMR 2719-8) Section 8.2 Lactation
June 17, 2022	Labeling supplement	Add 0.9% Sodium Chloride Injection, USP, and Lactated Ringer's Injection, USP, as alternatives to Sterile Water for Injection (SWFI) for reconstitution of Entyvio in the Dosage and Administration section
January 25, 2023	CMC supplement	Alternate manufacturing process for the drug substance (b) (4) and other process changes
March 28, 2023	Fulfilment of PMR 2719-25 (submitted 11/18/2020) A dose-ranging study to determine the pharmacokinetics/pharmacodynamics, safety, and tolerability of Entyvio (vedolizumab) in pediatric patients 2 to 17 years of age with moderately to severely active UC or CD who have failed conventional therapy	Issued Fulfillment of Postmarketing Requirement letter

Marketing History

As of the data lock point of the BLA resubmission, May 19, 2022, Entyvio (vedolizumab) for injection has been approved to treat adult patients with moderately to severely active UC or CD in 71 countries. Entyvio (vedolizumab) injection has been approved for subcutaneous use for maintenance treatment of UC or CD in 44 countries globally.

3.2. Summary of Presubmission/Submission Regulatory Activity

See Table 2 in the Unireview for the original BLA 761133 submission, submitted to DARRTS December 17, 2019, for a listing of relevant clinical submission regulatory background that preceded the original submission on March 7, 2019.

Provided below is a summary of regulatory activity following the Complete Response letter for the original BLA submission on December 17, 2019.

August 14, 2020: Meeting minutes for two type A teleconferenced meetings provided Agency feedback on the Applicant's responses to the deficiencies contained in the FDA Complete Response letter dated December 17, 2019. The Agency clarified expectations for no clogging during the intended storage (5°C)/use conditions and within the temperature range of 25°C to -40°C, comparison of needle shields, cap removal force as a release specification, and what to submit for the human factors study.

November 24, 2020: The Applicant's request for an extension to December 2021 to resubmit BLA 761133 was granted.

October 2, 2020: The Applicant submitted a human factors (HF) validation study protocol for under IND 118980 and indicated that the PFS user interface changed (revisions to the Instructions for Use). Review dated December 3, 2020.

December 8, 2020: The Agency recommended the Applicant conduct comparative analysis and determine whether they need to submit the results of a HF validation study for the PFS. If the Applicant determined that an HF validation study is not needed for their product, the Agency recommended submission of use-related risk analysis, comparative analyses, and justification for not submitting the HF validation study to the Agency for review.

April 30, 2021: The Applicant submitted a HF validation study protocol under IND 118980 for the PFS. Review dated September 1, 2021.

September 2, 2021: Advice provided on the Applicant's proposed HF validation study protocol for the PFS.

October 12, 2021: Preliminary comments provided for the granted type C meeting on the Applicant's proposal to replace the (b) (4) tip cap with an alternate (b) (4)) tip cap, inclusion of Takeda Austria GmbH as a drug product manufacturer, and strategy for stability testing. BLA resubmission would be classified as a Class 2 resubmission. The Applicant cancelled the teleconference guidance meeting after receipt of the Agency's letter. In the comments, the Agency provided feedback.

March 29, 2022: Applicant's request for an extension to March 29, 2023, to resubmit BLA 761133 was granted.

May 23, 2022: Issued meeting minutes for a type C meeting on the Applicant's proposal for providing safety information in the planned BLA resubmission. The Agency agreed with the Applicant's proposal to include new data from completed Study SC-3031 (phase 3 study of vedolizumab subcutaneous injection in patients with CD) and ongoing Study SC-3030 (long-term extension study for subjects with UC and CD) in the resubmission in a format consistent with

the Day 120 Safety Update. A 120-day Safety Update will not be required to support review of the resubmission.

September 7, 2022: Issued meeting minutes for a type B pre-BLA meeting on product stability information to be provided with the resubmission to support the planned shelf-life. A separate application was planned to support the use of vedolizumab injection, for subcutaneous use in adult patients with moderately to severely active CD. The Applicant's proposal to submit additional stability data no later than 3 months after the BLA resubmission was found to be reasonable. The Applicant's proposed CMC information to support the introduction of the (b) (4) tip cap was also found to be reasonable.

March 27, 2023: Resubmission of BLA 761133.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Two clinical sites were inspected during review of the original BLA 761133 submission and received classification of 'No Action Indicated'. Overall, the quality of the data was considered sufficient to support continued review and reliance upon trial results to make regulatory decisions. No additional inspections were planned for the resubmission of BLA 761133.
See Section 4.1 in the original Unireview, submitted to DARRTS December 17, 2019, for a description of the inspections.

No new clinical data was provided in the BLA resubmission and therefore, no inspections were conducted during this review cycle.

4.2. Product Quality

From a product quality, facility, microbiology and sterility assurance perspective, the Office of Pharmaceutical Quality (OPQ) recommends approval of BLA 761133 for vedolizumab SC manufactured by Takeda Pharmaceutical U.S.A., Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of vedolizumab SC is well-controlled and leads to a product that is pure and potent.

The vedolizumab drug product for intravenous infusion for the induction and maintenance treatment of moderately to severely active UC and CD under BLA 125476 is supplied as a sterile, lyophilized powder. The new vedolizumab drug product proposed in BLA 761133 intended for treatment of adults with moderate to severely active UC is supplied as a 108 mg/0.68 mL

injectable solution for subcutaneous use in a single-use prefilled syringe (PFS) assembled with a Needle Safety Device (NSD) or an autoinjector pen (AI).

The original submission of BLA 761133, submitted March 7, 2019, received a Complete Response action on December 17, 2019, citing major review issues with the originally proposed device and formulation. A major issue identified was needle clogging during stability testing; the Applicant failed to adequately identify and investigate the root cause of identified clogging, nor did they adequately provided mitigation strategies and controls to ensure that this issue was addressed. Additional deficiencies were identified pertaining to inadequate procedures in place to identify and mitigate problems occurring during manufacturing of the final combination product, and insufficient human factors validation study data to support safe and effective use of the proposed prefilled pen presentation.

The CDRH review team determined that the previous unresolved device-related issues were adequately addressed during the BLA resubmission review cycle (See Section 4.4 Devices and Companion Diagnostic Issues). From an OPQ-perspective, adequate information and data were provided by the Applicant in the BLA resubmission to demonstrate that the Chemistry Manufacturing and Controls (CMC) changes implemented to address the Complete Response deficiencies will not adversely impact vedolizumab SC product quality attributes upon release, during long-term storage through the 18-month expiry (including toxicological safety profile), during commercial shipment, and upon exposure to in-use storage conditions (i.e., 25°C up to 7 days).

The Complete Response Letter for December 17, 2019, contained additional comments related to product quality that were not approvability issues. From an OPQ perspective, the Applicant also provided adequate information and data to address those comments.

The manufacturing processes and overall control strategies for vedolizumab SC as described in the license are appropriately established to ensure consistency and quality of the final product. The screening, confirmatory, and specificity anti-drug antibody (ADA) assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

The Applicant added Takeda Austria GmbH (Linz Austria) as an alternate site for drug product lot release and stability testing because it was determined during the review cycle that most of the supporting data in the BLA resubmission were generated by this site. To support the addition of this site, OPQ requested the Applicant submit additional data on the sterility, endotoxin, and container closure integrity test methods. This information was reviewed by OPQ and determined to be acceptable.

Manufacturing and testing performed at each facility was determined to be acceptable based on the currently acceptable Good Manufacturing Practice (cGMP) compliance status and recent

relevant inspectional coverage. A post-approval device inspection is recommended for Takeda Austria GmbH (see additional discussion below in Section 4.4 Devices and Companion Diagnostic Issues).

The overall vedolizumab SC control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. OPQ is requesting a postmarketing commitment (PMC) to address the low endotoxin recovery (LER) study included in the BLA. The LER study was performed at 2°C to 8°C and does not accurately reflect the (b) (4) (b) (4) conditions during the manufacturing process in which the bulk solution may be stored (b) (4)°C for up to (b) (4) days). A study using the vedolizumab drug product spiked with reference standard endotoxin or control standard endotoxin and stored up to (b) (4) days at (b) (4) (b) (4)°C should be conducted to verify that the (b) (4) drug product manufacturing process has no impact on endotoxin recovery. The Applicant agreed to conduct the PMC and to submit the final report by December 2024.

Categorical exclusion is claimed by the Applicant and deemed acceptable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

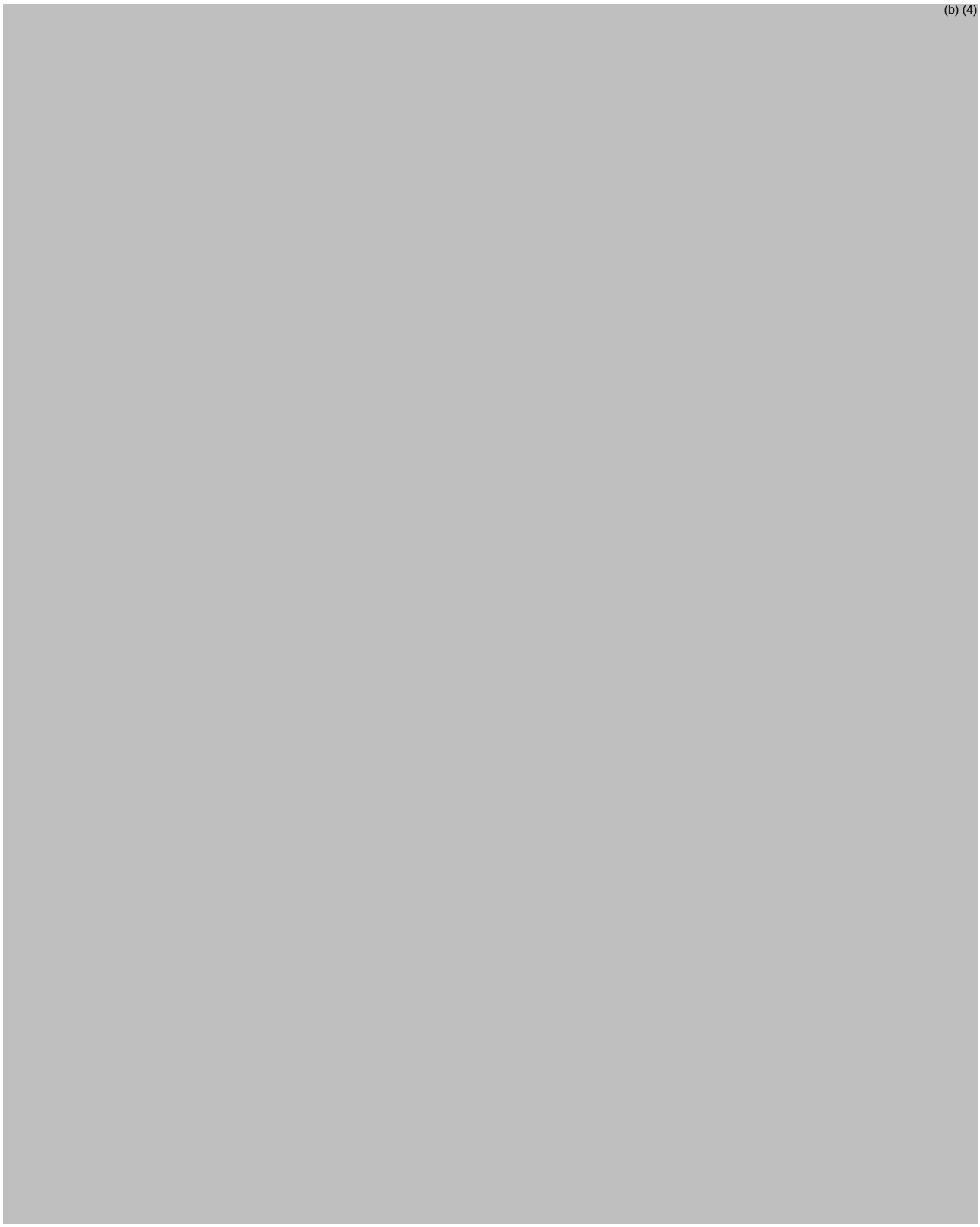
The original BLA received a Complete Response on December 17, 2019, as described above for product quality issues. The deficiencies under the purview of CDRH included: needle clogging, quality systems, and cap removal.

In the BLA 761133 resubmission, the Applicant made changes to the device needle tip cap (b) (4) that CDRH has determined adequately resolves the deficiency related to needle clogging. The Applicant also adequately addressed the other remaining CDRH deficiencies in the December 17, 2019, CR letter in the resubmission. There are no remaining deficiencies and CDRH recommends approval.

The following is a synopsis of these deficiencies from the Complete Response Letter and the actions taken by the Applicant to address the deficiencies in the resubmission.

1. Needle Clogging

(b) (4)



(b) (4)

Other Review Issues

Facility Inspections

The Complete Response letter of December 17, 2019, noted the following:

> During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved in a future resubmission.

The facilities in the original BLA submission (b) (4) were replaced with Takeda Austria GmbH (Linz Austria) responsible for the drug product function and testing for both the PFS+AI and PFS+NSD.

Takeda Austria GmbH will require a post-approval inspection because there has not been a previous inspection for devices, although was inspected for other reasons (drug GMP and coronavirus activities) and classified NAI. The other

facilities included in the BLA did not require inspection.

Human Factors

The original BLA 761133 submission on March 7, 2019, contained the results of a HF study for the AI. DMEPA reviewed the study results and recommended the Applicant implement the provided revisions along with additional mitigations that they determine to be necessary to address the use-related issues and conduct and submit results of another HF validation study to demonstrate that the mitigations are effective and do not introduce new risks. The application received a CR on December 17, 2019, with a deficiency related to HF:

> Revise the user interface, including device design, device label/labeling, (b) (4) and the Instructions for Use (IFU) to improve prominence, clarity and understanding of important information.

The resubmission included the results of the second HF validation study with separate parts to evaluate the PFS and the AI. DMEPA evaluated the study design, errors/close calls/use difficulties observed and provided recommendations on whether the results indicated the user interface has been appropriately designed to support the safe and effective use of the proposed product.

The results of the HF validation study demonstrated several use errors, close calls, and use difficulties with critical tasks that may result in harm. However, based on DMEPA's review of the available participants' subjective feedback, the Applicant's mitigation strategies and root cause analysis, they did not identify additional risk controls to address the use errors, close calls, and use difficulties. The risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. The deficiency has been addressed and there are no further recommendations for the resubmission.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant did not submit any new nonclinical study reports in this submission. The Applicant made a manufacturing change in the prefilled syringe device tip cap after completion of clinical studies. The tip cap was changed (b) (4) (b) (4). The Applicant has conducted extractable and leachable studies with the drug product with the new tip cap (b) (4). The results of the extractable and leachable studies do not appear to raise a significant safety concern from nonclinical standpoint. There are no approvability issues from the nonclinical perspective.

5.1.1. Other Toxicology Studies

Extractable/Leachable Evaluation

The Applicant made a manufacturing change in the tip cap after completion of clinical studies. The change was made in the tip cap (b) (4) (b) (4). The Applicant has conducted extractable and leachable (E/L) studies with the drug product with the new (b) (4) tip caps (b) (4)).

Extractables Studies (RPT-010832 and RPT-011760)

The extractables study was conducted on the syringe barrel, rubber stopper, and (b) (4) rigid needle shield under exaggerated conditions using three different solvents (pH 3 buffer, pH 10 buffer, and 50% isopropanol) at elevated temperature of 50°C for 72 hours and acid digestion (5% nitric acid and 1% hydrochloric acid, 90-95°C for 2 hours). The extractants were analyzed for semi-volatile and non-volatile organic compounds, inorganic elements and for volatile organic compounds for dry components of syringe barrel with needle, rigid needle shield, and stopper. Extractable compounds at levels below the analytical evaluation threshold (AET) of (b) (4) µg/mL) were not considered to be a concern for patient safety. Conversely, extractable compounds which exceed the AET were identified and assessed for toxicity.

Based on the dosage of the subcutaneous vedolizumab injection, human daily exposure (HDE, µg per day) was calculated assuming worst-case, lifelong dosing for all identified and quantified extractable substances of the study. All organic extractables were characterized for potential toxicity based on available literature data and compared to the safety concern threshold (SCT) of 1.5 µg/day) for mutagenic/genotoxic substances. All organic extractables were below the SCT, except that one organic compound, (b) (4) had a human equivalent dose (HDE) of (b) (4) µg/day) above the SCT (1.5 µg/day). However, the (b) (4) had a calculated HDE of less than the qualification threshold (QT) of 5 µg per day for sensitizers/irritants[1]. In addition, the (b) (4), which is most likely either (b) (4) according to reported molecular mass and formula, is considered to have a low level of toxicity at the calculated HDE. It is to be mentioned here that (b) (4) was not found in the leachable study. Two inorganic elements, (b) (4) were detected in the syringe barrel at levels of (b) (4) µg/mL, respectively (HDE of (b) (4) µg/day, respectively). These levels are above the permitted daily exposures (PDE) of (b) (4) µg/day) and (b) (4) µg/day) for parenteral drug products per the ICH Q3D(R2) Guideline for Elemental Impurities.[2] High levels of elemental (b) (4) might be from the injection needle, for which a solvent (b) (4) was likely too aggressive for the stainless steel needle. However. (b) (4) were not detected in the

[1] Diane P, et al., 2013, The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP), PDA J Pharm Sci & Tech, 2013, 67, 430-447.
[2] Q3D(R2) Elemental Impurities, Guidance for Industry, https://www.fda.gov/media/148474/download.

leachable study. Thus, there is no safety concern for (b) (4) detected in the extractable study.

Leachable Study (RPT-013207)

A leachable study (on-going) is being performed on the subcutaneous vedolizumab drug product in 1 mL prefilled syringes with the (b) (4) tip cap for which three lots of drug product were stored horizontally at 5°C for 36 months ((b) (4) , at the accelerated storage condition of 25°C±2°C and 60%±5% relative humidity (RH) over 6 months, as well as at the stress storage condition of 40°C/75% RH for 3 months. At each designated timepoint, the leaching aliquots and controls were analyzed. The leachable data collected so far for all three DP lots at t=0, t=3 months at 25°C and 40°C, t=6 months at 25°C, and t=12 months at 2°C to 8°C, showed no organic compounds but only three inorganic elements ((b) (4)]). Based on the dosage of the subcutaneous vedolizumab drug product, the HDE values calculated for leachable (b) (4) were (b) (4) µg/day, respectively. Per the ICH Q3D(R2) guidance, PDEs of (b) (4) have not been established due to their low inherent toxicity. Based on the threshold of toxicological concern (TTC) of 1.5 µg/day, the low inherent toxicity per the ICH Q3D(R2) guidance, the calculated HDEs for (b) (4) represent a negligible safety risk from a toxicological perspective. In addition, per the CDER guidance for (b) (4) content and labeling recommendations,[3] the maximum daily exposure of (b) (4) is (b) (4) µg/kg/day, which is higher than the HDE of (b) (4) µg/day or (b) (4) µg/kg/day) from the leachable study. Overall, the results of the leachable study do not appear to raise a significant safety concern from the nonclinical standpoint.

6 Clinical Pharmacology

6.1. Summary of Clinical Pharmacology Assessment

In this resubmission of BLA 761113, as stated above, the Applicant has addressed product quality deficiencies in the Complete Response letter dated December 17, 2019. The Applicant originally submitted BLA 761113 on March 7, 2019, seeking marketing approval of vedolizumab for subcutaneous administration as a maintenance regimen for the treatment of moderately to severely active UC in adults. The Applicant's proposed subcutaneous dosage regimen is 108 mg every 2 weeks starting at Week 6 following two intravenous loading doses (i.e., vedolizumab 300 mg infused intravenously over 30 minutes at Weeks 0 and 2). The clinical pharmacology

[3] CDER Clinical/Medical Guidance, Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations, December 2022, https://www.fda.gov/media/163799/download

program supporting the subcutaneous dosing regimen was reviewed under the original submission and was found to be acceptable.

The Applicant is also proposing that patients may switch from intravenous infusion to subcutaneous injection for maintenance treatment at timepoints beyond Week 6. In summary, during the original BLA review the Applicant was asked to conduct pharmacokinetic (PK) simulation using the population PK model to predict PK profiles for intravenous to subcutaneous switching. The Applicant also provided clinical data from subjects with UC who completed Study SC-3027 (6 weeks of intravenous induction followed by 46 weeks of subcutaneous maintenance) and continued in Study SC-3030 for 24-weeks. Based on the combined evidence, the clinical pharmacology review recommended intravenous to subcutaneous switching could be initiated at 3-4 weeks but no later than 8 weeks after the last intravenous infusion (i.e., at the time of the next scheduled intravenous infusion). See additional discussion on this topic in Section 6.1.2 'Switching from Intravenous to Subcutaneous Maintenance Regimen'.

Entyvio (vedolizumab) for injection for intravenous infusion was approved in May 2014 under BLA 125476 in adults for the treatment of moderately to severely active UC and for the treatment of moderately to severely active CD. The approved intravenous Entyvio dosing regimen for both UC and CD is 300 mg at Weeks 0, 2, 6 and every 8 weeks thereafter.

The Complete Response Letter of December 17, 2019, mentioned that if major changes in formulation or device were made to address the identified major product quality deficiencies, additional clinical pharmacology studies may be necessary to bridge between the to-be-marketed and clinical trial formulations/presentations.

In the resubmission of BLA 761113, the Applicant did not change the formulation, hence a pharmacokinetic bridging study is unnecessary. As such there are no new clinical pharmacology issues that affect approvability of this resubmission.

6.1.1. Immunogenicity

In the resubmission, the Applicant provided additional immunogenicity data from ongoing Study SC-3030, which is an open-label extension phase of the phase 3 trial, Study SC-3027. In Study SC-3030, eligible patients with UC who completed the maintenance period of Study SC-3027 were enrolled. In addition, patients who were not randomized to the maintenance period of Study SC-3027 due to non-responsiveness at Week 6 but responded at Week 14 after intravenous loading doses, were also enrolled in Study SC-3030 and received 108 mg as a subcutaneous injection every two weeks.

It was determined during the original BLA 761133 review that the overall anti-drug antibody (ADA) method validation data adequately supports the tolerance of the assay to detect ADA in

the presence of 35.8 mcg/mL of vedolizumab, which was the mean steady state trough concentration in Study SC-3027.

Study SC-3027

In Study SC-3027, the reported rate of anti-vedolizumab (AVA) antibodies was 6% (6/106) in subjects who received vedolizumab SC treatment. Four of these 6 AVA positive subjects in the vedolizumab SC arm had persistent AVA (at two or more consecutive study visits). Three patients developed neutralizing antibodies to vedolizumab SC. Development of AVA was associated with low vedolizumab trough concentrations. Pharmacokinetic data are available for 74 subjects at Week 46 of the maintenance period (Week 52 of the study). Results are missing in other subjects due to a non-sufficient sample for analysis or results below the level of quantitation. At steady state (Week 46), mean vedolizumab trough serum concentration in the vedolizumab SC treatment arm was 6.84 µg/mL in AVA positive subjects (N=1) and 36.25 µg/mL in AVA negative subjects (N=73). None of the 6 subjects with positive AVA achieved clinical remission at Week 52 in vedolizumab SC arm. In the vedolizumab IV treatment arm, the AVA incidence rate was 6% (3/54) and mean vedolizumab trough serum concentrations were 1.81 µg/mL in AVA positive subjects (N=1) and 12.21 µg/mL in AVA negative subjects (N=39) at Week 46.

There were 105/106 subjects randomized to the vedolizumab SC arm in Study SC-3027 with at least one AVA sample available. While there were 6 subjects randomized to the vedolizumab SC arm with positive AVA, only 4 of these subjects were AVA positive during the maintenance period. Two subjects assigned to the vedolizumab SC arm were AVA positive only at Week 6 (first dose of vedolizumab SC) and Week 8 but not at later time points. Although the Applicant attributed AVA in these subjects to vedolizumab IV administered during the induction period, potential effects of the vedolizumab SC dose at Week 6 cannot be completely ruled out. Neither subject reported injection site reactions nor hypersensitivity reactions.

The overall incidence of injection site reactions in the vedolizumab SC arm was 9% (10/106). The incidence of injection site reactions was 10% (1/10) in AVA positive subjects compared to 9% (9/101) who were AVA negative. Note that the number of subjects with injection site reactions was 11 as reported in Table 40 of the original Unireview, which was an error. The corrected number is 10 as reported in the original Unireview (Table 27 of Section 8.2.5.1) being referenced for more details.

The overall incidence of hypersensitivity reactions in vedolizumab SC arm in Study SC-3027 was 15% (16/106). Of the 16 subjects who experienced a hypersensitivity reaction, none were AVA positive. Refer to table 4.c (pg. 110) in the Summary of Clinical Safety Report available in m2.7.4 of the original BLA 761133 submission (SD 1).

Overall, there were insufficient data to draw a conclusion on the effect of AVA on pharmacokinetics, effectiveness, and safety of vedolizumab IV for two doses followed by vedolizumab SC over the 52 weeks in Study SC-3027.

Study SC-3030

In the resubmission, the immunogenicity incidence in Study SC-3030 in subjects with UC was evaluated with the additional long-term data provided (up to 200 weeks). The incidence of injection site reactions and hypersensitivity reactions by AVA status is shown in Tables 3 and 4, respectively.

In Study SC-3030, there were 285/288 subjects with at least one AVA sample available. Of those, 6% (17/285) were AVA positive. The overall incidence of injection site reactions was 5% (14/288). The incidence of injection site reactions was 18% (3/17) in AVA positive subjects compared to 4% (11/268) who were AVA negative (Table 3). The overall incidence of hypersensitivity reactions was 20% (58/288). The incidence of hypersensitivity reactions was 47% (8/17) in AVA positive subjects compared to 19% (50/268) who were AVA negative (Table 4).

Of the subgroup of subjects who received the vedolizumab SC 108 mg in both Study SC-3027 and SC-3030, 88/90 subjects had at least one AVA sample available, and 3 subjects were ADA positive. One AVA positive subject from SC-3027 discontinued early from Study SC-3030. The overall incidence of injection site reactions was 2% (2/88) and both subjects were AVA negative (Table 3). The incidence of hypersensitivity reactions was 33% (1/3) in ADA positive subjects compared to 20% (17/85) in ADA negative subjects (Table 4). Due to the small number of AVA positive patients, there is insufficient data to make a definitive conclusion regarding the effect of AVA on injection site or hypersensitivity reactions in this subgroup.

Table 3. Summary of Overall AVA Status by Injection Site Reactions for Subjects with UC Receiving Vedolizumab SC 108 mg Q2W During Study SC-3030

Previous Treatment in Study SC-3027	Nonrandomized Week 14 Responders N = 107	PBO N = 52	VDZ SC 108 mg N = 90	VDZ IV 300 mg N = 39
At least 1 non-missing AVA sample	106	52	88	39
Any Injection Site Reactions (Yes/No) Overall AVA Status				
Yes				
Number of Subjects	2	7	2	3
AVA negative[a]	2 (100.0)	4 (57.1)	2 (100.0)	3 (100.0)
AVA positive[b]	0	3 (42.9)	0	0
Transiently positive AVA[c]	0	3 (42.9)	0	0
Persistently positive AVA[d]	0	0	0	0

Previous Treatment in Study SC-3027	Nonrandomized Week 14 Responders N = 107	PBO N = 52	VDZ SC 108 mg N = 90	VDZ IV 300 mg N = 39
Positive neutralizing AVA[e]	0	3 (42.9)	0	0
No				
Number of Subjects	104	45	86	36
AVA negative[a]	100 (96.2)	39 (86.7)	83 (96.5)	35 (97.2)
AVA positive[b]	4 (3.8)	6 (13.3)	3 (3.5)	1 (2.8)
Transiently positive AVA[c]	2 (1.9)	3 (6.7)	1 (1.2)	1 (2.8)
Persistently positive AVA[d]	2 (1.9)	3 (6.7)	2 (2.3)	0
Positive neutralizing AVA[e]	4 (3.8)	5 (11.1)	1 (1.2)	1 (2.8)

Source: Adapted from the Applicant's submission; BLA 761133 SD 52 received on March 27, 2023, Module 2.7.4 Summary of Clinical Safety – Resubmission Safety Update, Table 4.a on page 102. Verified by reviewer.
AVA: anti-vedolizumab antibody; PBO: placebo; SC: subcutaneous; IV: intravenous; VDZ: vedolizumab.
[a] Negative AVA was defined as a negative (not confirmed positive) AVA result at all visits.
[b] Positive AVA was defined as a confirmed AVA positive result at 1 or more visits.
[c] Transiently positive AVA was defined as a confirmed positive AVA result for at least 1 visit and no consecutive positive results.
[d] Persistently positive AVA was defined as a confirmed positive AVA result at 2 or more consecutive visits.
[e] Positive neutralizing AVA was defined as a positive result in the neutralizing AVA assay.

Table 4. Summary of Overall AVA Status by Hypersensitivity Reactions for Subjects with UC Receiving Vedolizumab SC 108 mg Q2W During Study SC-3030

Previous Treatment in Study SC-3027	Nonrandomized Week 14 Responders N = 107	PBO N = 52	VDZ SC 108 mg N = 90	VDZ IV 300 mg N = 39
At least 1 non-missing AVA sample	106	52	88	39
Any Hypersensitivity Reactions (Yes/No) Overall AVA Status				
Yes				
Number of subjects	27	9	18	4
AVA negative[a]	2 (100.0)	5 (55.6)	17 (94.4)	3 (75.0)
AVA positive[b]	2 (7.4)	4 (44.4)	1 (5.6)	1 (25.0)
Transiently positive AVA[c]	1 (3.7)	4 (44.4)	1 (5.6)	1 (25.0)
Persistently positive AVA[d]	0 1 (3.7)	0	0	0
Positive neutralizing AVA[e]	2 (7.4)	3 (33.3)	0	1 (25.0)
No				
Number of subjects	79	43	70	35
AVA negative[a]	77 (97.5)	39 (86.7)	68 (97.1)	35 (100.0)
AVA positive[b]	2 (2.5)	5 (11.6)	2 (2.9)	0
Transiently positive AVA[c]	1 (1.3)	2 (4.7)	0	0
Persistently positive AVA[d]	1 (1.3)	3 (7.0)	2 (2.9)	0
Positive neutralizing AVA[e]	2 (2.5)	5 (11.6)	1 (1.4)	0

Source: Adapted from the Applicant's submission; BLA 761133 SD 52 received on March 27, 2023, Module 2.7.4 Summary of Clinical Safety – Resubmission Safety Update, Table 4.c on page 104. Verified by reviewer.
AVA: anti-vedolizumab antibody; PBO: placebo; SC: subcutaneous; IV: intravenous; VDZ: vedolizumab.
For subjects without a baseline value available in Study SC-3030, baseline information is coming from parent study

final visit (Week 14 [nonrandomized Week 14 Responders] or Week 52/Early Termination).
Percentages are based on the number of subjects with at least 1 non-missing AVA sample in each category (yes/no).
All subjects with missing data for determination of endpoint status are categorized as negative.
[a] Negative AVA was defined as a negative (not confirmed positive) AVA result at all visits.
[b] Positive AVA was defined as a confirmed AVA positive result at 1 or more visits.
[c] Transiently positive AVA was defined as a confirmed positive AVA result for at least 1 visit and no consecutive positive results.
[d] Persistently positive AVA was defined as a confirmed positive AVA result at 2 or more consecutive visits.
[e] Positive neutralizing AVA was defined as a positive result in the neutralizing AVA assay.

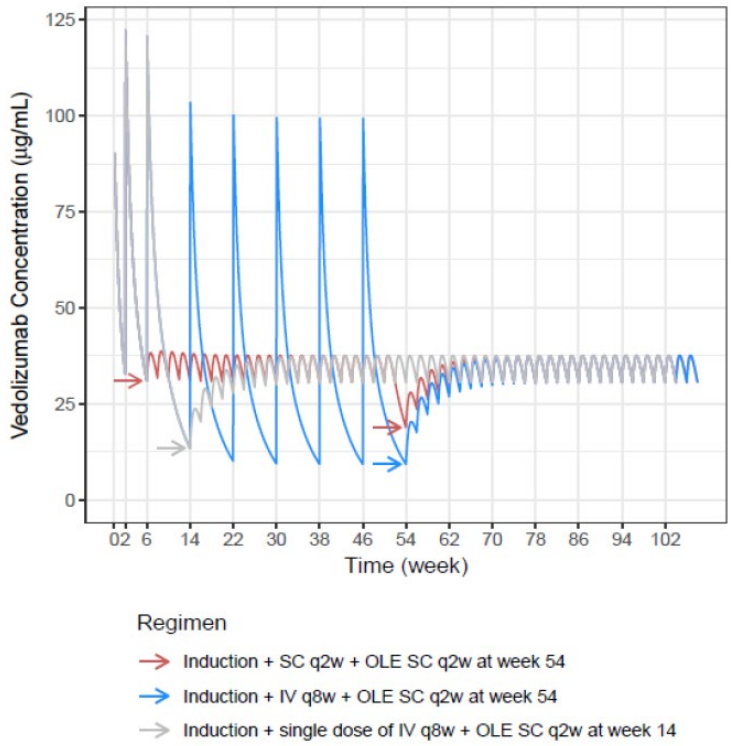
6.1.2. Switching from Intravenous to Subcutaneous Maintenance Regimen

Compared to intravenous Entyvio, vedolizumab SC provides patients with a convenient option that allows for caregiver or self-administration at home instead of in an infusion center. To support an option for switching from intravenous to subcutaneous maintenance treatment at timepoints beyond Week 6, which was not studied in Study SC-3027, the Applicant provided evidence based on PK simulation and data from Study SC-3027 (randomized, placebo-controlled study) and exploratory analyses from Study SC-3030 (open-label extension study) in the original BLA submission and the resubmission.

Pharmacokinetic Simulation

The results of PK simulation were described in the original Unireview. For the intravenous dose, though the predicted C_{avg} immediately after switching was lower than $C_{avg,ss}$, C_{trough} still remains higher than $C_{trough,ss}$. Moreover, C_{avg} continues to increase over 8 weeks (intravenous dosing interval) and attain steady state by Week 10-12 as suggested by PK simulation (Figure 1). Therefore, the lower C_{avg} immediately after switching is unlikely to have an impact on long-term efficacy and the simulation supports switching at 3 to 4 weeks, but no later than 8 weeks (the next scheduled intravenous infusion), after the last intravenous infusion.

Figure 1. Simulated Vedolizumab Concentration-Time Profiles Following Intravenous and Subcutaneous Dosing Regimens



Note: Arrows indicate the time at which dosing switches to SC Q2W.
The grey line indicates vedolizumab IV infusion at Week 0, 2, 6 followed by switching to vedolizumab SC 108 mg Q2W at Week 14.
The red line indicates vedolizumab SC 108 mg Q2W from Week 6 to Week 50 followed by continued vedolizumab SC 108 mg Q2W from Week 54.
The blue line indicates IV maintenance treatment up to Week 46 followed by switching to vedolizumab SC 108 mg Q2W at Week 54.
IV: intravenous; SC: subcutaneous.

Observed Data from Study SC-3030

To further explore the potential for switching to vedolizumab SC at timepoints other than 6 weeks after the first two doses of vedolizumab IV, the Applicant provided limited data from exploratory analyses of Study SC-3030. As described above, Study SC-3030 was an open-label long-term extension safety study that was a follow-on to Study SC-3027 in which all subjects received vedolizumab SC. The study also collected data for clinical response and remission. Patients were eligible for Study SC-3030 if they did not achieve clinical response at Week 6, withdrew early, or completed Week 52 in Study SC-3027. Subjects randomized to vedolizumab SC in Study SC-3027 continued on vedolizumab SC in Study SC-3030, and those who were randomized to vedolizumab IV or placebo in Study SC-3027 were switched to vedolizumab SC in Study SC-3030.

The exploratory efficacy analysis of the proportion of subjects who were in clinical remission at Week 0 and remained in clinical remission at Week 24 of Study SC-3030 for randomized completers in Study SC-3027 was conducted by the Applicant through the interim data lock date of May 19, 2022. Randomized completers are the subgroup of subjects who initiated vedolizumab SC treatment in Study SC-3030 following 2 doses of vedolizumab IV at Week 0 and Week 2, achieved clinical response at Week 6, then completed 52 weeks of treatment with vedolizumab IV in Study SC-3027.

Table 5 provides descriptive data that includes all randomized subjects who completed the Week 52 visit in Study SC-3027 and then enrolled in extension Study SC-3030. Subjects who withdrew from Study SC-3030 or with missing data for determination of endpoint status (i.e., clinical remission) at Week 0 or Week 24 were categorized as non-remitters/non-responders. In addition, subjects who escalated dosing of vedolizumab SC from every 2-week dosing to weekly dosing between Week 0 and Week 24 were categorized as non-remitters/non-responders. For the analyses with data cut of May 19, 2022, all subjects were included in the analyses. There was a total of 15 subjects who either discontinued (n=3) from Study SC-3030 before Week 24 or had missing data (n=12) at Week 24 and were therefore counted as non-remitters/non-responders.

The proportion of subjects who were in clinical remission at Week 0 and Week 24 was 89% (24/27) in the subgroup of randomized completers of vedolizumab IV in Study SC-3027 who switched to vedolizumab SC in Study SC-3030. The proportion of subjects who were in clinical remission at Week 0 and Week 24 was 85% (53/63) in the subgroup of subjects who remained on continuous vedolizumab SC treatment in both Studies SC-3027 and SC-3030.

Table 5. Proportion of UC Subjects in Clinical Remission at the Start of Study SC-3030 (Week 0) and in Clinical Remission at Week 24; Randomized Completer Subjects[a]

Treatment Assignment in Maintenance Phase of Study SC-3027	Clinical Remission[b] Results in Study SC-3030 While Receiving Vedolizumab SC	
	Week 0	Week 24
Vedolizumab IV	27/35 (77%)	24/27 (89%)
Vedolizumab SC	63/69 (91%)	53/63 (84%)
Placebo	11/20 (55%)	9/11 (82%)

Source: Reviewer's table adapted from Applicant's submission to BLA 761133 SD72 received September 25, 2023, Table 2.

[a] Randomized completer subjects are those who completed the maintenance phase (Week 52) of Study SC-3027 with data available at Weeks 0 and 24 in Study SC-3030 at interim data lock point of May 19, 2022.

[b] Clinical remission was defined as a partial Mayo score of ≤2 points and no individual subscore >1 point.

In summary, the data from PK simulation supports switching at 8 weeks (the next scheduled intravenous infusion), after the last intravenous infusion at time points beyond Week 6. Limited interim data in the subgroup of subjects in clinical remission at Week 0 and Week 24 of Study

SC-3030 suggests that response to vedolizumab is not adversely impacted by switching between intravenous and subcutaneous routes of administration at later time points beyond Week 6.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6. Clinical Studies

Trial ID Design*	Treatment/ Sample Size	Endpoints
Study SC-3027 A 52-week MC trial with a 6-wk open-label induction phase and a 46- week R, DB, double dummy treatment period for those had clinical response.	N randomized: • Vedolizumab SC Q2W + placebo IV Q8W =106 • Vedolizumab IV Q8W + placebo SC Q2W =54 • Placebo SC Q2W and IV Q8W =56	**Primary endpoint**: clinical remission, defined as a complete Mayo score of ≤2 points with no individual subscore >1 point. **Secondary endpoints**: • Proportion of subjects with mucosal healing, defined as Mayo endoscopic subscore of ≤1 point, at Week 52. • Proportion of subjects with durable clinical response, defined as clinical response at Weeks 6 and 52, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. • Proportion of subjects with durable clinical remission, defined as clinical remission at Weeks 6 and 52. • Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52. **Safety Assessments**: • Safety for maintenance therapy as assessed by adverse events (AEs), adverse events of special interest (AESIs) (including serious infections and opportunistic infection, such as progressive multifocal leukoencephalopathy [PML], liver injury, malignancies, infusion-related or injection site reactions or systemic reactions and hypersensitivity), serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and results of 12-lead electrocardiograms.

Trial ID Design*	Treatment/ Sample Size	Endpoints
Study SC-3030 Ongoing 52-week open label extension study from parent studies SC-3027 and SC- 3031	N = 288 Total • Patients with UC or CD who completed the maintenance phase (Week 52) received vedolizumab SC 108 mg Q2W. • Patients with UC or CD who withdrew early received vedolizumab SC 108 mg QW. • Patients with UC or CD who did not achieve clinical response at week 6 but did at week 14 received vedolizumab SC 108 mg QW.	**Primary endpoint**: Subject-year–adjusted treatment emergent AEs and SAEs during long-term vedolizumab SC treatment. **Secondary endpoints**: • Subject-year–adjusted AESIs during long-term vedolizumab SC treatment. • Proportion of subjects with clinical response during long-term vedolizumab SC treatment using partial Mayo scores (defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding score of ≥1 or absolute rectal bleeding subscore of ≤1) in UC subjects. • Proportion of subjects with clinical remission during long-term vedolizumab SC treatment using partial Mayo scores (defined as a partial Mayo score of ≤2 and no individual subscore >1 point) in UC subjects.

Source: Reviewer's table summarizing submission contents. Created from information provided in the Applicant's clinical study report for Study SC-3030 (BLA 761133, SD 52, received March 27, 2023) and the original Unireview, Section 7.1, documented in DARRTS December 17, 2019.
Abbreviations: MC: multicenter, R: randomized, DB: double-blind, QW: once weekly, Q2W: once every two weeks, Q8W: once every eight weeks, SC: subcutaneous, IV: intravenous, UC: ulcerative colitis, CD: Crohn's disease.

7.2. Review Strategy

The effectiveness of vedolizumab SC in adults for the maintenance of moderately to severely active UC was previously established during the review of the original BLA submission. The efficacy evaluation was primarily based on a single adequate and well-controlled study (SC-3027) and the prespecified efficacy comparison between the vedolizumab SC arm and the placebo arm. The study was powered for comparison of the vedolizumab SC arm to placebo, with a vedolizumab IV arm included for descriptive efficacy/safety comparison.

The safety of vedolizumab SC in adults with UC was previously established during the review of the original BLA submission using data from Study SC-3027 and supportive safety data from UC patients enrolled in Study SC-3030, an open-label long term extension study. The original BLA submission contained results up to a mean of 60 weeks of exposure to vedolizumab SC in Study SC-3030.

In the BLA resubmission, there was no new clinical efficacy data. As described in Section 8.1.2 additional efficacy analyses were performed during review of the BLA submission to support labeling claims for subgroups of the multiplicity-controlled endpoints based on prior exposure to TNF-alpha blockers and the secondary endpoint of subjects with clinical remission at both Weeks 6 and 52.

There was no new safety information from Study SC-3027 included in the resubmission of BLA 761133. Longer-term safety data from Study SC-3030 was provided by the Applicant in the resubmission compared to what was included in the original BLA. The mean duration of exposure to vedolizumab SC in the total safety population was extended to 200 weeks. The number of subjects remained the same, except for one new subject. The subject was randomized to placebo in SC-3027 and received open-label vedolizumab SC in Study SC-3030.

The BLA resubmission also included safety results from subjects with CD who received vedolizumab SC in the open-label extension Study SC-3030. These subjects with CD had participated in a separate double-blind, randomized, placebo-controlled study (Study SC-3031) prior to enrollment in Study SC-3030. In general, the safety findings from SC-3031 were similar to those in Studies SC-3027 and SC-3030 and the general safety profile of vedolizumab IV (data not shown). Given the different disease population included in SC-3031 (CD vs UC), subjects with CD were not included within the safety population analyzed to support the safety of vedolizumab SC in the treatment of UC. The safety and efficacy data from subjects with CD in Studies SC-3030/SC-3031 will be comprehensively reviewed in as part BLA 761359, submitted June 30, 2023, to support an indication for vedolizumab SC for the treatment of moderately to severely active CD.

The clinical reviewer's safety review for the BLA resubmission included verification of the safety analyses completed during review of the original BLA submission for Study SC-3027, and review

of the safety data collected from subjects with UC who were exposed to open-label vedolizumab SC between the original BLA data lock date of May 31, 2018 through the resubmission BLA data lock date of May 19, 2022 in Study SC-3030. For Study SC-3027, the primary safety analysis was performed in the population of subjects who exhibited a clinical response to 6 weeks of induction treatment with vedolizumab IV and were randomized into the double-blind maintenance period. Specifically, subjects who received vedolizumab SC were compared to subjects who received placebo during the 46-week, randomized, placebo-controlled maintenance therapy period. In addition, descriptive analyses of subjects who received vedolizumab IV were compared to subjects who received vedolizumab SC in Study SC-3027, and safety data from vedolizumab SC in Study SC-3027 were compared to the labeled safety risks for vedolizumab IV in previously conducted clinical trials of UC and CD subjects.

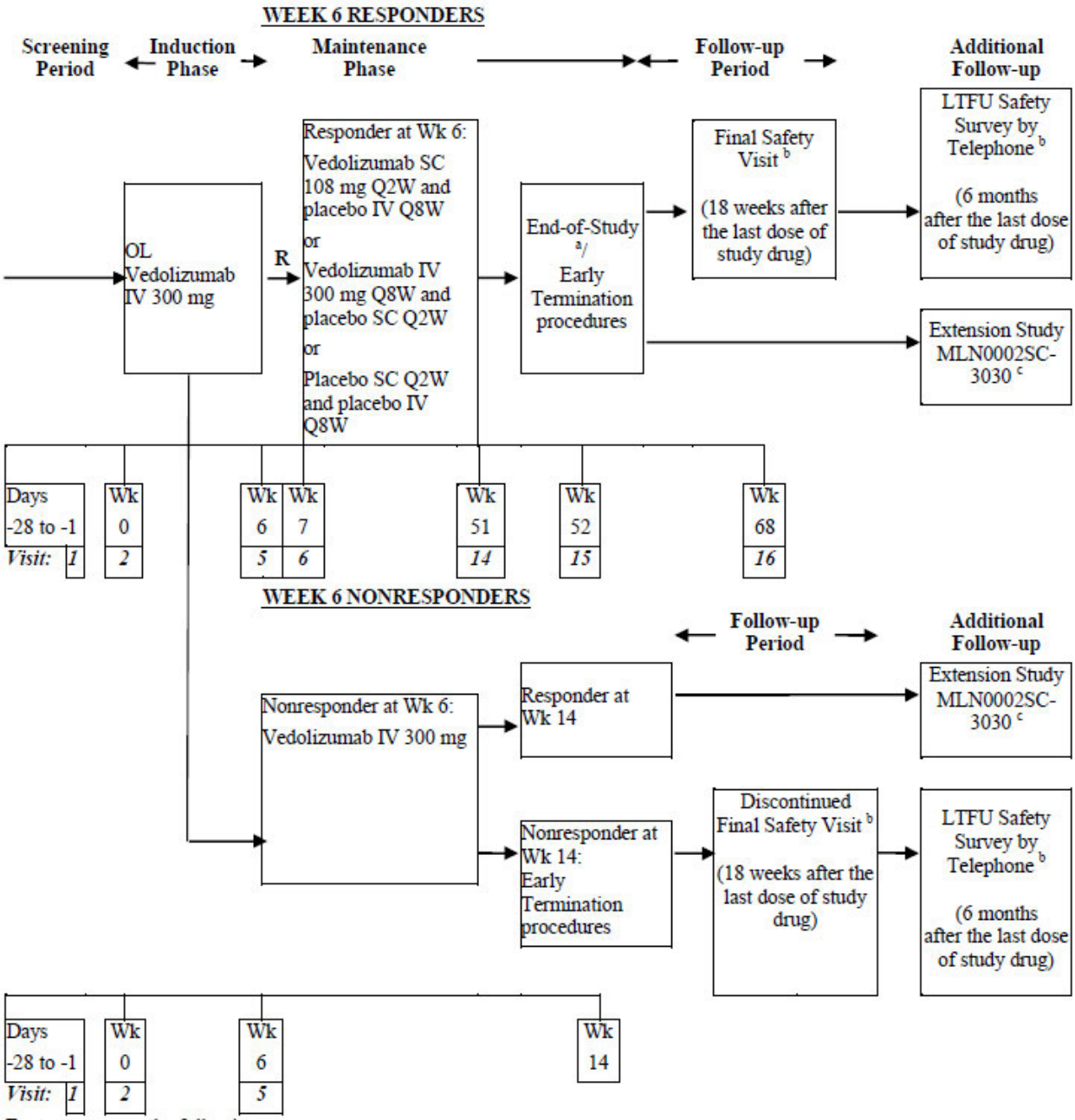
8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study SC-3027

The BLA contains the report of a single efficacy and safety study, SC-3027, designed to demonstrated efficacy of vedolizumab SC in achieving clinical remission at Week 52 in subjects with moderate to severely active UC. As shown in Figure 2, all patients received 2 doses of vedolizumab IV (week 0 and 2) and then patients who achieved a clinical response at Week 6 were randomized to one of three arms: vedolizumab SC, vedolizumab IV, or placebo. The study was powered for comparison of vedolizumab SC arm to placebo, with the vedolizumab IV arm included for descriptive comparison. Vedolizumab IV 300 mg/vial was provided in a single-use vial as a lyophilized solid formulation that was reconstituted in sterile water prior to injection. Vedolizumab SC 108 mg/vial was provided as a liquid formulation in single-use 1 mL long prefilled syringes with a backstop and plunger rod assembled together. The primary efficacy endpoint was clinical remission at Week 52, defined as complete Mayo score ≤2 and no individual subscore >1 point. The study demonstrated efficacy of the vedolizumab SC regimen on the primary and first two ranked secondary endpoints, and the safety profile of vedolizumab SC was generally comparable to that of vedolizumab IV. See original Unireview, Section 8.1.1. and 8.1.3 for a complete review of Study SC-3027 and results used to support efficacy and safety of vedolizumab SC.

Figure 2. SC-3027 Study Design



Footnotes are on the following page.

Source: Clinical Study Report for Study No. MLN0002SC-3027, Figure 9.a. included in Module 5.3.5.1, BLA 761133 received March 7, 2019.

IV: intravenous; LTFU: long-term follow-up; OL: open-label; Q2W: once every 2 weeks; Q8W: once every 8 weeks; R: randomization; SC: subcutaneous.

[a] Subjects who consented to participate in the extension study (MLN0002SC-3030) were permitted to begin the extension study dosing after end-of-study visit procedures had been completed at the Week 52 visit.

[b] Subjects who did not enter the extension study (MLN0002SC-3030) (including early terminators and Week 14 nonresponders) were to complete the final safety visit 18 weeks after their last dose of study drug and participate in a follow-up safety survey by telephone 6 months after the last dose of study drug.

[c] Visit 1 of Extension Study MLN0002SC-3030 was within 1 week of completing Week 52 (Visit 15) procedures. Subjects not randomized into the maintenance phase (Week 6 nonresponders) and responding to treatment with intravenous Entyvio 300 mg at Week 14 were also eligible for entry into the extension study.

Demographics Characteristics

Baseline (i.e., Week 0) demographic and baseline characteristics of the Study SC-3027 population for the maintenance phase are summarized in Table 7. Overall, the study population had higher proportions of subjects who were White (84%), male (60%), and less than 65 years of age (94%). Most of the subjects (87%) were enrolled at study sites outside of North America. Ethnicity information is missing for 90% of subjects, so analyses based on ethnicity are not described.

The majority of demographic characteristics were similar between vedolizumab SC and placebo subjects in the safety population, except for race and geographic region categories. As compared to the placebo arm, the vedolizumab SC arm enrolled more subjects in European study sites (74% vs. 55%), and who were White (87% vs. 75%). These differences are unlikely to meaningfully impact efficacy results.

Table 7 is similar to the demographics table included in the original Unireview (see Table 16) with a few minor discrepancies which do not change the overall conclusions. Of note, the final column in Table 7 includes the demographic information for the trial population described in labeling, which will be based only on the results of the placebo and vedolizumab SC arms.

Table 7. Demographic and Baseline Characteristics in Study SC-3027 for Maintenance Phase

Demographic and Baseline Characteristics	Placebo (N = 56)	Vedolizumab SC 108 mg (N = 106)	Vedolizumab IV 300 mg (N = 54)	Total (N = 216)	Total (Excluding Vedolizumab IV Arm) (N=162)
Age (years)					
Mean (SD)	39.4 (11.7)	38.1 (13.1)	41.7 (14.1)	39.3 (13.1)	38.56 (12.6)
Median (min, max)	37.0 (21, 66)	36.0 (18, 69)	40.5 (18, 68)	38.0 (18, 69)	37.0 (18,69)
Age Group, n (%)					
<65	53 (95)	100 (94)	50 (93)	203 (94)	153 (94)
≥65	3 (5)	6 (6)	4 (7)	13 (6)	9 (6)
Sex, n (%)					
Female	22 (39)	41 (39)	23 (42.6)	86 (39.8)	63 (39)
Male	34 (61)	65 (61)	31 (57.4)	130 (60.2)	99 (61)
Race, n (%)					

Demographic and Baseline Characteristics	Placebo (N = 56)	Vedolizumab SC 108 mg (N = 106)	Vedolizumab IV 300 mg (N = 54)	Total (N = 216)	Total (Excluding Vedolizumab IV Arm) (N=162)
American Indian or Alaska Native	1 (2)	0 (0)	0 (0)	1 (0)	1 (1)
Asian	13 (23)	14 (13)	5 (9)	32 (15)	27 (17)
Black or African American	0 (0)	0 (0.0)	2 (3.7)	2 (1)	0 (0)
White	42 (75)	92 (87)	47 (87)	181 (84)	134 (83)
Ethnicity, n (%)					
Hispanic or Latino	1 (2)	0 (0)	0 (0)	1 (<1)	1 (1)
Missing	49 (88)	99 (93)	46 (85)	194 (90)	148 (91)
Not Hispanic or Latino	6 (11)	7 (7)	8 (15)	21 (10)	13 (8)
Geographic Region, n (%)					
Africa/ Asia/ Australia	15 (27)	16 (15)	6 (11)	37 (17)	31 (19)
Europe	31 (55)	78 (74)	37 (69)	146 (68)	109 (67)
North America	9 (16)	9 (9)	10 (19)	28 (13)	18 (11)
South America	1 (2)	3 (3)	1 (2)	5 (2)	4 (2)

Source: Reviewer's analysis generated using MedDRA-Based Adverse Event Diagnostics Demographics Tool. Datasets 'adsl.xpt' received March 7, 2019, to BLA 761133 SD 01 Sequence 0000.

8.1.2. Study Results

A detailed and thorough review of efficacy results for SC-3027 was conducted as part of the review of the original BLA submission. As described in the December 17, 2019 Unireview, the review team concluded the original BLA application contained substantial evidence of the effectiveness of vedolizumab SC in inducing remission by Week 52 in patients with moderately to severely active UC, who demonstrated clinical response after two intravenous doses of vedolizumab based on Study SC-3027. Of note, the review team identified site misclassification and stratification errors in the Interactive Web Response System (IWRS) randomization strata for the original submission of data received March 7, 2019. A sensitivity analysis was conducted to evaluate the impact of misclassification of stratification and the analysis results were consistent with the reported efficacy results. Therefore, the conclusions did not change and the efficacy data appeared to be adequate. See Section 8.1.3 (Patient Disposition) in the original Unireview for a detailed description of site misclassification and stratification errors.

Labeling negotiations were not performed at the time of the original BLA submission as a Complete Response letter was issued for reasons related to product quality and the device. The efficacy section of this Unireview will focus on additional analyses performed to support labeling claims.

In the original Unireview, efficacy results for the multiplicity-controlled secondary endpoints were reported for the UC population as a whole, without reporting the results for subpopulations based on prior TNF exposure (results for the primary endpoint were reported by prior TNF exposure).

As subgroup analysis results based on prior TNF-alpha failure status (Yes/No) are considered important for informing patients and prescribers, the statistical review team conducted subgroup analyses for prior TNF-alpha failure status for the primary and multiplicity-controlled secondary endpoints during review of the BLA resubmission. Subgroup results based on prior TNF-alpha failure status will be included in labeling for all endpoints that demonstrated statistical significance based on the pre-specified multiple testing procedure. The errors in the IWRS randomization strata affected prior TNF-alpha failure status. For the purpose of labeling, the primary efficacy analyses in the total population, which included all randomized subjects who received at least 1 dose of study drug in the maintenance phase, will be based on the original IWRS randomization stratification factors to preserve the study randomization; however, subgroup analyses based on prior TNF-alpha failure status will use the corrected TNF-alpha failure status stratification factor to avoid including subjects in the incorrect subgroup. Table 8 displays the primary analysis results and subgroup results based on prior TNF-alpha failure status for all statistically significant multiplicity-controlled endpoints.

The comparison of the vedolizumab SC arm to the placebo arm in the statistical reviewer's subgroup analysis used the same method as used in the primary analysis for the total population, except the analyses did not include prior TNF-alpha failure or concomitant immunomodulator use as a stratification factor. If the number of events in either treatment arm was >5, then the risk difference was based on the Mantel-Haenszel weighted average of within stratum risk differences with concomitant use of oral corticosteroids and clinical remission status at Week 6 as stratification factors. The 95% confidence interval was constructed using the Sato variance and Wald method. Note, this analysis included the concomitant use of oral corticosteroids and clinical remission status at Week 6 stratification factors 'as randomized' instead of the corrected stratification factors. If the number of events in either treatment arm was <5, the 95% confidence intervals were based on exact unconditional intervals. P-values are not reported for the subgroup analyses because these analyses are considered exploratory.

Table 8 shows that the observed treatment difference was consistent across subgroups for the primary and statistically significant secondary endpoints. With respect to the primary endpoint, the risk difference of clinical remission at Week 52 between the vedolizumab SC 108 mg arm

and placebo arm and 95% confidence interval are 25 (-1, 44) for those with prior TNF-alpha failure, and 34 (17, 50) for those without prior TNF-alpha failure. The risk difference for "mucosal healing" at Week 52 in Week 6 responder between vedolizumab SC 108 mg arm and placebo arm and 95% confidence interval are 38 (9, 57) for those with prior TNF-alpha failure and 33 (14, 51) for those without prior TNF-alpha failure. The risk difference for clinical response at Week 52 in Week 6 responder between vedolizumab SC 108 mg arm and placebo arm and 95% confidence interval are 48 (15, 68) for those with prior TNF-alpha failure and 27 (8, 46) for those without prior TNF-alpha failure.

Table 8. Proportion of Subjects with UC Meeting Efficacy Endpoints at Week 52 in Study SC-3027

Endpoint	Placebo[a]	Vedolizumab SC 108 mg Every 2 Weeks[b]	Estimate of Treatment Difference vs. Placebo (95% CI)	P-value[c]
Clinical remission[d] at Week 52				
Total Population	N=56 14%	N=106 46%	32 (20, 45)[e]	<0.001
Prior TNF blocker failure	N=20 10%	N=40 35%	25 (-1, 44)[f]	
Without prior TNF blocker failure	N=36 17%	N=66 53%	34 (17, 50)[e]	
Improvement of endoscopic appearance of the mucosa at Week 52[g]				
Total Population	N=56 21%	N=106 57%	36 (22, 49)[e]	<0.001
Prior TNF blocker failure	N=20 10%	N=40 48%	38 (9, 57)[f]	
Without prior TNF blocker failure	N=36 28%	N=66 62%	33 (14, 51)[e]	

Endpoint	Placebo[a]	Vedolizumab SC 108 mg Every 2 Weeks[b]	Estimate of Treatment Difference vs. Placebo (95% CI)	P-value[c]
Clinical response at both Weeks 6 and 52[h]				
Total Population	N=56 29%	N=106 64%	36 (21, 51)[e]	<0.001
Prior TNF blocker failure	N=20 20%	N=40 68%	48 (15, 68)[f]	
Without prior TNF blocker failure	N=36 33%	N=66 62%	27 (8, 46)[e]	

[a] The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.
[b] Starting at Week 6 following two doses intravenous doses of ENTYVIO 300 mg administered as an intravenous infusion at Weeks 0 and 2.
[c] P-value based on Cochran-Mantel-Haenszel test
[d] Clinical remission: Complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52
[e] Estimated treatment difference and 95% confidence interval based on Mantel-Haenszel stratified risk difference
[f] Estimated difference is unadjusted for covariates and 95% confidence interval based on unconditional exact method
[g] Improvement of endoscopic appearance of the mucosa: Mayo endoscopic subscore of ≤1 point
[h] Clinical response: reduction in complete Mayo score of ³3 points and ³30% from baseline with an accompanying decrease in rectal bleeding subscore of ³1 point or absolute rectal bleeding subscore of ≤1 point.

Although previously agreed to by the Division, the secondary endpoint of the proportion of subjects with “durable clinical remission”, defined as the proportion of subjects who achieved clinical remission at Week 6 and at Week 52, was considered difficult to interpret in the original December 17, 2019 Unireview because randomization occurred at Week 6 and, therefore, Week 6 clinical remission did not reflect the effect of the vedolizumab SC 108 mg dose or placebo on efficacy. The previous Unreview instead proposed to “replace” this endpoint with clinical remission at Week 52 in the subgroup of subjects who were Week 6 remitters. The statistical review team for the resubmission considers this endpoint to be more meaningful and interpretable given the design of the study. For the vedolizumab SC 108 mg dose arm, 64% (16/25) of subjects in clinical remission at Week 6 were also in clinical remission at Week 52. For the placebo arm, 20% (3/15) of subjects in clinical remission at Week 6 were also in clinical remission at Week 52. The stratified analysis using the corrected stratification factors in the previous Unireview showed a risk difference of 40.8% with a 95% confidence interval of (12.2, 69.3) and a p-value of 0.013. However, because the number of responders and sample size for the placebo arm are small, this review team recommends instead using the unstratified exact analyses pre-specified in the statistical analysis plan for when the number of events in either treatment arm was <5 (i.e., Fisher exact test and exact unconditional confidence intervals).

Using this method, the risk difference between vedolizumab SC 108 mg and placebo is 44% with a 95% confidence interval of (8.9, 68.7) and a p-value of 0.009. Note the pre-specified "durable clinical remission" endpoint did not demonstrate statistical significance. However, had the endpoint definition preferred by the review team and currently recommended in the draft guidance for industry *Ulcerative Colitis: Developing Drugs for Treatment* (April 2022)[4] (clinical remission at Week 52 in the subgroup of subjects who were Week 6 remitters) been used in the multiple testing procedure instead, statistical significance would have been demonstrated. Therefore, the review team considers it appropriate to include information on the preferred endpoint definition in labeling.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical reviewer's approach to the safety review of Studies SC-3027 and SC-3030 in the BLA submission included:

1) Verification of the safety analysis for Study SC-3027 completed in the original Unireview. The analysis for Study SC-3027 was successfully verified and unchanged; safety analysis by demographic subgroups focused on overall SAEs, TEAEs, and injection site reactions for Study SC-3027 (see Section 8.2.6). Additional analysis of blood creatine phosphokinase (CPK) levels is included in Section 8.2.4.6.

2) Review safety data with up to 200 weeks of exposure to vedolizumab SC in Study SC-3030 in subjects with UC. This analysis replaces the safety review of Study SC-3030 in the original Unireview. Of note:

   - Subjects with CD in Study SC-3030 are not included in the safety review for this BLA resubmission.
   - Safety results reported in Study SC-3030 were compared between subject arms based on treatment assignment (including non-randomized Week 14 responders) during Study SC-3027. There were no meaningful differences between treatment arms. Therefore, for the purposes of the safety review for this BLA resubmission, results from Study SC-3030 will be reported as a whole.

3) Compare the adverse reaction profile associated with vedolizumab SC in Studies SC-3027 and SC-3030 in subjects with UC and what is described in the approved labeling for

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-developing-drugs-treatment

previously conducted clinical trials of Entyvio administered intravenously.

In addition to an assessment of deaths, SAEs, discontinuations, and TEAEs, the Applicant also identified the following Adverse Events of Special Interest which will be discussed individually by the clinical reviewer for subjects with UC in Studies SC-3027 and SC-3030:

- Injection Site Reactions
- Hypersensitivity Reactions
- PML
- Malignancies/Neoplasms
- Infections
- Liver Injury

8.2.2. Review of the Safety Database

Overall Exposure

Study SC-3027 (unchanged from the previous review)

- 106 subjects with UC received at least 1 dose of vedolizumab SC during the maintenance phase
- Mean duration of exposure was 439 days in the vedolizumab SC arm, 437 days in the intravenous Entyvio arm, and 396 days in the placebo arm

Study SC-3030

- 288 subjects with UC received at least 1 dose of open-label vedolizumab SC during the extension study
- Mean duration of exposure was 1397 days, and on average, subject received 94 injections

Total Safety Population (Pool 1) for Subjects with UC

- 304 subjects[5] with UC received at least 1 dose of vedolizumab SC in Studies SC-3027 and/or SC-3030 at the time of the data cut (May 2022)
    - During Study SC-3027, 106 subjects were assigned to the vedolizumab SC arm. During Study SC-3030 90 subjects who were enrolled in Study SC-3027 and treated in the vedolizumab SC arm (90/106) continued with vedolizumab SC treatment. An additional 198 subjects were enrolled into Study SC-3030 where they received open-label vedolizumab SC. (Total enrollment: 288)

[5] The initial submission of BLA 761133 included a total of 303 subjects with UC. One new subject was added in the resubmission. The subject was randomized into the placebo arm of Study SC-3027, completed that study, then entered Study SC-3030.

- Mean duration of exposure was 1198 days, and on average, subjects received 84 injections
- Vedolizumab SC exposure was ≥6 months in 291 subjects, ≥12 months in 247 subjects, ≥24 months in 198 subjects, and ≥36 months in 168 subjects

Adequacy of the safety database:

The number of subjects exposed to vedolizumab SC in Studies SC-3027 and SC-3030 provides adequate safety information to support the overall safety of vedolizumab SC as a maintenance regimen for the treatment of UC patients with moderately to severely active UC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no major concerns about data quality and integrity.

Categorization of Adverse Events

Medical Dictionary for Regulatory Activities version 21.0 was used for coding treatment emergent adverse events (TEAEs) in the vedolizumab SC studies and data pools. When this reviewer deemed it necessary to combine similar preferred terms into one term to facilitate a more accurate analysis, this was performed, and subsequent analysis of AEs reflect these groupings. Refer to Appendix 15.1.1. for details of recoding of AEs.

Routine Clinical Tests

Clinically relevant tests were collected at various time intervals throughout the studies and included laboratory tests (e.g., chemistry, hematology, anti-vedolizumab antibodies, fecal calprotectin), vital signs, weight, height, 12 lead electrocardiograms (ECGs) and endoscopy. These safety assessments and time intervals were reasonable for the studied population.

8.2.4. Safety Results

8.2.4.1. Deaths

There were no treatment-emergent adverse events (TEAEs) leading to death reported in Study SC-3027 as discussed in the previous Unireview.

In the resubmission, there was a total of three deaths reported for subjects with UC participating in Study SC-3030. No deaths were assessed as treatment-related by the Applicant.

The three deaths in UC subjects are summarized below:

Hypoglycemia: An 80-year-old white male with type II diabetes, hypertension, hyperlipidemia, coronary artery disease, and heart attack died in a natural manner in his home; the death certificate lists acute hypoglycemia as the cause of death. The subject was a nonrandomized Week 14 responder in Study SC-3027, enrolled in Study SC-3030 and received vedolizumab SC every two weeks for UC from (b) (6), (b) (6). On (b) (6) the subject suffered a severe syncopal episode; the subject had a history of syncopal episodes with ischemic cardiomyopathy and conduction abnormalities. The event of syncopal episode was considered to be life threatening and medically significant. On (b) (6), the subject had acute hypoglycemia of intense severity and passed away.

The clinical reviewer concurs with the Applicant that the events of acute hypoglycemia and syncopal episode appear unrelated to the study treatment given the patient's medical history of diabetes and cardiac disease.

Subileus and peritonitis: A 65-year-old white male died of life-threatening subileus and peritonitis. The subject completed participation in Study SC-3027 before enrolling in Study SC-3030 where he received vedolizumab SC every two weeks for UC starting (b) (6) (b) (6) and discontinued after his last dose was received on (b) (6). The subject was suffering from advanced atherosclerosis with abdominal aorta aneurysm and stricture of left internal femoral artery, after recent Hartmann operation (plus splenectomy) because of sigmoid diverticulum perforation was complaining at abdominal pain of increasing intensity. On (b) (6), the subject had subileus of severe intensity, followed by peritonitis of severe intensity on (b) (6). The subject underwent laparotomy because of peritonitis and paralytic ileus. A segmental bowel resection (plus appendectomy) was done with side-by-side intestinal anastomosis. On (b) (6), the subject died due to post-surgery complications with cardiopulmonary failure.

Subileus is a complication associated with underlying UC, and peritonitis is consistent with ileal perforation, therefore, the clinical reviewer concurs with the Applicant that these events appear to be associated with UC and the surgical procedure and unrelated to the study treatment.

Rectal cancer: A 41-year-old white female with a history of UC and CD died of fatal rectal cancer (malignant neoplasm of the rectum). The subject received vedolizumab SC during Study SC-3027, enrolled in Study SC-3030 and received vedolizumab SC once every two weeks from (b) (6). On (b) (6) after starting vedolizumab, the subject was hospitalized with complaints of general weakness, shortness of breath, frequent stools up to 7-10 times a day with an admixture of blood, pus, tenesmus, and pain in the small pelvis. Despite symptomatic therapy, the patient died on (b) (6). An assessment of causality between study drug and

rectal cancer is confounded given that patients with UC have a higher risk for developing colorectal cancer and the risk increases with the duration of the disease. However, since rectal cancer was diagnosed while receiving study drug, the relationship between the event and vedolizumab SC cannot be excluded.

8.2.4.2. Serious Adverse Events

See the original Unireview, Section 8.2.4, for a discussion of the SAEs reported in Study SC-3027. In summary, in Study SC-3027, 11% (23/216) of subjects reported a serious adverse event (SAE). The frequency of SAEs was similar across treatment arms (11% in placebo, 9% in vedolizumab SC, 13% in vedolizumab IV). UC was the most common SAE (4%, 9/216) and occurred more frequently in the placebo arm (9%, 5/56) compared to either vedolizumab arm (4%, 4/106 in vedolizumab SC; 2%, 1/54 in vedolizumab IV). Exacerbation of UC is likely due to lack of drug efficacy. The second most common SAE was anemia (1%, 3/216) with a similar incidence between the vedolizumab SC (2%, 2/106) and placebo (2%, 1/56) arms. These were reported as SAEs due to brief hospital stays. All other SAEs occurred in one subject each.

In the resubmission, in Study SC-3030, a total of 21% of subjects (60/288) reported 1 or more SAEs, as shown in Table 9. Similar to what was reported in Study SC-3027, UC and anemia were the only SAEs reported with a frequency ≥2%. Other SAEs occurring in more than one subject included appendicitis (3 subjects, 1%), and acute pancreatitis, acute kidney injury, COVID-19, and muscle weakness occurring in 2 subjects each. Most SAEs were reported in no more than one subject.

Table 9. Serious Adverse Events Reported in Study SC-3030 in Subjects with UC

Serious Adverse Event (AEDECOD)	Number of Subjects
Colitis ulcerative	21
Anemia	11
Appendicitis	3
Acute kidney injury	2
COVID-19	2
Muscular weakness	2
Pancreatitis acute	2
Anal fissure	1
Appendiceal abscess	1
Arthralgia	1
Arthritis	1
Atrial fibrillation	1
Cholelithiasis	1
Colon cancer	1
Colorectal adenoma	1

Serious Adverse Event (AEDECOD)	Number of Subjects
Cytomegalovirus enteritis	1
Deep vein thrombosis	1
Diverticulitis	1
Dyspepsia	1
Femoral hernia	1
Fibrin D dimer increased	1
Gastrointestinal hemorrhage	1
Gastrointestinal organ contusion	1
Glomerulonephritis rapidly progressive	1
Headache	1
Hypoglycemia	1
Ischemic stroke	1
Large intestine polyp	1
Liver contusion	1
Lumbar vertebral fracture	1
Malignant melanoma stage II	1
Meniscus injury	1
Multiple fractures	1
Myalgia	1
Myocardial infarction	1
Pancreatitis	1
Pancreatitis chronic	1
Pancreatitis necrotizing	1
Patellofemoral pain syndrome	1
Peritonitis	1
Pleural effusion	1
Pulmonary pneumatocele	1
Pyelonephritis acute	1
Rectal cancer	1
Rectal polyp	1
Rotator cuff syndrome	1
Spinal compression fracture	1
Subileus	1
Superficial vein thrombosis	1
Syncope	1
Tooth abscess	1
Ureterolithiasis	1

Serious Adverse Event (AEDECOD)	Number of Subjects
Urinary tract infection	1
Uterine leiomyoma	1
Wound	1

Source: Reviewer's analysis of ADAE dataset. Analysis limited to events occurring during Study SC-3030 (open-label extension), includes those flagged as 'Serious' and occurred during treatment with vedolizumab SC. Adverse event terms are AEDECOD (See Appendix 15.1 for details).

Overall, the types and frequency of SAEs reported in Study SC-3030 are similar to Study SC-3027. SAEs reported in Study SC-3030 that were not reported in Study SC-3027 are of low-frequency and do not raise safety concerns.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

See the original Unireview, Section 8.2.4, for a discussion of the AEs leading to study discontinuation in Study SC-3027. In summary, in Study SC-3027, the overall incidence of was 6% (12/216). The frequency of discontinuations was highest in the placebo arm (9%, 5/56) compared to the vedolizumab SC (5%, 5/106), and vedolizumab IV (4%, 2/54) arms. UC disease worsening or exacerbation was the reason for study discontinuation in 5% (10/216) of subjects. One subject from the vedolizumab IV arm discontinued from the study due to injuries suffered in a road traffic accident (1.8%, 1/54) and another subject from the vedolizumab SC arm discontinued due to elevated liver enzymes (<1%, 1/106).

In the resubmission, in Study SC-3030, the overall incidence of AEs leading to study discontinuation in subjects with UC was 7% (19/288). Similar to Study SC-3027, the AE with the highest incidence leading to study discontinuation was UC disease worsening or exacerbation (3%, 8/288). One subject who discontinued due to UC also had an AE of autoimmune hemolytic anemia. The remaining AEs leading to discontinuation included single events of iron deficiency anemia, anemia, polyarthritis, spinal ligament ossification, syncope, glomerulonephritis rapidly progressive, lower abdominal pain, cytomegalovirus enteritis, and osteoporosis. One subject discontinued treatment due to colon cancer, and another subject discontinued treatment due to follicular lymphoma and diffuse large cell B-cell lymphoma (see Section 8.2.5.4 Malignancies and Neoplasms below for further details).

Overall, the types and frequency of TEAEs leading to discontinuation of treatment are consistent between Study SC-3027 and Study SC-3030.

8.2.4.4. Significant Adverse Events

In both studies, TEAEs were classified into categories of intensity (severity) by the Applicant and defined 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.

See the original Unireview, Section 8.2.4, for a discussion of the Significant Adverse Events in Study SC-3027. In summary, in Study SC-3027, 5% (10/216) of subjects had AEs that were classified as severe. The frequency of AEs classified as severe was similar between treatment arms with 2% (1/54) of subjects in the vedolizumab IV arm, 6% (6/106) of subjects in the vedolizumab SC arm, and 5% (3/56) in the placebo arm. Each of these severe AEs were included as SAEs and/or discontinuations except for two subjects who continued on study drug; one subject experienced blood creatine phosphokinase (CPK) increased and recovered, and one subject experienced worsening of UC.

In Study SC-3030, 12% (35/288) of subjects with UC reported an AE classified as severe. Each of these AEs are described in the sections on SAEs, discontinuations, and/or deaths above. Ten subjects (3%) reported UC as the most common severe AE, and 4 subjects (1%) reported anemia. All other severe AEs were reported with <1% of subjects.

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

See the original Unireview, Section 8.2.4 Safety Results, for a discussion of common TEAEs reported in Study SC-3027. In summary, in Study SC-3027, TEAEs were reported in 71% (153/216) of subjects. This included 77% (43/56) of subjects from the placebo arm, 65% (69/106) of subjects in the vedolizumab SC arm, and 76% (41/54) of subjects from the vedolizumab IV arm.

In the resubmission, in Study SC-3030, a total of 228 (79%, 228/288) subjects with UC reported TEAEs. The majority of TEAEs were mild (30%, 87/288) or moderate (37%, 106/288) in severity. The most common (≥5%) TEAEs are listed in Table 10.

Table 10. Study SC-3030 - Most Common (≥5%) TEAEs in Subjects with UC

	Number of Subjects (%)
Adverse Events	**N = 288**
Colitis ulcerative	65 (23%)
Nasopharyngitis	46 (16%)
Upper respiratory tract infection	41 (14%)

Adverse Events	Number of Subjects (%) N = 288
Anemia	28 (10%)
COVID-19	22 (8%)
Headache	22 (8%)
Diarrhea	21 (7%)
Cough	19 (7%)
Abdominal pain	18 (6%)
Arthralgia	17 (6%)
Blood creatine phosphokinase increased	15 (5%)
Bronchitis	15 (5%)
Gastroenteritis	15 (5%)
Injection site reaction	14 (5%)
Influenza	14 (5%)
Sinusitis	14 (5%)
Back pain	13 (5%)

Source: reviewer's analysis of ADAE dataset. Analysis limited to events occurring during Study SC-3030 (open-label extension), includes treatment-emergent events that occurred during treatment with vedolizumab SC.

Overall, the safety profile of vedolizumab SC in Studies SC-3027 and SC-3030 is similar to what is labeled for intravenous Entyvio, including arthralgia, upper respiratory tract infection, bronchitis, and rash. See Appendix 15.1.2 Adverse Reaction Comparison for a full comparison of adverse reactions reported in labeling compared to Study SC-3027. Adverse events reported with vedolizumab SC but not included in the labeling for intravenous Entyvio included: anemia, increased blood creatine phosphokinase (CPK) and injection site reaction.

Anemia

In Study SC-3030, the frequency of anemia was 10% (28/288) as a TEAE with vedolizumab SC. In Study SC-3027, the frequency of anemia as a TEAE was similar across treatment arms with 6% (6/106) in the vedolizumab SC arm, 4% (2/54) in the vedolizumab IV arm, and 2% (2/56) in the placebo arm. Anemia is commonly reported in patients with UC and is attributed to UC as a chronic disease that can cause blood loss in the stool leading to iron deficiency and/or inadequate nutritional intake due to GI symptoms. Therefore, anemia is not considered an adverse reaction associated with vedolizumab SC.

Increased CPK as an AE

In the original Unireview, in Study SC-3027, 6 TEAEs of increased blood CPK were reported in 5 subjects with the highest incidence reported in the vedolizumab IV arm (6%, 3/54) compared to the placebo (2%, 1/56) and vedolizumab SC (1%, 1/106) arms. The original Unireview stated that consideration should be given to potentially including increased CPK as a less common

adverse reaction in labeling based upon the results of the 6 TEAEs in Study SC-3027. However, it is noted that the incidence in the vedolizumab SC arm was less than placebo. To understand the potential relationship between drug exposure and increased CPK, blood CPK measurements were assessed for marked laboratory abnormalities in Study SC-3027 during review of the resubmission. See Section 8.2.4.6 below for a discussion of grade 3 and 4 elevations in laboratory CPK values compared between treatment arms. It was concluded from this data that the laboratory increases of greatest magnitude were not substantively different between vedolizumab SC and placebo in Study SC-3027.

In the resubmission, in Study SC-3030, 19 TEAEs of increased CPK were reported in 15 (5%) subjects with UC:

- One 41-year-old male subject (MLN0002SC-3027 (b) (6)) experienced 5 TEAEs of increased CPK including 1 TEAE that was classified as severe and 4 TEAEs of mild severity. The increased CPK TEAE reported as severe decreased to mild severity by the next visit and resolved without intervention. The succeeding 3 TEAEs in this subject were mild in severity and not reported across continuous blood measurements. The final TEAE did not have a follow-up blood measurement after (b) (6), but it is reported that treatment continued for this subject. An information request was sent to the Applicant on June 30, 2023, that asked for additional information on case including potential causal factors and date of resolution of increased CPK. The Applicant responded on July 14, 2023, reporting that abnormal values were also found for potassium, lipase, GGT, and sodium; lipase levels were elevated at screening and at Day 1 suggesting a pre-existing etiology. These abnormalities do not fit a pattern suggestive of drug toxicity and may be attributed to concomitant use of prednisolone as elevated CPK levels are listed (b) (4).

- The other 14 subjects reported only one TEAE of increased CPK each. Three subjects reported increased CPK of moderate severity, while the remaining 11 subjects reported increased CPK of mild severity.

For 11 of the 15 subjects, the investigator did not attribute study drug as the cause of increased CPK, including the subject who reported 5 TEAEs. It is unclear what caused the increased CPK in this study; “High CPK value – caused by strength training” is listed as the reported term for one subject, but no cause is reported for the other subjects. Although CPK can become increased due to non-drug-related events (i.e., strenuous physical activity, injury), the contribution of drug exposure to increased CPK cannot be excluded. However, there were no SAEs related to increased CPK and no subject discontinued due to these AEs in either Study SC-3027 or Study SC-3030.

To further understand if increased CPK was seen in postmarketing experience, either with intravenous or subcutaneous administration, the Division of Pharmacovigilance (OSE/DPV) searched the Food and Drug Administration Adverse Event Reporting System (FAERS) for cases

of increased CPK or rhabdomyolysis with vedolizumab and did not identify any cases attributable to vedolizumab. The reports that contained diagnostic information either had a strong alternate etiology for the events or did not provide information to assess for common etiologies of the events.

In summary, increased CPK in Study SC-3027 and SC-3030 with vedolizumab was not considered to be an adverse reaction that should be included in labeling in either the clinical trials or postmarketing subsections.

Injection Site Reactions

For a discussion of injection site reactions, see Section 8.2.5.1.

8.2.4.6. Laboratory Findings

See the original Unireview, Section 8.2.4 Safety Results, for a discussion of laboratory findings in Study SC-3027. In summary, in Study SC-3027, no clinically meaningful differences between the vedolizumab SC, vedolizumab IV, and placebo arms were observed in hematology and chemistry parameters except for CPK and liver enzymes. No Hy's law abnormalities were reported. See the original Unireview, Section 15.1.3, for shift tables of ALT, AST, bilirubin, and ALP in Study SC-3027.

The following laboratory findings for CPK and liver enzymes were assessed from Study SC-3030. While not included in the original Unireview, an assessment of grade 3 and 4 elevations in CPK from Study SC-3027 is included in below.

Grade 3 or 4 Elevations in Creatine Phosphokinase

Grade 3 (>5x – 10x ULN) and grade 4 (>10x ULN) CPK increases by treatment arm in Study SC-3027 are shown in Table 11. Collectively, the results do not show a trend for greater elevations in CPK between the vedolizumab SC arm compared to either the placebo or vedolizumab IV arms. It is worth noting that in the Applicant's analysis of grade ≥3 CPK increase, one additional subject (MLN0002SC-3027 (b) (6) from the placebo arm was included (5%, 3/56). However, upon further inspection, the single grade ≥3 CPK measurement occurred during the induction period while this subject was receiving vedolizumab IV (Week 2). As a result, this subject was not included in the assessment of grade 3 and 4 elevations during the randomized maintenance period of Study SC-3027.

Table 11. Proportion of Subjects with Grade 3 or 4 Creatine Phosphokinase Serum Elevations by Treatment Arm During the Randomized Maintenance Period of Study SC-3027

CPK Serum Level	Placebo N = 56 n (%)	Vedolizumab SC N = 106 n (%)	Vedolizumab IV N = 54 n (%)
Grade 3 (>5x - 10x ULN)	0	4 (4)	1 (2)
Grade 4 (>10x ULN)	2 (4)	2 (2)	2 (4)

Source: Reviewer's analysis of ADLB dataset for Study SC-3027. Grade levels determined by NCI-CTCAE Version 5.0 for 'CPK increased'.
ULN: upper limit of normal.

In Study SC-3030 in subjects with UC, grade 3 CPK increases were measured in 3% (9/288) of subjects and grade 4 CPK increases were measured in 2% (6/288) of subjects. In most cases, these abnormal CPK values were sporadic. No trends were seen between prior treatment and increased grade ≥3 levels.

In summary, no trend of increased laboratory values for CPK grade ≥3 was observed for vedolizumab SC in Studies SC-3027 and SC-3030.

Liver Transaminases

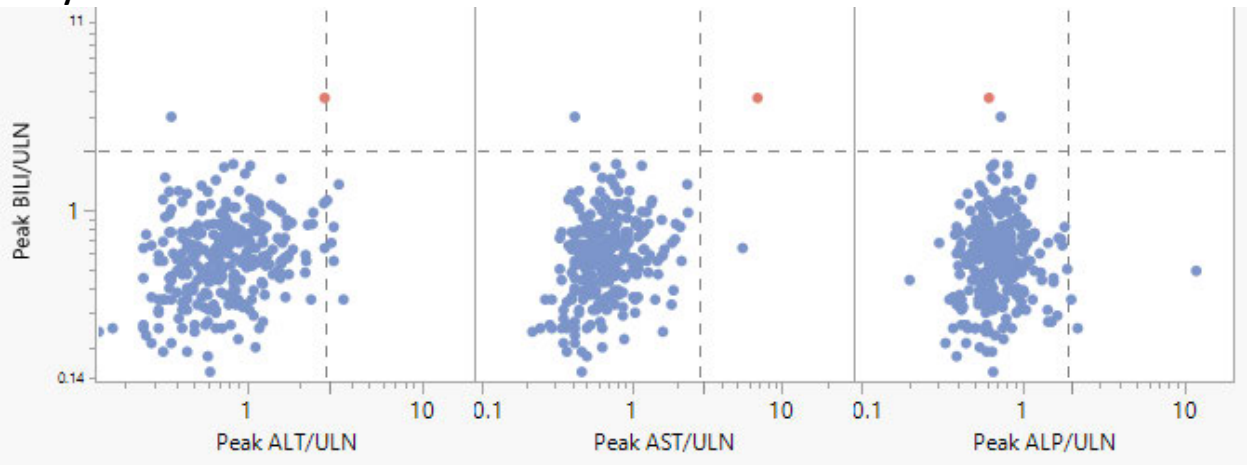
Shift analyses for liver enzymes in Study SC-3030 are shown in Table 12 and peak liver enzyme measures are displayed in Figure 3. Subjects were excluded from enrolling in Study SC-3030 if they had an ALT, AST, or ALP >3x the upper limit of normal (ULN).

Table 12. Liver Enzyme Shift Analyses – Unique Subjects in Study SC-3030

Liver Enzymes	Vedolizumab SC (Study SC-3030) N=288 n (%)
ALT ≥3x ULN	6 (3)
ALT ≥5x ULN	0
AST ≥3x ULN	2 (<1)
AST ≥5x ULN	2 (<1)
AST ≥10x ULN	0
TBL ≥2x ULN	2 (<1)
ALP ≥1.5x ULN	14 (5)
ALP ≥2x ULN	2 (<1)
ALT or AST ≥3x ULN and concurrent TBL ≥2x ULN	1 (<1)

Source: Reviewer's table created with JMP Clinical 8.0 using the Study SC-3030 dataset. Verified data provided by Applicant in response to IR (SD 58 received July 14, 2023). Numbers represent unique subjects.
Abbreviations: ALT, alanine aminotransaminase; ULN, upper limit of normal; AST, aspartate aminotransferase; TBL, total bilirubin; ALP, alkaline phosphatase.

Figure 3. Peak Liver Enzymes (ALT, AST, and ALP)/ULN vs. Peak Bilirubin/ULN by Subject in Study SC-3030



Source: Reviewer's figure with created with JMP Clinical 8.0 using the Study SC-3030 dataset.
Abbreviations: ALT, alanine aminotransaminase; ULN, upper limit of normal; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase.
The orange dot represents the one case (Subject (b) (6)) that met criteria for biochemical Hy's Law (AST >3x ULN and Bilirubin >2x ULN).
Blue dots represent all additional subjects in Study SC-3030.

There was one case that met the criteria of biochemical Hy's Law (Subject (b) (6)); this subject is represented as an orange dot in the peak liver enzyme measurements of Figure 3 above. Subject (b) (6), a 25-year-old male who continued vedolizumab SC dosing in Study 3030 and was still in the study as of the data cut-off date for the BLA resubmission (May 19,

2022). Relevant medical history included UC since (b) (6), acute pancreatitis induced by azathioprine, and gastritis. At Week 88 of Study SC-3030, the central laboratory reported increased levels of ALT (117 U/L [normal range: 10-40 U/L]), AST (312 U/L [normal range: 10-43 U/L]), and total bilirubin (69.96 µmol/L [normal range: 0-18.81 µmol/L]). CPK was also increased to 10,417 U/L (normal range: 24-207 U/L). Alkaline phosphatase was within normal limits. Within two weeks (Week 90), ALT, AST, and CPK returned to normal limits. The investigator determined the elevated ALT and AST in conjunction with markedly increased CPK in this subject are likely to be of muscle origin. It is noted that bilirubin was elevated in Studies SC-3027 and SC-3030 in this subject at most visits, including screening; the continued elevated bilirubin was assessed by the investigator as Gilbert's syndrome.

For other laboratory parameters, fluctuations were reported throughout the 52-week study; however, the fluctuations were not considered clinically meaningful and did not lead to any AEs.

8.2.4.7. Vital Signs

As described in the original Unireview, generally there were no clinically relevant findings in Study SC-3027 regarding mean changes from baseline for vital signs, including blood pressure, pulse, respiratory rate, temperature, and body weight.

Similarly, in the resubmission, in Study SC-3030, there were no trends or clinical safety concerns related to vital signs in subjects with UC. Transient variations of blood pressure and pulse rate were reported, which may be attributed to injection-related reactions, or as isolated incidence without clinical significance. Elevated temperature was reported; potential causes include infection, inflammation due to UC, or injection related reaction/hypersensitivity reaction. Overall, the data are consistent with known safety profile of vedolizumab, and no new safety concerns were identified.

8.2.4.8. Electrocardiograms (ECGs)

There were no clinically significant changes in ECGs after treatment with vedolizumab SC in subjects with UC in Studies SC-3027 or SC-3030.

8.2.4.9. QT

A thorough QT study was previously conducted with vedolizumab IV and reviewed as part of BLA 125476. No AEs consistent with QT prolongation were reported in Studies SC-3027 and SC-3030.

8.2.4.10. Immunogenicity

Immunogenicity evaluation encompassed assessment of anti-drug antibodies and their potential impact on efficacy and pharmacokinetics (described in Section 6.3.2 of the original

Unireview, and Section 6.1 of this Unireview), as well as clinical signs and symptoms of immune-related reactions, including local injection site reactions and potential systemic immune reactions, both of which are described in Section 8.2.5 below under Analysis of Submission-Specific Safety Issues.

8.2.5. Analysis of Submission-Specific Safety Issues

AEs of special interest previously identified for vedolizumab IV include: hypersensitivity reactions, progressive multifocal leukoencephalopathy (PML), malignancies, infections, and liver injury. In this application for a new subcutaneous route of administration for vedolizumab, injection site reactions were also analyzed as a submission-specific safety issue.

8.2.5.1. Injection Site Reactions

See the original Unireview, Section 8.2.5.1 Injection Site Reactions for a discussion of injection site reactions in Study SC-3027. In summary, injection site reactions were more common in subjects who received vedolizumab SC (9%, 10/106) compared to vedolizumab IV (2%, 1/54) or placebo (0%). Injection site reactions in the vedolizumab SC arm were identified in Study SC-3027 with an AE high-level term of 'injection site reactions', which included all of the following lower-level terms 'injection site reaction', 'injections site erythema', 'injection site rash', 'injection site swelling', 'injection site bruising', and 'injection site hematoma'. No injection site reactions were serious, severe, or led to study discontinuation. Two injection site reactions were of moderate severity, and all others were mild. Each of these TEAEs resolved within 5 days. While most subjects reported only 1 to 3 injection site reactions, there were three subjects who had 10, 13, and 21 reactions.

In the resubmission, in Study SC-3030, injection site reactions were reported in a total of 14 (5%, 14/288) unique subjects; two of these subjects were assigned to the vedolizumab SC arm of Study SC-3027, while the other 12 subjects received vedolizumab SC for the first time in Study SC-3030. Injection site reactions were identified in Study SC-3030 with lower-level terms 'injection site reaction', 'injections site erythema', 'injection site pruritus', 'injection site swelling', and 'injection site pain'. No injection site reactions were serious, severe, or led to study discontinuation. Injection site reactions of moderate severity were reported for two unique subjects, and mild severity for all other subjects. Six (2%, 6/288) subjects reported >3 injection site reactions during participation in Study SC-3030. Most injection site reactions resolved within 5 days, while 4 unique subjects reported injection site reactions that resolved after a longer duration of 6, 7, 14, or 110 days. Overall, the frequency and type of injection site reactions reported in Study SC-3030 is consistent with the results of Study SC-3027.

An additional analysis was completed to assess whether the overall incidence of injection site reaction increases with longer duration of exposure to vedolizumab SC. Subjects assigned to the vedolizumab SC arm of Study SC-3027 (N = 106) were followed in their participation in Study SC-

3030 (N = 90). In Study SC-3030, only two unique subjects who were assigned to the vedolizumab SC arm in Study SC-3027 reported injection site reactions during their participation in Study SC-3030. One of these two subjects (MLN0002SC-3027 (b) (6)) reported 21 TEAEs of injection site rash in Study SC-3027 and reported an additional 23 TEAEs of either non-specific injection site reaction or injection site pruritus in Study SC-3030. The other unique subject reported 6 TEAEs of injection site erythema during participation in Study SC-3030 only. The reported reactions did not lead to study discontinuation for either subject. Neither of these two subjects were positive for anti-vedolizumab antibodies.

8.2.5.2. Hypersensitivity

Hypersensitivity was defined in the Statistical Analysis Plan as including any of the following events:

- Anaphylactic/anaphylactoid shock conditions
- Angioedema
- Hypersensitivity

See the original Unireview, Section 8.2.5.2 for a discussion of hypersensitivity reactions in Study SC-3027. In summary, in Study 3027, the overall incidence of hypersensitivity AEs was more common in those subjects treated with vedolizumab SC (15%, 16/106) or vedolizumab IV (13%, 7/54) compared to those treated with placebo. All reactions were reported as nonserious and of mild or moderate severity with no anaphylaxis or severe hypersensitivity reaction and none leading to discontinuation of treatment (see original Unireview, for details).

In the resubmission, in Study 3030, the overall incidence of hypersensitivity AEs was 19% (56/288) in subjects with UC. No hypersensitivity SAEs were reported. Moderate hypersensitivity TEAEs were reported in 3% of subjects and mild hypersensitivity TEAEs were reported in 16%. The most common hypersensitivity TEAEs were allergic rhinitis (3%), rash (3%), conjunctivitis (2%), pruritus (2%), and stomatitis (2%). There were no reports anaphylaxis or severe hypersensitivity reactions and no TEAEs leading to discontinuation of treatment.

8.2.5.3. Progressive Multifocal Leukoencephalopathy

Natalizumab, another integrin antagonist, is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis and CD. To date, one case report of definite PML and one case report of possible PML have been reported with postmarketing use of intravenous Entyvio.

- One postmarketing case report of definite PML (from a diagnostic ascertainment perspective) in an Entyvio-treated patient with multiple contributory factors is described in the WARNINGS AND PRECAUTIONS section of the currently approved label (Section 5.3). The patient had concomitant human immunodeficiency virus [HIV] infection with a clusters of differentiation 4 (CD4) count of 300 cells/mm^3 and prior and concomitant immunosuppressants use. Therefore, the causal association between vedolizumab and PML was assessed as possible given the presence of factors with contributory role.

- An additional postmarketing case report of possible PML (from a diagnostic ascertainment perspective) was directly reported to the FAERS on June 8, 2023, during review of the BLA 761133 resubmission (FAERS case 22541700). The causal association between vedolizumab and PML was considered unassessable in view of limited or missing information on critical PML risk factors and the presence of confounding factors. See Section 8.2.8.1 for details and Division of Pharmacovigilance neurologist impression of the case report.

8.2.5.4. Malignancies/Neoplasms

See the original Unireview, Section 8.2.5.4 for a discussion of two subjects who reported AEs in the neoplasms benign, malignant, and unspecified (including cysts and polyps) AE system organ class in Study SC-3027. One subject in the vedolizumab IV arm reported basal cell carcinoma under the right eye, 56 days after starting study drug; no action was taken with the study drug, and the subject was reported as recovered from the AE (no additional information provided) on Day 181 (after 126 days) and continued study drug as planned. Another subject was diagnosed with rectal adenocarcinoma during the open-label induction period and was not eligible for the maintenance study. The event was considered related to long-standing UC disease. The patient underwent colectomy.

The original Unireview also described 3 subjects who reported 4 (1%, 4/288) neoplasm TEAEs that were not SAEs while participating in Study SC-3030. Two TEAEs included melanocytic nevus and benign neoplasm of skin; both subjects recovered. One subject reported diffuse large B-cell and Grade 3B follicular lymphoma and study drug was withdrawn in response to the event.

In the resubmission, the Applicant provided updated safety information from Study SC-3030 that included an additional 5 (2%, 5/288) subjects with UC who developed at least 1 SAE of malignancy, as described below. Overall, the contribution of vedolizumab to occurrences of malignancy is possible, although the assessment is confounded by exposure to prior immunosuppressants.

1. Colon cancer: A 29-year-old Asian male subject was diagnosed with stage 4 colon cancer 10 months and 20 days after starting treatment on study drug. This subject was assigned to the vedolizumab SC arm during Study SC-3027. The subject experienced abdominal

pain and distension on (b) (6) (4 days after his last dose of study drug) that was later attributed to obstruction of the proximal colon due to colon cancer. A total colectomy was not performed because of metastasis progress. The subject was discontinued on study drug and started chemotherapy. The subject refused further assessments and follow-up was not possible, so the SAE was closed with an outcome of 'not resolved'. No additional information was provided after of (b) (6). The Applicant reviewed the case and deemed this event unrelated to study drug.

Since colon cancer was confirmed while receiving study drug, the relationship between the event and vedolizumab could not be excluded. It is noted that patients with UC have a higher risk for developing colorectal cancer and the risk increases with the duration of the disease. Although UC patients with longstanding disease have an increased risk of developing colon cancer, the contribution of drug exposure to this event cannot be excluded.

2. Malignant melanoma stage II: A 55-year-old white male developed a superficial melanoma after 1 year 2 months and 19 days of starting treatment with the study drug. This subject was a non-randomized Week 14 responder in Study SC-3027. The subject underwent an atypical nevus removal with subsequent histologic diagnosis of superficial melanoma. The melanoma was removed and there was no evidence of lymph node metastases. The subject recovered from the event of melanoma. The subject received his last dose of study drug three weeks after removal of the melanoma and was prematurely discontinued due to lack of efficacy.

   Based on limited information provided in the case file, a relationship between the drug and event can neither be confirmed nor excluded.

3. Uterine leiomyoma: A 31-year-old Asian female developed uterine leiomyoma (uterine myomas) 4 years 10 months and 5 days after starting treatment with the study drug. This subject was a non-randomized Week 14 responder in Study SC-3027. Uterine myomas were identified by abdominopelvic CT after the subject visited the emergency room with symptoms right flank pain, fever, and myalgia associated with acute pyelonephritis. The subject underwent myomectomy and recovered from the surgery. Treatment with the study drug was not changed or discontinued.

   Based on limited information provided in the case file, a relationship between vedolizumab and event can neither be confirmed nor excluded.

4. Colorectal adenoma: A 43-year-old Asian female developed a colon adenoma 1 year 9 months and 24 days after starting treatment on study drug. This subject was assigned to the placebo arm during Study SC-3027. The colon adenoma was removed by endoscopic mucosal resection and the subject recovered from the event. No action was

taken with the study drug and no additional follow-up was provided. This TEAE was classified as treatment-related due to the temporal association between study drug and onset of colon adenoma. Given that colorectal cancer is a complication associated with underlying UC, the Applicant deemed this event unrelated to study drug.

An assessment of causality in this case is confounded by the patient's history of UC and concomitant use of medications such as azathioprine; however, the contribution of vedolizumab to this event cannot be excluded.

5. Rectal cancer: (see Section 8.2.4.1 Deaths for details on this subject). This subject was assigned to the vedolizumab SC arm during Study SC-3027.

In the resubmission, in Study SC-3030, the Applicant included an additional 5 (2%) subjects with UC who reported neoplasm TEAEs that were not considered SAEs (Table 13). Each of these subjects continued study drug without study discontinuation. The Applicant deemed each of these cases unrelated to study drug. However, a relationship between vedolizumab and these TEAEs cannot be ruled out.

Table 13. Neoplasms Reported in Subjects in Study SC-3030 and Not Classified as an SAE

Diagnosis	Age	Sex	Time on drug when diagnosed	Outcome
Benign neoplasm of skin	49	M	Unknown	Continued drug without discontinuation
Oral neoplasm	56	M	622	Resolved; Continued drug without discontinuation
Penile neoplasm	53	M	888	Resolved; Continued drug without discontinuation
Seborrheic keratosis	44	F	Unknown	Continued drug without discontinuation
Skin papilloma	26	M	Unknown	Resolved; Continued drug without discontinuation

Source: Reviewer's analysis of ADAE datasets for Study SC-3030.

Overall, the contribution of vedolizumab to occurrence of malignancies and neoplasms is possible, although is confounded by exposure to prior immunosuppressants.

8.2.5.5. Infections

In the original Unireview, in Study SC-3027, the number of patients who reported infections in each arm was 52% (29/56), 43% (46/106), and 63% (34/54) in the placebo, vedolizumab SC, and vedolizumab IV arms, respectively (see original Unireview, Section 8.2.5.5 for details). The most frequent infection TEAE was upper respiratory tract infections, while additional infection TEAEs

included lower respiratory tract and lung infections, abdominal and gastrointestinal infections, urinary tract infections, viral infections, and dental and oral soft tissue infections.

In the resubmission, in Study SC-3030, infection TEAEs of infection were reported in 55% (157/288) of subjects with UC. The most frequently reported infections included nasopharyngitis (16) and upper respiratory tract infection (14%). Other high-level terms of infections with an overall frequency of ≥3% included COVID-19 (8%), bronchitis (5%), gastroenteritis (5%), influenza (5%), sinusitis (5%) pharyngitis (4%), urinary tract infection (4%), and oral herpes (3%).

A total of 3.5% of subjects (10/288) developed at least 1 infection SAE including appendicitis (1%), COVID-19 (<1%), and appendiceal abscess, diverticulitis, peritonitis, cytomegalovirus enteritis, tooth abscess, pyelonephritis acute, and urinary tract infection occurring in one subject each. One subject was withdrawn from study treatment due to cytomegalovirus enteritis infection at 4.5 months after starting treatment with study drug. The severity of the event was considered moderate, and the subject is reported to have recovered.

A total of 8% (22/288) of subjects reported a TEAE of COVID-19 infection including 2 subjects (<1%) with a COVID-19 infection SAE. No COVID-19 infection TEAEs were reported as severe or life threatening. No cases of COVID-19 infection were reported in Study SC-3027 in the original Unireview and Study SC-3027 was completed prior to the onset of the global COVID-19 pandemic.

8.2.5.6. Liver Injury

Liver injury was defined for both studies and was defined in the Statistical Analysis Plan as including any of the following events:

- Cholestasis and jaundice of hepatic origin
- Hepatic failure, fibrosis and cirrhosis, and other liver damage–related conditions
- Hepatitis, noninfectious
- Liver related investigations, signs and symptoms
- Liver infections

In the original Unireview, in Study SC-3027, 7% (4/54) of subjects treated with vedolizumab IV, 2% (2/106) of subjects treated with vedolizumab SC, and none in the placebo arm met the definition of possible liver injury. It was determined that these events were consistent with the known risk of liver injury with vedolizumab IV and the risk with vedolizumab SC appeared similar to vedolizumab IV (see original Unireview, Section 8.2.5.6 for a discussion of liver injury cases).

In the resubmission, in Study SC-3030, 6% (16/288) of subjects with UC reported TEAEs that met the definition for possible liver injury. All AEs were mild or moderate in severity and none were reported as an SAE. No AEs led to study discontinuation. Hepatobiliary disorders

indicative of possible liver injury included one moderate-severity AE of cholestasis (<1%, 1/288), and mild-severity AEs of hepatic steatosis (1%, 3/288), hepatitis (<1%, 1/288), and hepatomegaly (<1%, 1/288). Liver related investigations included abnormal liver enzyme measurements (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT)) as well as AEs classified as 'hepatic enzyme increased' or 'liver function test increased'. Eleven (4%, 11/288) subjects reported a total of 18 elevated liver enzyme AEs that were either mild (15) or moderate (3) in severity. See Section 8.2.4.6 for an exploration of the laboratory values for ALT, AST, bilirubin, and ALP. One potential Hy's law case was identified, but it was determined that the subject had Gilbert's Syndrome and the elevated enzymes were not considered related to study drug.

8.2.6. Safety Analyses by Demographic Subgroups

As described in the original Unireview (see Section 8.2.6), in Study SC-3027, over 94% (203/216) of the safety analysis population was <65 years of age and the majority (84%, 181/216) was White. Therefore, while safety analyses for age (<65 and ≥ 65 years of age) and race by treatment arm are of limited usefulness, they are included below for completeness.

Safety analyses by demographic subgroups for the vedolizumab SC and placebo arms in Study SC-3027 focused on overall SAEs, TEAEs, and injection site reactions. SAEs and TEAEs by demographic subgroup are shown in Tables 14 and 15.

Table 14. Overview of SAEs Reported During the Randomized Maintenance Period of Study SC-3027 by Demographic Subgroup

	Vedolizumab SC	Placebo	Risk Difference
Subgroup	**n/N (%)**	**n/N (%)**	**(95% CI)**
Total Population	10/106 (9.4)	6/56 (10.7)	-1.28 (-13.26, 8.16)
Sex			
Female	3/41 (7.3)	2/22 (9.1)	-1.77 (-22.26, 13.36)
Male	7/65 (10.8)	4/34 (11.8)	-1 (-17.51, 11.81)
Age Group			
<65	8/100 (8.0)	6/53 (11.3)	-3.32 (-15.61, 6.27)
≥65	2/6 (33.3)	0/3 (0.0)	33.33 (-42.12, 77.72)
Race			
American Indian or Alaska Native	0/0 (--)	0/1 (0.0)	--
Asian	2/14 (14.3)	1/13 (7.7)	6.59 (-23.16, 36.28)
White	8/92 (8.7)	5/42 (11.9)	-3.21 (-17.67, 7.4)

Source: Reviewer's analysis generated using MedDRA-Based Adverse Event Diagnostics Demographics Tool.

Datasets 'adsl.xpt' and 'adae.xpt' received to BLA 761133 SD 01 March 7, 2019.

Table 15. Overview of TEAEs Reported During the Randomized Maintenance Period of Study SC-3027 by Demographic Subgroup

	Vedolizumab SC	Placebo	Risk Difference
Subgroup	**n/N (%)**	**n/N (%)**	**RD (95% CI)**
Total Population	67/106 (63.2)	40/56 (71.4)	-8.22 (-22.82, 7.74)
Sex			
Female	29/41 (70.7)	18/22 (81.8)	-11.09 (-31.54, 13.65)
Male	38/65 (58.5)	22/34 (64.7)	-6.24 (-25.72, 15.03)
Age Group			
<65	62/100 (62.0)	39/53 (73.6)	-11.58 (-26.26, 4.79)
≥65	5/6 (83.3)	1/3 (33.3)	50 (-22.6, 92.79)
Race			
American Indian or Alaska Native	0 (--)	1/1 (100.0)	--
Asian	13/14 (92.9)	9/13 (69.2)	23.63 (-8.17, 55.37)
White	54/92 (58.7)	30/42 (71.4)	-12.73 (-28.98, 5.8)

Source: Reviewer's analysis generated using MedDRA-Based Adverse Event Diagnostics Demographics Tool.
Datasets 'adsl.xpt' and 'adae.xpt' received to BLA 761133 SD 01 March 7, 2019.

A total of 11 unique subjects reported injection site reactions in Study SC-3027 (10 subjects treated with vedolizumab SC and one subject treated with vedolizumab IV), and no reactions were reported in subjects treated with placebo. Based on review of the individual subjects who reported injection site reactions in the vedolizumab SC arm (9%, 10/106), injection site reactions were reported in 10% (10/100) of subjects younger than 65 years of age (0 in those aged ≥65 years of age), 15% (6/41) of females compared to 6% (4/65) of males, and 8% (7/92) of White compared to 21% (3/14) of Asian subjects.

Despite no comparator arm in Study SC-3030, injection site reactions were assessed by demographic subgroup in Study SC-3030. A total of 14 unique subjects reported injection site reactions in Study SC-3030. Injection site reactions were reported in 5% (14/265) of subjects younger than 65 years of age (0 in those aged ≥65 years of age), 8% (9/120) of females compared to 3% (5/168) of males, and 4% (9/226) of White compared to 7% (4/58) of Asian and 50% (1/2) of Black subjects.

There were no clinically meaning differences between males and females identified for SAEs, TEAEs or injection site reactions. The demographic subgroups of age and race were too limited to make meaningful comparisons.

8.2.7. Additional Safety Explorations

The original Unireview describes safety explorations into Human Reproduction and Pregnancy, Pediatrics and Assessment of Effects on Growth, and Overdose, Drug Abuse Potential, Withdrawal, and Rebound (see original Unireview, Section 8.2.6, for details). Provided here are updates to safety explorations into Human Reproduction and Pregnancy, and Lactation.

Human Reproduction and Pregnancy

The use of vedolizumab in pregnant women has not been evaluated in clinical studies. No fetal harm was reported in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys.

A total of 14 pregnancies were reported by subjects participating in vedolizumab SC clinical studies through 19 May 2022. This includes 10 pregnancies reported since the initial submission. There were also 5 pregnancies of partners in vedolizumab studies. In most cases, the outcome of the pregnancy was not reported. One subject had an intrauterine fetal death occur approximately 1 month after the last dose; the investigator did not provide a causality assessment for the event of fetal death with the study drug. One subject had a stillbirth approximately 5 and a half months after her last menstrual period; no information was received relevant for a causal relationship between the stillbirth and study drug. One pregnancy previously reported in the original review provided an update where elective medical abortion was performed. Finally, the original Unireview reported a pregnancy where ultrasound revealed an intrauterine gestational sac and yolk sac, but no fetal pole was appreciated; this subject has a previous spontaneous abortion.

Recruitment for a non-interventional prospective observational cohort Study Vedolizumab-5001, “OTIS Entyvio Pregnancy Exposure Registry” is completed. This study enrolled women with UC or CD treated with Entyvio or other biologic agents for UC or CD during pregnancy. The study population included an Entyvio-exposed group, a diseased-matched comparison group and a non-diseased comparison group. The number of enrolled subjects in this study, as of the data cutoff of May 19, 2022, was 358. This study was conducted to satisfy postmarketing commitment 2719-7, and a final report for this study was received to BLA 125476 on June 28, 2023 and is currently under review.

Lactation

Vedolizumab is present in human milk. This BLA resubmission does not provide any new information on lactation or presence of drug in break milk or adverse events in breast-fed infants.

8.2.8. Safety in the Postmarketing Setting

8.2.8.1. Safety Concerns Identified Through Postmarketing Experience

The first marketing authorization of vedolizumab SC was granted in April 2020. As of May 19, 2022, vedolizumab SC has been approved in 44 countries.

In the resubmission, postmarketing use of vedolizumab SC outside the United States was assessed for SAEs and all injection site AEs (i.e., both serious and nonserious). In addition, during review of the submission a postmarketing case of possible PML in a patient who received vedolizumab IV was reported to FAERS. Postmarketing injection site reactions and hypersensitivity reactions with vedolizumab SC are discussed below along with the case of PML.

Foreign Postmarketing Adverse Events with Vedolizumab SC

On June 6, 2023, the Agency requested that the Applicant provide a cumulative summary of all serious AEs and all injection site AEs (i.e., both serious and nonserious) reported with postmarketing use of vedolizumab SC outside of the United States. In response, on June 23, 2023, the Applicant provided their analysis of adverse event reports received from foreign postmarketing sources through May 19, 2022 (i.e., the cut-off date for inclusion of data from the ongoing long-term study SC-3030). On July 27, 2023, the Applicant provided an updated analysis that included all postmarketing reports received through June 30, 2023. On August 16, 2023, the Applicant provided select report narratives in response to the Agency's August 9, 2023, request for: 1) case narratives for postmarketing cases (including serious and nonserious) with Preferred Terms (PTs) describing select injection site reactions or anaphylactic reaction, and 2) case narratives for the events of injection site hematoma in Studies SC-3027/SC-3030.

The Applicant compared the type and distribution of SAEs with vedolizumab SC among postmarketing data to what was observed in clinical trials and did not identify any new safety signals that emerged in the postmarketing setting.

Injection Site Reactions and Hypersensitivity Reactions

The Applicant compared the SAEs reported among patients treated with vedolizumab SC to those of patients treated with vedolizumab IV and identified differences in the distribution of PTs related to injection site reactions and certain PTs consistent with hypersensitivity that may indicate an allergic reaction; these events are further discussed below.

During review of the BLA 761133 resubmission, the Agency received FAERS case 22541700 as a postmarketing case report of possible PML. The causal association between vedolizumab and PML was considered unassessable in view of limited or missing information on critical PML risk factors and the presence of confounding factors. This case is described in detail below.

Injection Site Reactions

In their July 27, 2023, IR response, the Applicant provided the below table (Table 16), which summarizes all adverse events (i.e., serious and nonserious) within the High-Level Term (HLT) Injection site reactions among postmarketing data (source: Applicant's Global Safety Database through June 30, 2023) and clinical trials (i.e., Studies SC-3027/SC-3030 through May 19, 2022).

Table 16. Summary of Postmarketing Adverse Events Within Injection Site Reaction High Level Term for Vedolizumab SC

	Postmarketing Data	Studies SC-3027/SC-3030 [a]	Total [b]
Preferred Term	(b) (4)		
Injection site bruising	25 [0.05]	4 (0.5) [0.2]	29 [0.06]
Injection site discharge	70 [0.15]	0	70 [0.15]
Injection site discoloration	4 [0.10]	0	4 [0.01]
Injection site discomfort	7 [0.02]	0	7 [0.02]
Injection site erythema	113 [0.24]	15 (2.0) [0.7]	128 [0.28]
Injection site exfoliation	1 [<0.01]	0	1 [<0.01]
Injection site extravasation	4 [0.01]	0	4 [0.01]
Injection site haematoma	4 [0.01]	2 (0.3) [<0.1]	6 [0.01]
Injection site haemorrhage	23 [0.05]	0	23 [0.05]
Injection site hypersensitivity	9 [0.02]	0	9 [0.02]
Injection site hypoasthesia	1 [<0.01]	0	1 [<0.01]
Injection site induration	2 [<0.01]	0	2 [<0.01]
Injection site inflammation	8 [0.02]	0	8 [0.02]
Injection site injury	1 [<0.01]	0	1 [<0.01]
Injection site irritation	6 [0.01]	1 (0.1) [<0.1]	7 [0.02]
Injection site mass	28 [0.06]	0	28 [0.06]
Injection site nodule	2 [<0.01]	0	2 [<0.01]
Injection site oedema	5 [0.01]	0	5 [0.01]
Injection site pain	179 [0.39]	5 (0.7) [0.2]	184 [0.40]
Injection site papule	4 [0.01]	0	4 [0.01]
Injection site plaque	1 [<0.01]	0	1 [<0.01]
Injection site pruritus	63 [0.14]	4 (0.5) [0.2]	67 [0.14]
Injection site rash	29 [0.06]	2 (0.3) [<0.1]	31 [0.07]
Injection site reaction	54 [0.12]	14 (1.8) [0.6]	68 [0.15]
Injection site swelling	65 [0.14]	5 (0.7) [0.2]	70 [0.15]

Preferred Term	Postmarketing Data	Studies SC-3027/SC-3030 [a]	Total [b]
			(b) (4)
Injection site urticaria	12 [0.03]	0	12 [0.03]
Injection site vesicles	5 [0.01]	0	5 [0.01]
Injection site warmth	17 [0.04]	0	17 [0.04]

Source: Table modified from Applicant's submission received July 27, 2023, to BLA 761133 SD60.
Takeda Global Safety Database cut-off June 30, 2023 (postmarketing data) and Module 5.3.5.3 ISS Safety Update, Table 2.2.7.5 (clinical data), data cut-off May 19, 2022.
HLT: high level term.
[a] Pool 2 population: Includes data collected in the maintenance phase of Study SC-3027 for subjects randomized to vedolizumab SC, and data collected in the extension study (SC-3030) from subjects previously enrolled in Studies SC-3031 or SC-3027.
[b] Total events and total patient-years are respectively (b) (4) from clinical data and postmarketing data.

The Applicant identified nine serious postmarketing reports of injection site reactions, which had the following PTs: Injection site hypersensitivity (n=2), Injection site inflammation (n=2), Injection site erythema (n=1), Injection site pain (n=1), Injection site rash (n=1), Injection site reaction (n=1), Injection site urticaria (n=1). Of the nine serious injection site reaction reports, five had vedolizumab SC withdrawn (n=4) or switched to intravenous administration (n=1). The Applicant's summaries for five of the nine serious postmarketing injection site reaction reports described a notably long time to resolution, including: 4 weeks (n=1), 4 to 5 weeks (n=1), "several" weeks (n=1), 3.5 months (n=1), and one report that did not resolve.

On August 16, 2023, the Applicant provided postmarketing report narratives for select injection site reactions; these are summarized below:

- Injection site exfoliation (n=1): The report of injection site exfoliation was nonserious and involved a 63-year-old man who had "a bit of blood" on his abdomen "during last injection" (narrative does not indicate whether vedolizumab IV or SC was administered) and put a Band-Aid on the affected area; a few hours later, the area blistered, and when the patient removed the Band-aid, the skin peeled off.

- Injection site extravasation (n=4): All four reports with the PT Injection site extravasation were nonserious and described drops of medication on the skin following administration.

- Injection site hematoma (n=4): Four nonserious reports described injection site hematoma following vedolizumab SC use; three of the four hematomas were also associated with pain (n=1), swelling (n=1), or bleeding (n=1).

- Injection site hemorrhage (n=23): All 23 reports of injection site hemorrhage were nonserious and largely described small quantities of blood at the vedolizumab SC injection site. The injection site hemorrhage events had the following co-reported PTs: Injection site erythema (n=3), Injection site pain (n=3), Injection site mass (n=2), Injection site reaction (n=2), Injection site discharge (n=1), Injection site hematoma (n=1), Injection site hypersensitivity (n=1), Injection site inflammation (n=1), and Injection site vesicles (n=1); of note, the narrative for the report with Injection site vesicles does not indicate whether vedolizumab IV or SC was administered. One report [redacted] (b) (6)) was notable because the narrative described the hemorrhage as a "large amount of blood"; this report describes a 37-year-old woman who initiated vedolizumab SC 108 mg for colitis and within 24 hours experienced a "large amount of blood after the injection" and a "blue mark remained even a few days after the injection"; 3 days later, both events resolved.

- Injection site hypersensitivity (n=9): Of the nine reports with the PT Injection site hypersensitivity, two had a serious outcome and seven had a nonserious outcome. Five reports provided a description of the injection site hypersensitivity reactions, including: "a local reaction, redness and itchy patch", "painful and itchy, red and hard", around the site of injection, patient had a rather extensive allergic reaction", "local allergic reaction at injection site", and "bump, redness and sensitivity on injection site". Reports with the PT Injection site hypersensitivity also had the following PTs for the injection site reaction: Injection site erythema (n=2), Injection site hemorrhage (n=1), Injection site mass (n=1), Injection site pain (n=1), Injection site pruritus (n=1), and Injection site swelling (n=1).

- Injection site papule (n=4): The four reports with the PT Injection site papule were all nonserious; the report narratives provided the following descriptions of the papules: "bubbled under the skin", "surrounding area has come up raised, hot and red", "small, raised red area appeared around the injection site/was warm", and "injection site became raised in bubble and reddened".

- Injection site urticaria (n=12): Of the 12 reports with the PT Injection site urticaria, 11 had a nonserious outcome and 1 had a serious outcome. The 12 reports generally described the reactions as wheals (n=6), hives (n=4), or urticaria (n=2) around the vedolizumab SC injection site; some injection site urticaria events were also associated with injection site warmth (n=2), edema (n=1), pain (n=1), or swelling (n=1).

- Injection site vesicles (n=5): All five reports with the PT Injection site vesicles were nonserious; the narrative for one of the five does not indicate whether vedolizumab IV or SC was administered. The four reports of injection site vesicle reactions that occurred after vedolizumab SC administration provided the following descriptions: "painful raised

area at site of injection which blistered", "blistered with fluid", "blister was formed at the site of injection which turned blue", and "white bubble at the surface of the skin after injection".

Hypersensitivity Adverse Events, Including Anaphylaxis

The Applicant stated that the following SAE PTs may indicate an allergic reaction: Anaphylactic reaction (n=3), Chills (n=1), Choking sensation (number not provided), Circulatory collapse (number not provided), Dermatitis allergic (n=1), Dyspnoea (n=2), Erythema (n=3), Peripheral swelling (n=2), Pruritus (n=1), Pyrexia (n=1), Oedema peripheral (n=1), Throat tightness (n=1), Rash (n=2), Rash pruritic (n=1), Skin reaction (n=1), and Urticaria (n=1).

Of the three postmarketing reports with the PT Anaphylactic reaction, two occurred following vedolizumab SC administration and one occurred following vedolizumab IV administration; the two associated with vedolizumab SC administration are summarized below.

- Report# (b) (6) was reported by a physician and describes a 49-year-old woman with UC in remission who had been receiving vedolizumab for at least 1 year when she was switched to vedolizumab SC. Following the first injection of vedolizumab SC, the patient experienced dizziness. At the time of the second injection of vedolizumab SC, the patient was already hospitalized for an unknown reason; therefore, the second injection was administered by a healthcare professional. Shortly after receiving the second dose of vedolizumab SC, the patient experienced an anaphylactic reaction that included the following events: strange sensation in body, skin prickling, dizziness, tightening of throat, and bradycardia. The patient was treated with epinephrine, an antihistamine, and steroids. The outcome of the events was reported as unknown.

- Report# (b) (6) was reported by a physician and describes a 46-year-old woman who initiated vedolizumab SC and, on the same date, experienced an anaphylactic reaction that included the following events: throat irritation, feeling of hoarseness, dyspnea, redness, and pruritic rash itching all over the body; the patient was hospitalized for the events. The reaction did not resolve following administration of prednisolone and an antihistamine.

<u>Conclusions From Applicant's Analysis of the Foreign Postmarketing Experience with Vedolizumab SC</u>

- The Applicant compared SAEs with vedolizumab SC that were reported in the postmarketing setting (through June 30, 2023) to those that occurred in clinical trials (through May 19, 2022) with vedolizumab SC and did not identify new safety issues.

- The Applicant compared SAEs reported among patients treated with vedolizumab SC to those of patients treated with vedolizumab IV and identified differences in the distribution of PTs related to injection site reactions and certain PTs consistent with hypersensitivity that may indicate an allergic reaction.

- Two cases of anaphylactic reaction, one of which required hospitalization, were reported in the postmarketing setting following vedolizumab SC administration including events of bradycardia, dizziness, dyspnea, pruritic rash, redness, and throat tightness/irritation.

- The Applicant provided postmarketing report narratives for select injection site reaction PTs that were reported in the postmarketing setting but potentially were not described among clinical trials. The review team evaluated the requested report narratives and determined that injection site reactions with postmarketing vedolizumab SC use generally consist of the following events: erythema, pain, pruritus, swelling, or urticaria.

Postmarketing Case Report of Possible PML with Vedolizumab IV – FAERS Case 22541700

During review of the BLA 761133 resubmission, the Agency received FAERS case 22541700 as a postmarketing case report of possible PML. The case is possible PML from a diagnostic ascertainment perspective and is considered unassessable from a drug-event causal association perspective because of limited or missing information on PML risk factors and the presence of confounding factors. This case is described in detail below.

FAERS case 22541700 describes a 62-year-old female with past medical history significant for CD, rheumatoid arthritis, chronic kidney disease (CKD) 3b/4, deep vein thrombosis, and asthma with no prior therapies reported besides vedolizumab IV 300 mg every 8 weeks. In addition, the patient experienced multiple infections in recent months including septic arthritis, cellulitis, urinary tract infections, herpes simplex and cytomegalovirus (CMV) esophagitis, and diverticulitis, some requiring hospitalization. Concomitant medications reported include apixaban, bupropion, cefdinir, metronidazole, omeprazole, prednisone 10 mg, and valganciclovir. The vedolizumab initiation date was not reported. Approximately 5 months after the patient's most recently reported vedolizumab dose, the patient became symptomatic with cognitive impairment including abnormal thought processing, short term memory impairment, and word finding difficulty along with auditory hallucinations and possibly some gait deterioration. However, there is mention of recurrent encephalopathy and a couple of recent brain magnetic resonance imaging (MRI) studies prior to the presentation noted above.

Approximately 1 month after the emergence of cognitive impairment symptoms, the patient was hospitalized for encephalopathy investigation and a neurological examination showed cognitive impairment as noted above but did not reveal focal neurological deficits. Metabolic, nutritional, endocrine, inflammatory, and immune workup did not identify etiologies for the

encephalopathy. The patient underwent a lumbar puncture for cerebrospinal fluid (CSF) analyses which revealed normal opening pressure, <6 total nucleated cells, <3 red blood cells, protein 59 mg/dL, glucose 57 mg/dL, positive polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) (<10,000 IU/mL), enterovirus, BK virus, and John Cunningham virus (JCV) (all 3 qualitative only). The lower limit of detection of the CSF JCV deoxyribonucleic acid (DNA) PCR was 10 copies/mL. In addition, CSF angiotensin conversion enzyme was borderline at 3.1, while CSF cytology and immunotyping were negative. Infectious work-up including other body fluid serologies or PCRs revealed negative HIV-1/2 serologies, positive JCV PCR in blood (<50 IU/mL), positive CMV PCR in blood (14,218 IU/mL), and positive BK virus PCR in urine (13,395 copies/mL). A first brain MRI revealed several new findings compared to an MRI performed the prior month at the time of cognitive impairment symptoms emergence, including two areas of encephalomalacia in the left occipital lobe and left middle frontal gyrus with marginal contrast enhancement around both lesions and marginal diffusion restriction only around the left occipital lesion. There was also bihemispheric diffuse subcortical contrast enhancement sparing the cortex. A follow-up MRI a week later showed evolving findings in the left occipital and left frontal lobes with increasing mass effect and new abnormalities in the right occipital cortex. CT and MR angiogram did not reveal large or medium vessel abnormalities suggesting a vasculitic process. An electroencephalogram revealed background slowing over the right posterior quadrant without epileptiform activity. Serial complete blood counts (CBCs) from blood tests over the 4 prior months revealed fluctuating absolute lymphocyte counts (ALCs) ranging from normal to grade 1 lymphopenia including nadir ALC at 850/mm^3, and normal CD4 count. A neurology consultation indicated concerns for a central nervous system vasculitis and infectious cerebritis with PML lower on the differential diagnosis. Autoimmune encephalitis panel was pending at the time of report. A meningeal/brain biopsy was considered but not performed. The patient was discharged, but returned 2 weeks later with worsening encephalopathy, hypovolemic and distributive shocks, acute kidney injury on CKD, pneumatosis, and pneumoperitoneum. She was eventually transitioned to comfort care and died 4 days later. It is unknown whether an autopsy was performed.

Division of Pharmacovigilance Neurologist Impression of FAERS Case 22541700:

In summary, this case report is assessed as possible PML from a diagnostic ascertainment perspective and is considered unassessable from a drug-event causal association perspective.

This case report describes the development of PML approximately 5 months after the last dose of vedolizumab. According to the Berger's PML diagnostic criteria,[6] this case report could be considered possible PML from a diagnostic ascertainment perspective solely based on a positive qualitative CSF JCV DNA PCR because the neurological presentation and neuroimaging both had atypical features for PML. False positive CSF JCV DNA PCRs do occur particularly in the setting of

[6] Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013;80(15):1430-1438

immunocompetent patients and patients without compatible clinical or imaging features, and the positive predictive value is dependent on quantitative findings.[7] Traumatic lumbar puncture where blood JCV DNA contaminates the CSF specimen can also result in falsely positive CSF JCV DNA PCR. It is unclear whether there was evidence of a mildly traumatic lumbar puncture based on a reported CSF cell count of <3 red blood cells/mm^3. Lastly, a BK virus encephalitis is an equally possible diagnosis in view of the diffuse neuroimaging changes and positive CSF BK virus PCR.

From a causal association perspective, this case report is considered unassessable for an association between vedolizumab and PML because there is missing information on critical PML risk factors including vedolizumab treatment duration and prior immunosuppressants use as observed with natalizumab-associated PML[8] along with factors with confounding role. In addition, there was historical evidence of pre-existing immune compromise with multiple infections and microbiological diagnoses suggestive of innate as well as cellular and possibly humoral immunity impairment although no significant or sustained lymphopenia or neutropenia were reported prior to or at the time of presentation. Other factors with contributory or confounding role include rheumatoid arthritis and chronic prednisone use.[9] A latency of 4 to 5 months after the last dose of vedolizumab is not incompatible with a causal association in view of the product pharmacokinetics and precedents with natalizumab-associated PML developing up to 6 months after the last dose.[10]

In summary, this case report is assessed as possible PML from a diagnostic ascertainment perspective and is considered unassessable from a drug-event causal association perspective.

8.2.8.2. Expectations on Safety in the Postmarketing Setting

Based on information provided by the Applicant on postmarketing SAEs and injection site reactions reported with vedolizumab SC outside the United States, there were no new safety signals identified compared to clinical trial data and what is included in the current labeling for intravenous Entyvio. Given the similarity and shared mechanism of action between vedolizumab SC and intravenous Entyvio, the postmarketing safety experience with vedolizumab SC is expected to be comparable to that of intravenous Entyvio. As described in Section 8.2.5.1 (Injection Site Reactions) and 8.2.8.1 (Safety Concerns Identified Through Postmarketing Experience), injection site reactions are a unique adverse reaction identified with use of vedolizumab SC in both clinical trial and postmarketing settings. There does not

[7] Swinnen B, Saegeman V, Beuselinck K, et al. Predictive value of JC virus PCR in cerebrospinal fluid in the diagnosis of PML. Diagn Microbiol Infect Dis. 2019;95(3):114859.
[8] Tysabri (Natalizumab). Prescribing Information. Biogen Inc.; Cambridge, MA. Updated April 2023.
[9] Aksamit AJ. Review of progressive multifocal leukoencephalopathy and natalizumab. Neurologist. 2006;12(6):293-298.
[10] Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Progressive multifocal leukoencephalopathy after natalizumab discontinuation. Ann Neurol. 2014;75(1):108-115.

appear to be an increased risk of immunogenicity with vedolizumab SC, although the data in the BLA is limited (see Section 6.1).

One new postmarketing case report of possible PML (from a diagnostic ascertainment perspective) with an unassessable causal relationship to vedolizumab administration was received to the FAERS database on June 8, 2023 (described in Section 8.2.5.3). The Agency will continue to monitor for cases of PML with vedolizumab.

8.3. Statistical Issues

There are no remaining statistical issues. The analyses and issues were identified and discussed in the original Unireview. The additional analyses discussed in Section 8.1.2 are for the purposes of labeling.

8.4. Conclusions and Recommendations

As described in the original Unireview, the safety and effectiveness of vedolizumab SC in adults have been established based upon a single adequate and well controlled Study (SC-3027) with additional supportive long-term safety data (Study SC-3030) for the treatment of moderately to severely active UC in adults. In Study SC-3027, vedolizumab SC demonstrated efficacy in a higher proportion of subjects for the primary endpoint of clinical remission at Week 52 defined as a full Mayo score of ≤2 points and no individual subscore >1 point compared to placebo. Efficacy was also demonstrated on two of four prespecified secondary endpoints in the study (i.e., improvement of endoscopic appearance of the mucosa at Week 52 and clinical response at both Weeks 6 and 52).

No new efficacy data was provided in the resubmission of BLA 761133. Additional efficacy analyses conducted during the resubmission of BLA 761133 were limited to subgroups based on prior TNF-alpha status. Overall, the results from the analyses of the primary and the multiplicity-controlled secondary endpoints provided substantial evidence of effectiveness for vedolizumab SC in treating adult patients with moderately to severely active UC when administered as maintenance therapy following two vedolizumab IV induction doses.

The safety profile of vedolizumab SC for the treatment of moderately to severely active UC appears to be consistent with the labeled safety profile of intravenous Entyvio. Labeled risks with IV administration include, but are not limited to, hypersensitivity reactions, infections, and liver injury. The risks included in the label for intravenous Entyvio are consistent with what was reported with vedolizumab SC in Studies SC0-3027 and SC-3030. Moreover, Study SC-3027 and SC-3030 did not identify new safety concerns with vedolizumab SC when administered as maintenance therapy following two intravenous induction doses, except for injection site

reactions. The safety profile was similar between patients who were switched to vedolizumab SC in SC-3027 and patients in UC and CD clinical trials who received intravenous ENTYVIO.

The safety of vedolizumab SC, following two intravenous induction doses, was established in the original Unireview based on efficacy supported by 52-week data from Study SC-3027 (6 weeks of intravenous induction followed by 46 weeks of subcutaneous maintenance therapy) and safety supported by mean duration of exposure of 421 days from both Studies SC-3027 and SC-3030. In the resubmission, the Applicant provided updated data from Study SC-3030 to further support the safety of vedolizumab SC with a longer mean duration of exposure of 1198 days to supplement the original BLA.

In general, the safety profile of vedolizumab SC established in Studies SC-3027 and SC-3030 is similar to the safety profile established in clinical trials that supported approval of intravenous Entyvio. Labeled risks with IV administration include, but are not limited to, infusion-related reactions and hypersensitivity reactions, infections, liver injury, and PML. Studies SC-3027 and SC-3030 did not identify new safety concerns with vedolizumab SC when administered as maintenance therapy following two intravenous induction doses of vedolizumab IV, except for injection site reactions.

In Study SC-3027, injection site reactions were reported with vedolizumab SC in 9% of subjects including injection site erythema, rash, swelling, bruising, and hematoma. None of these reactions were serious, severe, or led to study discontinuation. Infusion-related reactions and hypersensitivity reactions have been reported in clinical trials for intravenous Entyvio, including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or intravenous hydrocortisone treatment. These types of reactions were not observed with vedolizumab SC.

In Study SC-3027, 6% (6/106) subjects were ADA-positive. There was no apparent increase in immunogenicity with vedolizumab administered as a subcutaneous injection compared to an intravenous infusion in the clinical trials. However, there is insufficient data to assess the effect of anti-vedolizumab antibodies on pharmacokinetics, effectiveness, and safety of vedolizumab SC administered as a subcutaneous injection in Study SC-3027.

SAEs and injection site reaction AEs reported with postmarketing use of vedolizumab SC in foreign countries were reviewed and compared to the safety profile established from Studies SC-3027 and SC-3030. Differences were identified in the distribution of PTs related to injection site reactions and certain PTs consistent with hypersensitivity, but no new safety issues. In addition, one new postmarketing case report of possible PML in a patient receiving vedolizumab IV was received during review of the BLA 761133 resubmission but was determined to have an unassessable causal relationship to vedolizumab. No new safety signals are expected postmarketing in the U.S.

In conclusion, the safety and effectiveness of vedolizumab SC as a maintenance regimen, following two vedolizumab IV induction doses have been established in adults for the treatment of moderately to severely active UC. The review team recommends approval of Entyvio injection and Entyvio Pen injection for subcutaneous use.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee was convened for this application because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class or in the intended population.

10 Pediatrics

BLA 761133 for Entyvio injection and Entyvio Pen injection, for subcutaneous use for the indication of treatment of moderately to severely active UC triggers the Pediatric Research Equity Act PREA because it contains a new dosage form (liquid injection), dosing regimen (every two weeks), and route of administration (subcutaneous).

The Applicant has an amended Agreed iPSP on file (dated January 5, 2023).

With this application, the Applicant requests a waiver of pediatric studies for subjects birth to 2 years of age, citing studies are impossible or highly impracticable. The Division agrees. The incidence of inflammatory bowel disease (IBD) in children under 2 years of age is very low. The patients under 2 years of age with very early onset IBD are more likely to have a different (monogenic) cause of their disease that requires different treatment as compared to more typical IBD. Based on diagnostic challenges and the very limited patient population, clinical studies are impossible or impracticable to conduct in this age group. A partial waiver for this population was granted for vedolizumab IV with the approval of BLA 125476.

The Applicant also requests a deferral request for pediatric studies for subjects 2 to 17 years of age because data from the proposed vedolizumab SC pediatric clinical studies will not be available at the time of vedolizumab SC BLA submission for treatment of adults; the adult studies are complete, and the product is ready for approval.

This pediatric program relies upon extrapolation of efficacy from 1) adult vedolizumab SC data which demonstrated efficacy in moderately to severely active UC and confirmed similarity in PK parameters between intravenous and subcutaneous maintenance treatment in adults with UC, and 2) results from the (ongoing) randomized, double-blind, controlled trial in pediatric subjects with moderately to severely active CD and UC, who will be treated with intravenous Entyvio.

Provided that the intravenous pediatric study demonstrates efficacy of exposures similar to those achieved by adults in the intravenous and subcutaneous studies, the necessary data to support approval of subcutaneous treatment in maintenance of UC requires demonstration of PK similarity and safety in pediatric subjects.

This application was discussed with the Pediatric Review Committee (PeRC) on August 29, 2023, and the PeRC agreed with the division's plan to issue a waiver for birth to less than 2 years of age and a deferral for 2 to 17 years. Details of the deferred studies to be conducted as PREA PMRs are found in Section 13.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

In the original review cycle, due to the product quality deficiencies in the BLA, labeling was not discussed with the Applicant. During the resubmission review, on August 25, 2023, the review team sent comments on the PI to the Applicant. The Applicant resubmitted the PI on August 31, 2023, and agreement was reached on September 14, 2023, as reflected in the table.

Table 17. Prescribing Information

Full Prescribing Information Sections[1]	**High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]**
INDICATIONS AND USAGE	No changes were made to this section by the Applicant. The indication is for the treatment of moderately to severely active UC in adults.
DOSAGE AND ADMINISTRATION	This section was reorganized to first describe the important administration information pertaining to all indications and uses (i.e., update immunizations prior to treatment; intravenous Entyvio is to be administered by a healthcare provider as a 30-minute infusion; and that a patients/caregivers can be trained to administer Entyvio subcutaneously using the prefilled syringe or pen. The recommended dosage information for the UC indication was revised to first describe the intravenous regimen and then that the subcutaneous regimen (108 mg every two weeks) is an option for patients starting at Week 6 after completion of the first two intravenous doses at Weeks 0 and 2.

Full Prescribing Information Sections[1]	**High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]**
	Information was also added on how to switch patients beyond Week 6 from intravenous infusion to subcutaneous injection. To switch patients in clinical response or remission, the first subcutaneous dose is administered in place of the next scheduled intravenous infusion and every two weeks thereafter. See Section 6.1.
ADVERSE REACTIONS	The safety information from Studies SC-3027 is briefly summarized following the description of safety for the clinical trials of intravenous Entyvio for UC and CD in the Clinical Trials Experience subsection. The safety profile was similar between both routes of administration except for injection site reactions (9%), including injection site erythema, rash, swelling, bruising, and hematoma. See Section 8.2.5.1. The subsection (b) (4) was deleted and the information moved (b) (4) (b) (4)
CLINICAL PHARMACOLOGY *Pharmacokinetics*	Pharmacokinetic parameters were added describing vedolizumab subcutaneous injection following intravenous infusion in healthy subjects and subjects with UC.
CLINICAL PHARMACOLOGY *Immunogenicity*	The immunogenicity information (b) (4) describing intravenous administration of vedolizumab for 52 weeks in clinical trials of UC and CD was moved to this new subsection and revised to follow the labeling guidance. A concluding sentence was added following the intravenous data to state: "Because of the low occurrence of persistent anti-vedolizumab antibodies, the effect on the safety and effectiveness of Entyvio in (b) (4) has not been fully characterized." The results from the 52-weeks of data from in Study SC-3027 (6 weeks of intravenous data plus 46 weeks of subcutaneous data) was added along with the conclusion that there is insufficient data to assess the effect of anti-drug antibodies on

Full Prescribing Information Sections[1]	**High-Level Summary of the Major Issues with the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]**
	pharmacokinetics, effectiveness, and safety of Entyvio in Study SC-3027. See Section 6.1.
CLINICAL STUDIES	The efficacy results for Study SC-3027 was added as "UC SC Trial". The trial is described as a randomized, double-blind, placebo-controlled trial in which patients received open-label vedolizumab IV at Weeks 0 and 2 and then, if they achieved clinical response, they were randomized to vedolizumab SC or placebo at Week 6. The third arm in the study of vedolizumab IV is not described because that arm was included in the study for descriptive purposes only and was not powered for statistical comparisons. Results of the primary endpoint (proportion of subjects in clinical remission at Week 52), along with the secondary multiplicity-controlled endpoints of improvement of the endoscopic appearance of the mucosa at Week 52 and clinical response at both Weeks 6 and 52 are described in a table for the total population and for the individual subgroups of prior/without prior TNF blocker failure. The third-ranked secondary endpoint of clinical remission at both Weeks 6 and 52 in the total population did not show statistically significant results. Although the endpoint was previously agreed to by the Division when the protocol was developed the Division's approach has evolved and, due to the study design, the analysis is no longer considered appropriate. Instead results for the subgroup of subjects who were in remission at Week 6 and maintained remission at Week 52 are included as descriptive text below the table. Although the subgroup analysis was not prespecified, it is considered to be clinically meaningful. Results by TNF blocker status for this endpoint are not described because of the small sample size in the subgroup. The fourth-ranked secondary endpoint of corticosteroid-free remission is not included because it did not demonstrate statistical significance. For additional discussion and rationale on the endpoints, see Section 8.1.2.

[1] Some sections may not be included because those sections may not have major issues (or changes).
[2] The finalized PI is the PI that will be approved or is close to being approved.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new safety signals were identified during this review that would warrant initiation of risk evaluation mitigation strategies.

13 Postmarketing Requirements and Commitment

There are two postmarketing requirements (PMRs) and one postmarketing commitment (PMC).

Postmarketing Commitment (PMC)
The Applicant agreed to the following PMC from OPQ/OBP in an information response dated August 14, 2023.

PMC 4493-1 Perform a supplemental low endotoxin recovery study to examine the effects of (b) (4) at (b) (4) °C on endotoxin recovery in the drug product spiked with reference standard endotoxin or control standard endotoxin and stored up to (b) (4) days at (b) (4) °C.

Final Report Submission: 12/2024

PREA Postmarketing Requirements (PMRs)
The Applicant agreed to complete the following two planned trials in pediatric subjects with UC as PREA PMRs on September 21, 2023.

PMR 4493-2 A study to evaluate the pharmacokinetics, immunogenicity, and safety of Entyvio (vedolizumab) as a subcutaneous injection for maintenance treatment in pediatric patients ≥2 to <18 years of age with ulcerative colitis or Crohn's disease who achieve clinical response following induction treatment with intravenous Entyvio (vedolizumab) for injection.

Final Protocol Submission: 10/2023
Study Completion: 06/2028
Final Report Submission: 12/2028

PMR 4493-3 A study to evaluate the long-term safety of Entyvio (vedolizumab) as a subcutaneous injection in pediatric subjects ≥2 to <18 years of age with ulcerative colitis or Crohn's disease.

Final Protocol Submission: 03/2024

Study Completion:	06/2033
Final Report Submission:	12/2033

14 Division Director (DHOT) Comments

Takeda proposes Entyvio (vedolizumab) injection and Entyvio Pen injection for subcutaneous use as a drug-device combination product with a new dosage form (injectable solution), two new presentations (a single-dose prefilled syringe with needle safety device and a single-dose prefilled pen with autoinjector), a new route of administration (subcutaneous), and a new dosage regimen (maintenance treatment following at least two initial intravenous induction doses of Entyvio for injection) for the treatment of adults with moderately to severely active UC.

This application successfully responds to the CR deficiencies and other additional non-approvability issues raised in the action letter dated December 17, 2019. All deficiencies and other issues listed in the CR letter have been resolved. A clinically meaningful and statistically significant benefit was demonstrated for the primary endpoint and two key secondary endpoints in Study SC-3027. This constitutes substantial evidence of effectiveness in a single adequate and well-controlled study supported by confirmatory evidence from existing adequate and well-controlled clinical investigations of Entyvio administered intravenously for both induction and maintenance therapy for the treatment of adults with moderately to severely active UC. These combination products provide additional flexibility and convenience for patients/caregivers and allow them the ability to administer vedolizumab at home rather than at an intravenous infusion center.

I agree with the review team that this application be approved.

15 Appendices

15.1. Clinical Appendices (Safety)

15.1.1. Adverse Event Recoding

Table 18. Adverse Event Recoding of AE Dataset for Study SC-3030

Count	Dictionary-Derived Terms		Recoded Terms
12	Abdominal pain		Abdominal Pain
4	Abdominal pain lower		
2	Abdominal pain upper		
6	Gamma-glutamyl transferase increased		Abnormal liver enzymes
4	Alanine aminotransferase increased		
3	Aspartate aminotransferase increased		
3	Blood alkaline phosphatase increased		
1	Hepatic enzyme increased		
22	Anemia		Anemia
5	Iron deficiency anemia		
1	Autoimmune hemolytic anemia		
15	Blood creatine phosphokinase increased		Blood creatine phosphokinase increased
1	Blood creatinine increased		
17	Cough		Cough
1	Allergic cough		
1	Productive cough		
10	Gastroenteritis		Gastroenteritis
2	Gastroenteritis viral		
2	Gastrointestinal infection		
1	Gastrointestinal viral infection		
19	Headache		Headache
1	Cluster headache		
1	Migraine		
1	Tension headache		
6	Injection site reaction		Injection site reaction
8	Injection site erythema		
3	Injection site pruritus		
2	Injection site swelling		
1	Injection site pain		
3	Rash macular		Rash
3	Rash		

Count	Dictionary-Derived Terms		Recoded Terms
2	Rash erythematous		
1	Rash papular		
4	Respiratory tract infection		Respiratory tract infection
3	Respiratory tract infection viral		
37	Upper respiratory tract infection		Upper respiratory tract infection
4	Viral upper respiratory tract infection		

Source: Reviewer's table showing regrouping of reported Dictionary-Derived Terms into grouped AE terms for the safety analysis of Study SC-3030.

15.1.2. Adverse Reaction Comparison

Table 19. Adverse Reactions Comparison – Intravenous Entyvio Label and Study SC-3027

	Entyvio PI – Section 6.1 (UC and CD subjects)		**Study SC-3027 (UC subjects)**		
Adverse Reaction	**INTRAVENOUS ENTYVIO† (N=1434)**	**Placebo‡ (N=297)**	**Vedolizumab IV (N=54)**	**Placebo (N=56)**	**Vedolizumab SC (N=106)**
Nasopharyngitis	13%	7%	~~19%~~	~~20%~~	~~10%~~
Headache	12%	11%	~~2%~~	~~11%~~	~~8%~~
Arthralgia	**12%**	**10%**	7%	2%	6%
Nausea	**9%**	**8%**	0%	0%	2%
Pyrexia	**9%**	**7%**	2%	0%	1%
Upper respiratory tract infection	**7%**	**6%**	4%	4%	**9%**
Fatigue	6%	3%	**NR**	**NR**	**NR**
Cough	**5%**	**3%**	~~4%~~	~~4%~~	~~4%~~
Bronchitis	**4%**	**3%**	4%	0%	3%
Influenza	4%	2%	~~2%~~	~~2%~~	~~2%~~
Back pain	4%	3%	~~2%~~	~~4%~~	~~3%~~
Rash	**3%**	**2%**	**7%**	4%	3%
Pruritus	**3%**	**1%**	2%	0%	2%
Sinusitis	3%	1%	~~0%~~	~~5%~~	~~1%~~
Oropharyngeal pain	**3%**	**1%**	2%	0%	2%
Pain in extremities	**3%**	**1%**	2%	0%	2%

Source: Reviewer's tables comparing adverse reactions labeled in Section 6.1 of the Prescribing Information for Entyvio (July 2023) and adverse reactions reported in the safety analysis of Study SC-3027. Adverse reactions in bolded font had higher frequencies reported for vedolizumab IV or SC compared to placebo. In the Study SC-3027 columns, numbers with a strikethrough represent those where the incidence of the adverse event is equal to or highest in the placebo arm.
NR: not reported.

15.2. Financial Disclosure

Study SC-3027 was used to establish effectiveness and demonstrate safety of vedolizumab SC. Study SC-3030 was an open-label, long-term extension used to provide additional support for the long-term safety of vedolizumab SC. In the original submission of BLA 761133, the Applicant disclosed financial arrangements with four clinical investigators. Form 3455 was submitted for both studies for each of the four investigators, the materials were reviewed, and no further action was indicated. See Section 15.2. of the original Unireview for details.

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable.

BLA 761339

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical Primary Reviewer	Bo Zhang	OTS/OB/DBIII	8.1 ☒ Authored ☐ Approved
	Signature: Bo Zhang -S Digitally signed by Bo Zhang -S Date: 2023.09.22 14:02:40 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical Team Leader	Paul Imbriano	OTS/OB/DBIII	8.1, 8.3 ☒ Authored ☒ Approved
	Signature: Paul M. Imbriano -S Digitally signed by Paul M. Imbriano -S Date: 2023.09.22 16:06:24 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology Primary Reviewer	Selim Fakhruddin	OTS/OCP/DIIP	6 ☒ Authored ☐ Approved
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Clinical Pharmacology	Insook Kim	OTS/OCP/DIIP	6 ☐ Authored ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Andrew Kelleher	OND/OII/DG	1, 2, 3, 4.1, 7, 8.1, 8.2, 8.4, 10, 15.1, 15.2 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Andrew R. Kelleher -S Digitally signed by Andrew R. Kelleher -S Date: 2023.09.22 15:16:03 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Joette Meyer	OND/OII/DG	All Sections ☒ Authored Sections 1.3 and11 ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Joyce Korvick	OND/OII/DG	All Sections ☐ Authored ☒ Approved
Signatory Authority	**Signature:** Joyce A. Korvick -S Digitally signed by Joyce A. Korvick -S Date: 2023.09.26 09:12:47 -04'00'		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D RICHARDS
09/27/2023 12:06:18 PM

JOYCE A KORVICK
09/27/2023 12:19:03 PM

BLA Multidisciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761133
Priority or Standard	Standard
Submit Date(s)	March 7, 2019
Received Date(s)	March 7, 2019
PDUFA Goal Date	January 7, 2020
Division/Office	Division of Gastroenterology and Inborn Errors Products/ODE III
Review Completion Date	December 16, 2019
Established/Proper Name	Vedolizumab
(Proposed) Trade Name	Entyvio Pen and Entyvio Syringe
Pharmacologic Class	α4β7 integrin antagonist
Code Name	MLN0002SC
Applicant	Takeda Development Center Americas, Inc.
Dosage Form	Subcutaneous injection
Applicant Proposed Dosing Regimen	108mg/0.68mL by subcutaneous injection every 2 weeks after 2 or more IV infusions
Applicant Proposed Indication(s)/Population(s)	For maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	Ul 64766004 Ulcerative colitis (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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APPEARS THIS WAY ON ORIGINAL

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OPQ = Office of Pharmaceutical Quality
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis

Glossary

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma time-concentration time curve
AVA	anti-vedolizumab antibody
BLA	biologics license application
CPK	creatine phosphokinase
CSR	clinical study report
ECG	electrocardiogram
ECL	electrochemiluminescence
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
GIT	gastrointestinal tract
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IND	investigational new drug
IV	intravenous
IWRS	Interactive Web Response System
NVOC	nonvolatile organic compounds
PDE	permissible daily exposure
PFS+NSD	prefilled syringe with needle safety device
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
SAE	serious adverse event
SC	subcutaneous
SVOC	semivolatile organic compound
TEAE	treatment-emergent adverse event

TNF	tumor necrosis factor
TNFα	tumor necrosis alpha
UC	ulcerative colitis
VOC	volatile organic compound

1. Executive Summary

1.1. Product Introduction

Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7. The mechanism of action of vedolizumab is independent of the mode of administration (IV or SC). In 2014, vedolizumab IV was approved for:

> inducing and maintaining clinical response and remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Vedolizumab for subcutaneous injection (referred to below as vedolizumab SC) is a new liquid formulation intended for subcutaneous (SC) administration. Two commercial presentations of vedolizumab SC have been developed (prefilled syringe with needle safety device [PFS + NSD] and prefilled syringe in an autoinjector/pen [PFS + AI]). The objective of vedolizumab SC is to allow an additional route of administration for patients who may not wish to continue intravenous (IV) administration after induction period.

1.2. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Vedolizumab solution for IV infusion was approved for the treatment of moderate to severely active ulcerative colitis (UC) in 2014. This biologics license application (BLA) proposes a combination product (drug plus device) for subcutaneous injection, to provide an alternate dosing option for patients who have received at least 2 doses of intravenous (IV) infusion and are responding. The recommended regulatory action is **Complete Response (CR).**

This BLA contains the report of a single efficacy and safety study, SC-3027, designed to demonstrated efficacy of subcutaneous (SC) vedolizumab in achieving clinical remission at Week 52 in subjects with moderate to severely active UC.[1] In study SC-3027, all patients received 2 doses of IV vedolizumab (week 0 and 2) and then patients who achieved a clinical response[2] at Week 6 were randomized to one of three arms: SC vedolizumab, IV vedolizumab, or placebo. The study was powered for comparison of SC arm to placebo, with IV arm included for descriptive comparison. The primary efficacy endpoint was clinical remission at Week 52, defined as complete Mayo score ≤2 and no individual subscore >1 point. The study demonstrated efficacy of the SC regimen on the primary and first two ranked secondary endpoints, and the demonstrated safety profile was generally comparable to that of the IV formulation (as labeled on the basis of the studies which supported initial approval).

The major review issues which preclude approval are device and formulation related. A major issue identified was needle clogging, which occurred during stability testing. **The Applicant failed to adequately identify and investigate the root cause of identified clogging, nor have they adequately provided mitigation strategies and controls to ensure that this issue is addressed, resulting in recommendation for CR.** While the Applicant proposes that (b) (4) (b) (4) (b) (4) This potential cause was not evaluated or excluded as a root cause. Additional (systematic) deficiencies were identified pertaining to inadequate procedures in place to identify and mitigate problems occurring (b) (4) (b) (4). See details in the table below and the CR letter.

[1] Moderate to severely active UC was defined as a full Mayo score of 6-12 inclusive.

[2] Clinical response was assessed using the full Mayo score, where clinical response was defined as a reduction in Mayo score of ≥3 points and ≥30% from week 0, and a decrease in rectal bleeding score of ≥1 or absolute rectal bleeding score of 0.

Additionally, human factors (HF) validation study data were determined insufficient to support safe and effective use of the proposed prefilled pen presentation. Deficiencies included observed use errors, close calls, and use difficulties in selecting correct injection site, removing device cap, placing the needle-end against the skin, administration of a full dose, and checking window to determine full dose was administered. The Applicant will need to implement mitigation strategies to address these issues, as well as conduct and submit results from an additional HF study to ensure these mitigations are effective and do not introduce new risks. On the basis of the Division of Medical Error Prevention and Analysis (DMEPA) team's assessment, **the prefilled pen presentation is not recommended for approval.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	➢ UC is an idiopathic, inflammatory condition that primarily affects the colon. It is a chronic and progressive disease, that when untreated, will result in serious morbidity (i.e., chronic diarrhea, rectal bleeding, weight loss, and extra-intestinal manifestations of disease), which may necessitate surgery and carries potential mortality risk.	UC is a serious, chronic disease that requires effective, long-term therapy to manage.
Current Treatment Options	➢ There are a number of approved pharmacological agents across multiple drug classes available for moderate to severe UC. ➢ Patients may be managed with conventional therapies (corticosteroids, azathioprine, 6-mercaptopurine) or "advanced therapies" which includes biologic agents (tumor necrosis factor [TNF] blockers, anti-integrin agent, IL12/23 antagonists) and small molecules (Janus kinase [JAK] inhibitors). ➢ Conventional orally administered immunomodulators (azathioprine, 6-mercaptopurine) are commonly used in clinical practice, but are not Food and Drug Administration (FDA) approved for this indication. These agents take an average of 12 weeks to take effect, often necessitating combination therapy with systemic corticosteroids in the initial phase of treatment, an approach which increases the risk of infection and other serious complications.	Vedolizumab is approved as an IV infusion, providing an option for a biologic therapy in UC. It offers a distinct mechanism of action when compared to other broadly immunosuppressive agents. For patients who are experiencing benefit from vedolizumab IV, the option to continue the medication as a subcutaneous injection, which can be administered at home, may offer convenience and flexibility, potentially aiding patients in reducing need for hospital/infusion center trips, missed work or school, and time spent receiving infusions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	➢ Loss of response to biologic agents is common (for example, in patients treated with TNF blockers, 30-40% will lose initial response within 1 year[3]). ➢ Adverse reactions associated with both conventional and biologic therapies are significant, and include risks of severe and opportunistic infections, and malignancies. ➢ Biologic agents are also associated with the risk of immunogenicity, which may over time result in loss of efficacy and/or hypersensitivity reactions (which can be severe and include anaphylaxis). ➢ Treatment effects for biologic therapies are modest, leaving a significant proportion of patients inadequately treated despite trials of the best available therapies.	
Benefit	➢ Vedolizumab IV infusion was demonstrated to be efficacious in the treatment of moderate to severely active UC. ➢ This application contains data which demonstrate that the SC formulation (subject of this application) is also efficacious, when administered as maintenance therapy to patients who have received at least 2 doses of IV vedolizumab and demonstrated clinical response. ➢ Vedolizumab SC was efficacious in achieving clinical remission at week 52 (primary endpoint, treatment difference 32%), mucosal healing (treatment difference 35%), and durable clinical response (treatment difference 36%).	The application contains substantial evidence of the effectiveness of vedolizumab SC in inducing remission by Week 52 in patients with moderately to severely active UC, who demonstrated clinical response after at least 2 IV doses of vedolizumab. Efficacy of SC vedolizumab was demonstrated on primary and key secondary endpoints.

[3] D'Haens, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response? American Journal of Gastroenterology. 106, 199-212 (2011). https://www.nature.com/articles/ajg2010392

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	➢ Results of additional secondary endpoints (durable clinical remission, corticosteroid free remission) were not significant.	
Risk	Device Related Safety Issues: ➢ Vedolizumab SC was proposed under this application for subcutaneous injection using one of two presentations – prefilled syringe with needle safety device (PFS-NDS) and prefilled pen (auto-injector). Device Clogging: ➢ Clogging was identified in accelerated stability testing; clogging may increase injection forces and render device unusable. ➢ (b) (4) ➢ The CDRH review team concluded that the Applicant has not adequately investigated and confirmed the root cause of the clogging. ➢ (b) (4) ➢ ➢	Full and/or partial clogging of the needle could result in negative impact to device performance, including problems with accuracy of dose delivered, injection forces, injection time. This creates risks related to unstable injection, incomplete injections, and possible administration subcutaneously of gelled material. These risks indicate the product may not be safe and effective as intended and precludе approval. The Applicant's corrective action/preventive action (CAPA) procedures are inadequate and not compliant with requirements under 21 CFR 820.100. Inadequate CAPA procedures result in lack of confidence that Applicant is adequately identifying and addressing instances of nonconforming product in order to assure that final manufactured product is safe and meets specifications, contributing to the recommended complete response action. Purchasing control procedures are not adequate to provide assurance that CMOs conform to specified requirements. Specific deficiencies were recently identified at the (b) (4) manufacturing facility and have not yet been satisfactorily addressed, thus

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	➢ The provided standard operation procedures for "Corrective Action/Preventive Action" (CAPAs) was considered inadequate and does not meet all requirements set forth in 21 CFR 820.100. ➢ Purchasing control procedures are considered inadequate. ➢ The qualification report and audit frequency of CMO (b) (4) is considered inadequate; inadequate CMO audit frequency may result in oversight of serious quality issues. ➢ Recent field inspection of (b) (4) manufacturing facility identified deficiencies that must be adequately resolved before application can be approved. ➢ Autoinjector cap removal force specification is too high, may result in users being unable to remove cap. Microbiology: ➢ (b) (4) Clinical Safety Profile: ➢ The safety profile of vedolizumab is well characterized by the larger studies which supported initial approval of the IV formulation. ➢ Serious risks identified in the IV program included infection and liver injury. ➢ Additional potential risk identified is progressive multifocal leukoencephalopathy (PML), which is known to be associated with another biologic in the same class (Natalizumab) and which is associated with John Cunningham (JC) virus and immunosuppressed status. ➢ This safety profile as demonstrated in study SC-3027, submitted in support of the SC formulation, was similar to that of the IV formulation.	precluding approval of the product manufactured at this facility at this time. Additionally, autoinjector cap removal force specification should be updated and design verification reports resubmitted to ensure users can operate the device as intended. Taken together there are multiple risks associated with the device(s) proposed for use in this combination product. The inadequate evaluation into the root cause of the needle clogging issue identified indicates poor quality control processes that result in risk of a product being manufactured that is unsafe and will not perform as intended. The CDRH reviewer concluded that correction of the clogging issue will likely require a new primary container – thus the current combination product is not recommended for approval. (b) (4) validation information for vedolizumab (b) (4) should be submitted. (b) (4) (b) (4) Overall, the adverse reactions seen in the SC development program were consistent with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	➢ Common AEs demonstrated in study SC-3027 (≥5% of SC treated patients) included upper respiratory tract infection, anemia, injection site reaction, arthralgia, and abdominal pain. ➢ Serious adverse events occurred with similar rate in placebo vs. SC arm. The most common SAEs were ulcerative colitis and anemia. ➢ Potential risk of malignancy associated with vedolizumab has not been fully characterized to date, and is being assessed in an ongoing postmarketing study issued at the time of initial approval of the IV formulation. Human Factors (AI): ➢ Review of the Human Factors validation study results for the prefilled pen presentation identified several use errors, close calls, and use difficulties with both critical and non-critical tasks. ➢ The Applicant has not implemented revisions/mitigations to the product user interface to address these issues.	what is known about the safety of vedolizumab based on IV formulation use. In general, patients and providers have been willing to accept these risks, due to the morbidity of active UC disease, as well as the risks of long-term untreated UC or inadequately treated disease (including a greatly increased risk of colon cancer). PML has been systematically assessed throughout this development program and in the postapproval setting for the IV formulation. Available data indicate only a single case reported to date, considered unlikely directly attributable to vedolizumab. The magnitude of the risk of PML related to vedolizumab is considered much less than that of natalizumab. There is uncertainty regarding the magnitude of the risks for AEs that have long latency periods (i.e., malignancies) for Envtio (IV or SC); ongoing surveillance continues. The available HF validation study results are insufficient to ensure safe and effective use. The prefilled pen presentation is not approvable without modifications and additional HF validation testing to ensure

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		mitigations are effective and do not introduce new risks.
Risk Management	A REMS (risk evaluation and mitigation strategy) was not proposed.	The application is not approvable due to device related issues identified above. A postapproval REMS is not necessary at this time.

2. Therapeutic Context

2.1. Analysis of Condition

Ulcerative colitis, a type of inflammatory bowel disease (IBD), is a chronic, idiopathic, intermittently relapsing disease of the colonic mucosa. The disease typically commences in the rectum and may extend proximally in an uninterrupted pattern into the colon; disease distribution may involve the entire colon (pancolitis), only a more distal portion of the colon, or may manifest as isolated rectosigmoid disease. The disease may present at any age, with the typical age of onset between the ages of 15 and 30.[4]

The clinical course tends to wax and wane with periods of remission interspersed with periods of active disease. Symptoms can vary depending on the severity of inflammation and extent of disease; patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus. Disease of moderate to severe activity may be associated with systemic symptoms, including, fatigue, fever, anorexia, nausea, weight loss, and dehydration.

UC also carries with it an increased risk of colorectal cancer, partially due to chronic inflammation in patients with long-standing UC.[5] The goals of UC treatment are to induce and maintain remission of clinical symptoms and mucosal inflammation in order to improve quality of life, decrease hospitalizations, and reduce the risk of surgery and colon cancer.[6]

2.2. Analysis of Current Treatment Options

See Table 1 for approved treatment options for adult patients with moderately to severely active ulcerative colitis. Of note, although corticosteroids and oral immunomodulators (azathioprine and 6-mercaptopurine) are frequently used in the treatment of moderately to severely active ulcerative colitis, they have never been approved for this indiaction.

[4] Loftus EV. Inflammatory Bowel Disease, 2007; 13(3):254-261.

[5] Velayos FS, Loftus EV, Jr., Jess T, Harmsen WS, Bida J, Zinsmeister AR, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case control study. Gastroenterology 2006;130 (7):1941-9.

[6] Hoentjen F, et al., Curr Gastroenterol Rep 2011;13:475-485.

Table 1. Additional Approved Treatment Options

Drug Class	Approved Product Name	Indication	Dosage/ Administration	Important Safety Information: Boxed Warnings
Human interleukin-12 and -23 antagonists	Stelara (ustekinumab)	For the treatment of adult patients with moderately to severely active ulcerative colitis.	IV (Induction)- A single intravenous infusion dose of using the weight-based dosage regimen: 260mg (up to 55kg 390mg (>55 – 85 kg) 520mg (>85 kg) SC (Maintenance): 90 mg dose administered 8 weeks after initial intravenous dose, then every 8 weeks thereafter	NO BOXED WARNING **WARNINGS AND PRECAUTIONS** □ Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing STELARA® until the infection resolves. □ Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL- 12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. □ Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. □ Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. □ Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. □ Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. □ Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic

				pneumonia and cryptogenic organizing pneumonia have been reported during postapproval use of STELARA®. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment.
Tumor Necrosis Factor Blockers (TNF blockers)	Humira (Adalimumab) AND Adalimumab Biosimilars: • Amjevita Cyltezo	Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.	SC 160 mg at week 0 80 mg at week 2 40 mg at week 4 and every other week	**WARNING: SERIOUS INFECTIONS AND MALIGNANCY** • Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. • Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment. • Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA. • Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA. • Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.

Tumor Necrosis Factor Blockers (TNF blockers) Anti-integrins	Remicade (Infliximab) AND Infliximab Biosimilars: • Inflectra • Ixifi • Renflexis •	Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.	IV 5 mg/kg at week 0, week 2 and week 6 hen every 8 weeks	**WARNING: SERIOUS INFECTIONS and MALIGNANCY** . • Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. • Discontinue REMICADE if a patient develops a serious infection. • Perform test for latent TB; if positive, start treatment for TB prior to starting REMICADE. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including REMICADE. • Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including REMICADE. Almost all had received azathioprine or 6mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of REMICADE cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males.

Tumor Necrosis Factor Blockers (TNF blockers)	Simponi (Golimumab)	In adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: • inducing and maintaining clinical response • improving endoscopic appearance of the mucosa during induction • inducing clinical remission achieving and sustaining clinical remission in induction responders	SC 200 mg week 0 100 mg at week then 100 mg every 4 weeks	**WARNING: SERIOUS INFECTIONS AND MALIGNANCY** • Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI • Discontinue SIMPONI if a patient develops a serious infection or sepsis • Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI • Monitor all patients for active TB during treatment, even if initial latent TB test is negative • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member
Anti-Ingerins	Entyvio IV (Vedolizumab)	• Inducing and maintaining clinical response and remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost	IV 300 mg at week 0, week 2 week 6 then every 8 weeks	NO BOXED WARNING **WARNINGS AND PRECAUTIONS-** • Hypersensitivity Reactions (including anaphylaxis): Discontinue Entyvio if anaphylaxis or other serious allergic reactions occur. • Infections: Treatment with Entyvio is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding Entyvio in patients who develop a severe infection while on treatment with Entyvio. • Progressive Multifocal Leukoencephalopathy: Although no cases have been observed in

		response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.		Entyvio clinical trials, JCV infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms.
Janus kinase (JAK) inhibitors	Xeljanz (Tofacitinib)	Treatment of adult patients with moderately to severely active UC who have had inadequate response or who are intolerant to TNF blocks. Limitations of Use: Use of Xeljanz in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.	PO 10 mg BID for at 8 weeks (16 weeks maximum); followed by 5 BID for maintenance. Use of 10mg BID past 8 weeks limited to those who lose response	**WARNING: SERIOUS INFECTIONS, MALIGNANCY AND THROMBOSIS** • Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. • If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. (5.1) • Prior to starting XELJANZ/XELJANZ XR, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR. • Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. • RA patients with at least one CV risk factor had a higher rate of all-cause mortality and thrombosis with XELJANX 10mg twice daily vs 5mg twice daily or TNF blocker

				• Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

Source: Reviewer's table adapted from current Prescribing Information November 2019

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Entyvio (vedolizumab) IV is currently indicated for:

inducing and maintaining clinical response, inducing and maintaining clinical remission, improving the endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

And

achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2. Relevant Clinical Presubmission Regulatory Background

Date	Action and Discussion
5/20/2014	Approval of vedolizumab IV for indications below: • Inducing and maintaining clinical response • Inducing and maintaining clinical remission • Improving the endoscopic appearance of the mucosa • Achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. AND • Achieving clinical response • Achieving clinical remission • Achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Date	Action and Discussion
9/30/2014 and 9/26/2014	Type B - EOP2 Meeting and WRO • Applicant completed phase 2 testing of the SC formulation and planned to submit a sBLA to support the approval for administration via single-use, prefilled syringe (PFS). • The objective of the vedolizumab SC development program was to switch to SC presentation after receiving vedolizumab IV at Week 0 and Week 2. • Division stated we did not require separate "induction" and "maintenance" trials, but trials should be designed in a manner that supports the proposed claims • Division did not agree that results from the proposed clinical development program of vedolizumab SC in UC would support vedolizumab SC in CD • Division acknowledged that Applicant's proposed choice of placebo as comparator appeared reasonable • Final decision on the adequacy of the safety database for approval would be made upon review of complete application. • Advised that JCV antibody testing not required prior to enrolling subjects into clinical studies with vedolizumab SC provided PML risk management and risk minimization strategies incorporated in Protocols SC-3027 and SC-3030 • Agreed on primary and secondary efficacy endpoints and that sensitivity analysis excluding PGA is reasonable. • (b) (4)
5/11/2015	Type C WRO re: Phase 3 Studies • Applicant's definition of "durable clinical remission" should be consistent with that in the IV trial • Division stated that the vedolizumab IV efficacy data should not be included (b) (4) (b) (4) because if either of two analyses (descriptive statistics or alternative NI analysis) suggested that there were differences between SC and IV, then it would be confusing for clinicians to understand the performance of the SC relative to IV • Primary, secondary endpoint and patient population agreed upon • Agreed to separate sBLAs for UC and CD indications Division recommended to include the following as exploratory endpoints: • Alternate definition of clinical remission (using the Mayo subscores of stool frequency, rectal bleeding, and endoscopy): - Stool frequency subscore =0 - Rectal bleeding subscore =0 - Endoscopy subscore =0 or 1 (modified so that a score of 1 does not include friability) • Alternate definition of clinical remission (using the Mayo subscores of stool frequency, rectal bleeding, and endoscopy): ➢ Stool frequency subscore =0 or 1 and a prespecified specific change of 1 or more from baseline ➢ Rectal bleeding subscore =0 ➢ Endoscopy subscore =0 or 1 (modified so that a score of 1 does not include friability) • Division stated "mucosal healing" (b) (4) (b) (4) provides only an assessment of the visual appearance of the

Date	Action and Discussion
	mucosa; therefore, any (b) (4) findings on endoscopy (without validated histological assessment of the mucosa) would be limited to the endoscopic appearance.
1/29/19	Type B Pre BLA • Proposed clinical data package appeared reasonable to support review of the planned BLA for vedolizumab SC for use as maintenance treatment of adults with moderately to severely active UC. • Final decision on the adequacy of proposed development program for filing and approvability to be made after submission • Agreement was gained on the layout/contents/pooling of the various efficacy/safety sections
3/7/19	BLA 761133 was submitted.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Two clinical sites were selected for inspection, including Dr. Paul Hellstern and Dr. Allan G. Coates. Both sites received classification of No Action Indicated. In addition, as result of mis-stratification identified during review of efficacy data, an Applicant inspection was conducted. Results of this inspection were classified as Voluntary Action Indicated, as the inspector concluded that the Applicant did not have adequate oversight in place to detect incorrect randomization/enrollment was occurring. A Food and Drug Administration (FDA) form 483 was issued. Takeda responded on November 14, 2019, and the clinical inspection group concluded that Takeda's plans for better oversight in future and ongoing studies appears reasonable. The effect of mis-stratification was assessed by the statistical reviewer in multiple post hoc analyses, which are described below in Section 8.1, and did not alter the overall conclusions on effectiveness. Despite the identified issues, overall the quality of the data were considered sufficient to support continued review and reliance upon trial results to make regulatory decisions.

Full details of the clinical inspection report are contained in the review by Dr. Zana Marks, dated December 4, 2019.

4.2. Product Quality

The Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, has concluded that the data submitted in this application are inadequate to support a conclusion that the manufacture of Entyvio (vedolizumab) injection, for subcutaneous use, will lead to a product that is safe, pure and potent for the duration of the shelf-life. While the deficiencies are related

to the manufacture and control of device-constituents of the proposed combination products (i.e., PFS+NSD and PFS+AI), changes that could significantly impact the manufacture and control of vedolizumab and the final combination products (b) (4) (b) (4) are recommended to address these deficiencies. Therefore, the current Chemistry, Manufacturing and Control information and data provided are considered inadequate to support the intended performance of the proposed combination products from a biologic product quality perspective. Office of Pharmaceutical Quality is recommending a Complete Response letter to be issued to Takeda Pharmaceuticals to outline the chemistry, manufacturing and control information and data that will be required to support approval.

4.3. Product Quality Microbiology

(b) (4) (b) (4) Additional (b) (4) validation data (b) (4) (b) (4) is required with the BLA resubmission. (b) (4) (b) (4)

4.4. Devices and Companion Diagnostic Issues

Revice of the device(s) (prefilled syringe (PFS) plus needle safety device and autoinjector (AI)) proposed in this biologics license application (BLA) presented approvability issues that ultimately result in the recommended Complete Response action.

The major device related issue applies to both devices (PFS and AI) and pertains to identified issue of needle clogging. The Applicant's investigation into the root cause of clogging and proposals to mitigate this concern are not adequate. (b) (4) (b) (4)

In addition, the cap removal force specification for AI is higher than other similar marketed products. This could result in users being unable to remove the cap. This was communicated to the Applicant and not adequately addressed.

Please refer to detailed review by Rumi Young (ICCR 1900197) dated November 8, 2019.

4.5. Division of Medication Error Prevention (DMEPA)

Prefilled Syringe (PFS):

A use related risk analysis (URRA) and comparative analyses for the prefilled syringe (PFS) were previously submitted under IND 118980 and were deemed acceptable; a human factors (HF) validation study was not required to be submitted to support the application for the PFS.

Prefilled Pen / Entyvio Pen:

A human factors (HF) validation study (the protocol for which FDA reviewed and provided comments on during development) was conducted and results were submitted for review on March 7, 2019. DMEPA identified several use errors, close calls, and use difficulties with critical and non-critical tasks within the study results. The applicant has not implemented revisions/ mitigations to the product user interface to address these use-related issues. Upon review of the subjective feedback from study participants and Applicant's identified root cause analyses, the DMEPA team identified several recommendations to revise the user interface, including revisions to: device design, device label/labeling, (b) (4) and the Instructions for Use (IFU) to improve prominence, clarity, and understanding of important information. In order to fully address these concerns, the Applicant will need to implement the recommended revisions along with any additional mitigations that they determine to be necessary to address the observed use-related issues, and then conduct and submit results of another HF validation study to demonstrate that the mitigations are effective and do not introduce new risks. The prefilled pen presentation is not recommended for approval at this time. Refer to full DMEPA review by Matt Barlow dated 12/13/19 and language in CR letter for details.

4.6. Clinical Outcomes Assessments

Within the initially proposed labeling, the Applicant included (b) (4)
(b) (4)

The review team consulted with Clinical Outcome Assessment staff regarding the inclusion of any of these measures in future labeling. (b) (4)

(b) (4)

[redacted]

For additional detail, refer to review memo by Onyekachukwu Illoh dated November 22, 2019.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This BLA was submitted for vedolizumab (MNL0002) injection, for subcutaneous (SC) use. Vedolizumab is a humanized IgG1 monoclonal antibody to the human α4β7 integrin. This BLA is intended to support the use of vedolizumab SC administered once every two weeks (Q2W) for maintenance treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have an inadequate response with, lost response to, or were intolerant to either conventional therapy or tumor necrosis alpha (TNFα) antagonist. The recommended SC maintenance dosage in UC is 108 mg, administered Q2W after 2 or more vedolizumab intravenous infusions. The Applicant did not submit any nonclinical study report in this BLA except the report of a local SC tolerance study (MLN0002-63672) in rabbits. The Applicant has referred to investigational new drug (IND) 118980 and BLA 125476 (Entyvio) for vedolizumab injection for intravenous (IV) use for nonclinical information. There are no nonclinical approvability issues.

5.2. Referenced NDAs, BLAs, DMFs

BLA 125476 (Vedolizumab, Entyvio, Takeda Pharmaceuticals USA, Inc.)

5.3. Pharmacology

No pharmacology studies were submitted in this application. Pharmacology studies were reviewed under BLA 125476. Vedolizumab has been shown to be a selective α4β7 integrin antagonist and it does not bind to α4β1 or αEβ7 integrins. In an in vivo animal efficacy study with ACT-1 (murine homologue of vedolizumab) in cotton-tap Tamarin monkeys with naturally occurring chronic colitis, ACT-1 showed efficacy (resolution of diarrhea, reduced inflammatory

activity i.e., reduced leukocyte infiltration of the gut lamina propria and decreased mucosal density of α4β7 lymphocytes).

5.4. ADME/PK

No absorption, distribution, metabolism, excretion studies were submitted in this application. Absorption, distribution, metabolism, excretion studies were reviewed under BLA 125476. In a single dose intravenous pharmacokinetic/pharmacodynamic study of vedolizumab in cynomolgus monkeys at 10 and 100 mg/kg, C_{max} of 214 and 2090 µg/mL, respectively, was observed at a T_{max} of 0.5 hour postdose, and the $AUC_{0\text{-}161hr}$ values were 32,700 and 54,2000 µg.hr/mL at 10 and 100 mg/kg, respectively. The $t_{1/2}$ ranged from 14 to 15 days.

5.5. Toxicology

5.5.1. General Toxicology

No general toxicology studies were submitted in this application except the report of a SC tolerance study in rabbits. Toxicology studies were reviewed under BLA 125476. Toxicology studies were conducted with vedolizumab (MLN0002) in two species (rabbit and cynomolgus monkeys) by IV route to support the chronic IV use of vedolizumab. A 3-month IV toxicity study was conducted with vedolizumab in New Zealand white rabbits at 30 and 100 mg/kg and 3- and 6-month IV toxicity studies were conducted with vedolizumab in cynomolgus monkeys at 10, 30 and 100 mg/kg administered once every two weeks. In rabbits, histopathological changes were observed in the spleen (minimal to mild lymphoid hyperplasia in the periarteriolar lymphoid sheaths) and ileum (hyperplasia of submucosal lymphoid nodules) of treated and control animals. However, incidence and severity were not dose related and these changes were also seen in control animals and the relation to the treatment was uncertain. In monkeys, histopathological changes were observed in the gastrointestinal tract (GIT) (minimal to mild lymphoid depletion in the Peyer's patches of the GIT in males at 10, 30, and 100 mg/kg and increased epithelial regeneration in the stomach with lymphoplasmacytic gastritis in both sexes at 10, 30, and 100 mg/kg). The GIT changes in Peyer’s patches of males and an analogous decrease in leukocytes expressing the α4β7 integrin in crypt epithelium appeared to be due to the pharmacologic effect of vedolizumab (decreased trafficking of peripheral lymphocytes to the gut). The relation to the treatment was not clear in the absence of a dose response.

General Toxicology: Additional Studies

Study title/ number: Local Tolerance Study of Subcutaneously Injected MLN0002 in Rabbits (Report No. MLN0002-63672, Study No.12-115/LO)

Key Study Findings:

- Slight erythema was observed at the injection sites receiving the saline, vehicle and MLN0002 1 to 2 days postdose, however, the incidence was slightly higher at the injection sites of MLN0002 than those of the saline and vehicle. Minimal edema and focal fibrosis were observed at 1 injection site each receiving MLN0002 on 2 and 14 days, respectively, after the dosing.Based on these results, it was concluded that the single SC injection of MLN0002 at 160 mg/mL/site caused slight local irritant effects in rabbits.

Conducting laboratory and location: Takeda Pharmaceutical Company Limited, 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan

GLP compliance: Yes

Methods

In this study, New Zealand white rabbits (n=4/group) were each injected with 1 mL/site of saline (negative control), vehicle (a solution containing L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sodium citrate dihydrate, citric acid monohydrate and polysorbate 80) and MLN0002 SC (160 mg/mL/site), each injection in a separate site on the abdomen. The rabbits were sacrificed and examined 2 or 14 days after administration (4 rabbits at each time point).

Dose and frequency of dosing: 160 mg/mL/site

Route of administration: Subcutaneous

Formulation/Vehicle: Vehicle: A solution containing L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sodium citrate dihydrate, citric acid monohydrate and polysorbate 80; Negative control: Saline

Species/Strain: Male New Zealand white rabbits

Number/Sex/Group: 8

Age: 17 weeks

Satellite groups/unique design: None

Deviation from study protocol affecting interpretation of results: No

Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weights	There no significant treatment-related effects on body weight.
Gross pathology	Very slight erythema was observed at the injection sites receiving the saline, vehicle and MLN0002 at 1 to 2 days postdose; however, incidence was slightly higher at the injection sites of MLN0002 than those of the saline and vehicle.
Histopathology	Minimal edema and focal fibrosis were observed at 1 injection site each receiving MLN0002 on 2 and 14 days, respectively, after the dosing.

5.5.2. Genetic Toxicology

Genetic toxicity studies have not been conducted with vedolizumab. Genotoxicity studies are not generally applicable for biologics.

5.5.3. Carcinogenicity

Conventional carcinogenicity studies (i.e., rodent bioassays) have not been conducted with vedolizumab as it lacks pharmacological activity in mice and rats. However, carcinogenic potential of ACT-1 (murine homologue of vedolizumab) was assessed in an in vitro study using human tumor cells that expressed α4β7 integrin. In this study, ACT-1 did not stimulate the growth or cellular proliferation of human B-cell lymphoma cell that express the α4β7 integrin.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Fertility and early embryonic development studies have not been conducted with vedolizumab.

Embryo-Fetal Development

An intravenous embryofetal development study with vedolizumab in New Zealand white rabbits was submitted under BLA 125476. This study was reviewed under BLA 125476. In this study, vedolizumab did not show adverse effects on embryofetal development in rabbits when administered on gestation day 7 at single intravenous doses up to 100 mg/kg (about 6.5 times the recommended human dose based on body surface area).

Prenatal and Postnatal Development

A pre- and postnatal development study with vedolizumab in cynomolgus monkeys was submitted under BLA 125476. This study was reviewed under BLA 125476. In this study, there

was no evidence of any adverse effect on pre- and postnatal development at vedolizumab intravenous doses up to 100 mg/kg (about 6.5 times the recommended human dose based on the body surface area).

5.5.5. Other Toxicology Studies

Impurities

Elemental Impurities

Elemental impurities were assessed on the vedolizumab SC drug product (DP) per the International Conference on Harmonisation (ICH) Q3D guidance. The limits were derived from the recommended permissible daily exposure (PDE) for each element using option 1 (daily doses of not more than 10 g/day) in the above guidance to convert to µg/g units. Furthermore, a control threshold was established for this assessment to provide further safety regarding elemental impurities. The (b) (4)% of the parenteral product PDE limit was calculated to define the control threshold values for each elemental impurity per the ICH Q3D guidance. A risk assessment was then performed to evaluate the impact of elemental impurities from the DS and excipients, water, manufacturing equipment and container closure systems of the DP. The findings are shown in Table 3 (from page 3 of Report No. 000161754 Ver. 2.0 in Section 3.2.P.5.5 of the submission) below.

Table 3. Evaluation for Potential Risk of Each Elemental Impurity in Drug Substances and Excipients of Vedolizumab SC in Risk Assessment

Elements	Control threshold (ng/g, ppm)	Each potential risk							Potential risk for drug substances and excipients
		MLN0002	(b) (4) Arginine Hydrochloride	Citric Acid Monohydrate	(b) (4) Histidine	(b) (4) Histidine Monohydrochloride	Sodium Citrate Dihydrate	Polysorbate 80	
(b) (4)		Low	(b) (4)						Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low
		Low							Low

Overall, as shown in the above table, all the elemental impurities were found to be below control threshold.

Extractables and Leachables

Methods

A risk assessment was performed to evaluate the likelihood that product contact material can contribute leachables that may impact the purity and safety of vedolizumab SC drug product (DP). Several factors (extraction capability, length of contact time, surface area of the material in contact with the process solution, temperature during contact with the solution, inherent propensity or resistance to extraction process, whether material is certified to meet USP Class VI, (b) (4)) were considered during the risk assessment to prioritize drug product components that should be evaluated during extractable studies. Based on the evaluation, the following materials were considered of a higher risk to contribute leachables to final DP and additional studies were performed on these materials:

- (b) (4)
- Drug product container and closure.

Extractable studies were performed on all high-risk materials. Materials representative of those used during GMP manufacturing were extracted using the aggravated conditions (different solvents, times and temperatures) as shown in Table 4 below (from page 25 of the Report No. DN-000173305 Ver 1.0 in Section 3.2.P.2.3 of the submission).

Table 4. Summary of Extraction Data on Vedolizumab SC DP Container/Closure

Vedolizumab SC	Material	Extraction Conditions (Solvent, Time, Temperature)	Analytical Methods for Extractables	Manufacturing Conditions (Solvent, Time, Temperature)
Drug Product	(b) (4)	(b) (4)	SVOC by Direct Injection GC/MS, VOC by (b) (4) GC/MS, NVOC by LC/UV and LC/MS, Metal Analysis by ICP/OES	(b) (4)
	(b) (4)		SVOC by Direct Injection GC/MS, VOC by (b) (4) GC/MS, NVOC by LC/UV and LC/MS, Metal Analysis by ICP/OES	
	Drug Product Container and Closure (syringe barrel, plunger, needle, needle shield)	160 mg/mL MLN0002 SC Drug Product in DP Container/Closure (b) (4)	SVOC by Direct Injection GC/MS, VOC by (b) (4) GC/MS, NVOC by LC/UV and LC/MS, Metal Analysis by ICP/OES, (b) (4) by ICP/OES	

ICP/OES = inductively-coupled plasma / optical emission spectrometry; (b) (4)
NVOC = non-volatile organic compounds; SVOC = semi-volatile organic compounds; VOC = volatile organic compounds.

Two extraction studies were conducted (b) (4). As shown in Table 4 above, a controlled (b) (4) extractable study was performed to identify and to estimate the amount of compounds that may be extracted from (b) (4) (b) (4) and vedolizumab SC formulation (b) (4) (b) (4). A second (b) (4) extractable study was performed using the same procedure used during GMP manufacturing. (b) (4) (b) (4) Extraction was performed using the conditions shown in the above table.

In addition, a controlled (b) (4) simulation study was performed to identify and to estimate the amount of compounds that may be extracted from container and closure components upon contact with 160 mg/mL vedolizumab SC in formulation (b) (4) (b) (4). The simulation study was performed under an accelerated aging factor conditions, which was designed to predict potential leachables that could originate from drug product contact with container closure components under normal product usage and long-term storage conditions of (b) (4) months at 5°C.

Each sample was analyzed by direct injection gas chromatography mass spectrometry (GC/MS) to screen for semivolatile organic compounds (SVOCs) and by (b) (4) GC/MS to screen for volatile organic compounds (VOCs), liquid chromatography mass spectrometry (LC/UV/MS) was used to screen for nonvolatile organic compounds (NVOCs) and metal analysis was performed using inductively-coupled plasma optical emission spectroscopy (ICP-OES). Results from the extraction studies were used to calculate the maximum expected amount of each extractable in the final drug product using the surface area of each component used in vedolizumab SC DP and an accelerated aging factor. In addition, the calculation assumed the highest risk of permissible daily exposure (PDE) of (b) (4) day of each extractable per dose of drug product.

Results: In the first (b) (4) extractable study, there were no reportable SVOCs, VOCs or NVOCs detected in the high and low pH water and vedolizumab SC formulation (b) (4). In the extraction using (b) (4), one VOC and one NVOC compound (details not provided) were detected. However, all the compounds detected in the (b) (4) SC formulation (b) (4) of the vedolizumab SC DP were calculated to be less than the (b) (4) µg/day PDE limit. In the second (b) (4) extractable study, there were no reportable SVOCs, VOCs or NVOCs detected in the (b) (4) vedolizumab SC formulation (b) (4) For the (b) (4), one NVOC was detected (details not provided). In addition, the extractable study (b) (4) (b) (4) generated several SVOCs, VOCs, and NVOCs (details not provided). However, the (b) (4) extractable study (b) (4) was conducted using a very aggressive condition, and it was used as a control to potentially identify extractable compounds that may be extracted from the filter upon contact with representative solvents used during drug product manufacturing process. Overall, all the compounds detected in the (b) (4) vedolizumab SC formulation (b) (4) of the vedolizumab SC DP were calculated to be less than (b) (4) /day PDE limit.

In the controlled simulation study of vedolizumab SC drug product container and closure components for 78 days at 50°C, there was only one reportable VOC compound (b) (4) which was identified as a common laboratory contaminant. No other reportable SVOCs, VOCs and NVOCs were detected in the vedolizumab SC drug product extractable solvent upon contact with container closure components in this accelerated aging study. (b) (4) was detected in the vedolizumab SC drug product solvent and this compound was expected to be

extracted [redacted (b) (4)]. Based on the results of the extraction and controlled simulation studies, no leachable study was conducted. Overall, the results of the extraction studies conducted under exaggerated conditions and the simulation study did not appear to raise safety concern as the daily exposure to the detected compounds would be less than the [redacted (b) (4)]/day PDE limit.

6. Clinical Pharmacology

6.1. Executive Summary

ENTYVIO (vedolizumab) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to the human α4β7 integrin. Vedolizumab injection for intravenous use (vedolizumab IV) was approved in May 2014 under BLA 125476 for the treatment of adult ulcerative colitis (UC) and for the treatment of adult Crohn's disease (CD). The approved vodolizumab IV dosing regimen for both UC and CD is 300 mg at Weeks 0, 2, 6 and every 8 weeks thereafter.

In the current BLA, the Applicant has proposed SC dosing regimen of vedolizumab (108 mg every 2 weeks or 108 mg Q2W) for the maintenance treatment of adult patients with UC. The Applicant has propoded two to-be-marketed (TBM) presentations for vedolizumab SC administration: prefilled syringe with needle safety device [PFS + NSD] and prefilled syringe in an autoinjector/pen [PFS + AI].

To support the proposed SC dosing regimen, the Applicant has submitted efficacy, safety, and PK data from a phase 3 trial (SC-3027). Because the PFS presenation was used in Study SC-3027, the Applicant has evaluated the PK comparability between the PFS and PFS+NSD presentations and between the PFS and PFS+AI presentations in four phase 1 studies (SC-1017, -1018, -1021, and -1022) in healthy subjects.

The key clinical pharmacology review findings with specific recommendations and comments are summarized in Table 5.

Table 5. Summary of Clinical Pharmacology Findings

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of vedolizumab SC injection for the treatment of UC in adults is established in the phase 3 trial (study SC-3027). The positive exposure-response relationship for efficacy based on data from the phase 3 trial provides supportive evidence of effectiveness.
General dosing instructions	The proposed dosing regimen of vedolizumab SC 108 mg Q2W as maintenance treatment is acceptable. The vedolizumab SC dosing regimen should be initiated following at least two IV infusions of 300 mg vedolizumab IV dosing regimen. See Section 6.3.2.2. for a discussion of recommended timing of IV→SC switch.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization based on intrinsic or extrinsic factors is not recommended.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed PFS+NSD and PFS+AI presentations have been demonstrated to have comparable PK versus the PFS presentation that was used in the phase 3 trial in UC patients..
Immunogenicity	The development of anti-vedolizumab antibodies (AVA) following vedolizumab SC injection was associated with up to 6-fold lower serum vedolizumab concentrations at steady state. Approximatey 10-fold lower serum vedolizumab concentrations were also found in patients who received vedolizumab IV infusions. Although the small numbers of AVA positive patients along with the limitations in the AVA assay confound the assessment of the extent to which the presence of AVA impacts overall efficacy, patients who developed AVA were generally associated with reduced efficacy.

6.1.1. Recommendations

From a clinical pharmacology standpoint, the information submitted in this BLA is sufficient to support a recommendation for approval of the vedolizumab injection for subcutaneous use in the maintenance phase of treatment in adult patients with moderately to severely active UC.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Absolute Bioavailability of Vedolizumab SC Injection

The absolute bioavailability of vedolizumab following SC injection in healthy subjects was estimated to be approximately 75% in study C13010 in which a single dose of 180 mg vedolizumab was administered via SC injection or IV infusion, and approximately 75% in another single dose study (SC-101) in healthy subjects with IV infusion of 300 mg, and SC injection with 54 mg, 108 mg and 160 mg. Note that Study C13010 used a lyophilized SC formulation and Study SC-101 used a liquid SC formulation.

PK Comparability Between the TBM PFS+NSD and PFS+AI Presentations and the PFS Presentation Used in the Phase 3 Trial

The PK comparability between the PFS and PFS+NSD presentations was demonstated in Study SC-1018. The PK comparability between the PFS and PFS+AI presentations was demonstated in Study SC-1022. In these two PK comparability studies, the point estimates and 90% confidence interval for geometic mean ratio of C_{max}, AUC_{last}, and AUC_{inf} were all within the [0.8, 1.25] "bioequivalence" boundaries.

PK of Vedolizumab SC Injection in Patients With UC

In study SC-3027, the mean±SD vedolizumab serum trough concentrations at steady state (Week 46) were 35.8±15.2 µg/mL with the proposed 108 mg Q2W SC regimen. The mean±SD serum trough concentrations were 12.0±6.4 µg/mL with 300 mg Q8W IV infusion regimen, which was consistent with the observed concentrations of 11.2±7.2 µg/mL in the previous phase 3 study (Study C13006) using the same IV dosing regimen.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. *General Dosing*

The Applicant has proposed a vedolizumab SC dosing regimen of 108 mg Q2W in the maintenance phase of treatment. The vedolizumab SC dosing regimen should be initiated following at least two IV infusions of the recommended 300 mg vedolizumab IV dosing regimen. The proposed SC dosing regimen is supported by the overall efficacy and safety data from the phase 3 trial (study SC-3027) and is acceptable.

6.2.2.2. *Therapeutic Individualization*

Therapeutic individualization is not necessary for vedolizumab SC injection. No intrinsic or extrinsic factors that would require adjustment of the proposed dosing regimen have been identified.

6.2.2.3. *Outstanding Issues*

There are no outstanding issues that would preclude the approval of the current BLA from a Clinical Pharmacology perspective.

Note that deficiencies in full and partial needle clogging for the proposed PFS+NSD and PFS+AI presentations were found during the examination of the stability data by the Agency. This is considered an approvability issue by the Center for Devices and Radiological Health (CDRH) review team. If major changes in formulation or device are to be made by the Applicant in order to address these deficiencies in a future resubmission of the BLA, additional clinical pharmacology studies may be necessary to bridge between the to-be-marketed and clinical trial formulations/presentations.

In addition, limitations in the sensitivity of the anti-vedolizumab antibody (AVA) assay in the presence of vedolizumab will need to be further studied and addressed in future either with resubmission of the BLA or as a post-marketing commitment. We found that the incidences of AVA reported in the phase 3 trial (SC-3027) were likely underestimated due to the limitation of the assay.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general clinical pharmacology, pharmacokinetics and immunogenicity of vedolizumab is provided in Table 6.

Table 6. Summary of Pharmacology, Pharmacokinetics, and Immunogenicity of Vedolizumab

Pharmacology	
Mechanism of action	Vedolizumab selectively binds to the α4β7 integrin on memory T lymphocytes and inhibits adhesion of these cells to mucosal addressin cell adhesion molecule 1 (MAdCAM 1) on gut epithelial cells, resulting in decreased migration of T lymphocytes into GI parenchymal tissue.
General Information	
Bioanalysis	Vedolizumab concentrations in human serum were quantified using a validated ELISA assay. The calibration range is 0.2-8.0 µg/mL. The validated method and in-study reports were acceptable. See Section 15.4 for additional details.
Clinical Pharmacokinetics	

Pharmacology	
PK in healthy subjects	The PK results in Studies C13010 and SC-101 showed that the absolute bioavailability of vedolizumab following SC injection in healthy subjects was estimated to be approximately 75%. The single dose of 108 mg SC injection generated 14% C_{max} and 21% of AUC of a single dose of 300 mg IV infusion to the healthy subjects.
PK in UC subjects	The mean±SD vedolizumab serum trough concentrations at steady state were 35.8±15.2 µg/mL at Week 46 with the proposed 108 mg Q2W SC dosing regimen which was approximately 3-fold of the serum trough concentrations (12.0±6.4 µg/mL) with 300 mg Q8W IV infusion regimen. A two-compartment model with zero order (IV infusion) and first order (SC) input and parallel linear and nonlinear elimination pathways was applied to describe the PK of vedolizumab. The PK simulation results showed that vedolizumab SC 108 mg Q2W regimen resulted in steady state C_{avg} exposures that were comparable to those with the IV 300 mg Q8W regimen.
Immunogenicity	

Pharmacology	
	During the maintenance treatment in study SC-3027, 5.7% (6/106) and 5.6% (3/54) patients developed AVA among patients who received vedolizumab SC treatment and vedolizumab IV treatment, respectively. Among the 6 AVA positive subjects who received vedolizumab SC treatment, 3 were characterized as positive for neutralizing antibodies. All the AVA positive subjects who received the vedolizumab IV treatment were positive for neutralizing antibodies.
Incidence	In the placebo arm (subjects who received 2 doses of vedolizumab during induction and were randomized to placebo during maintenance), the immunogenicity rate for AVA was 30.4% (17/56) and 12 of the 17 AVA positive subjects had neutralizing antibodies. However, the reported immunogenicity incidences in patients who were randomized to SC and IV vedolizumab treatment groups are likely underestimated due to the limitation of the ADA assay sensitivity in the presence of vedolizumab.
Impact on PK	Immunogenicity has a negative impact on systemic exposure of vedolizumab. At steady state (Week 46) in Study SC-3027, the mean vedolizumab trough serum concentrations in the SC treatment group was 6.8 µg/mL in AVA positive subjects, in comparison to 36.3 µg/mL in AVA negative subjects. In the IV treatment group, the mean vedolizumab trough serum concentrations were 1.81 µg/mL in AVA positive subjects, in comparison to 12.2 µg/mL in AVA negative subjects.
Impact on efficacy	Patients who developed AVA were generally associated with reduced efficacy in both SC and IV treatment groups in Study SC-3027. None of the 6 subjects who were AVA-positive in the SC treatment arm achieved clinical remission or mucosal healing at Week 52. None of the 3 subjects who were AVA-positive in the IV treatment arm achieved clinical remission at Week 52; however, 2 of the 3 AVA-positive subjects achieved mucosal healing at Week 52.

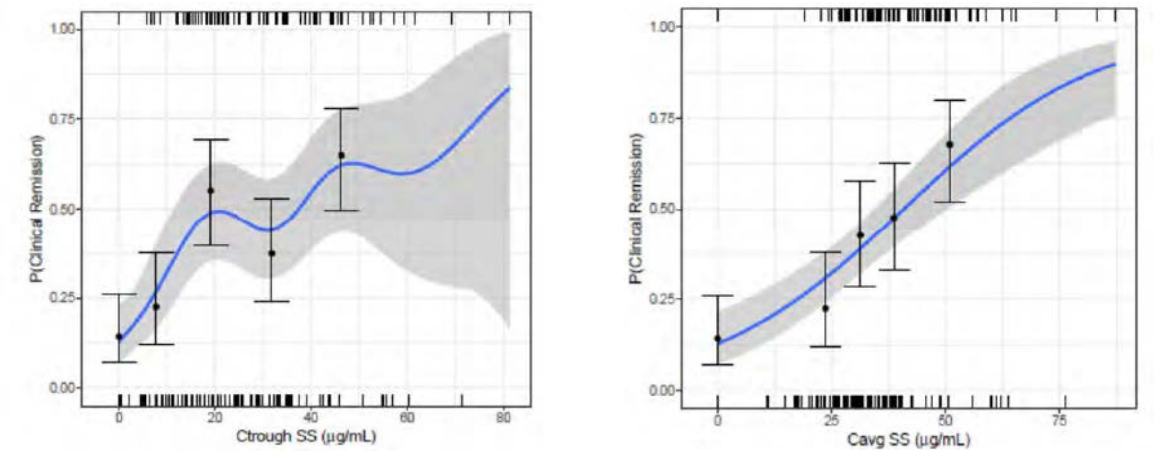
6.3.2. Clinical Pharmacology Questions

6.3.2.1. *Does the clinical pharmacology program provide supportive evidence of effectiveness?*

Yes. The exposure-response (E-R) relationships for efficacy (clinical remission at Week 52) in Study SC-3027 have provided supportive evidence of effectiveness.

The Applicant used quartile analyses and logistic regression to characterize the relationship between vedolizumab exposure and efficacy endpoints, for both the IV and SC treatment groups. A positive E-R relationship was observed for efficacy variables including clinical remission and mucosal healing at Week 52. Figure 1 shows the probability of achieving clinical remission at Week 52 versus vedolizumab steady state Ctrough and Cavg concentrations, indicating that higher clinical remission rates were associated with higher vedolizumab concentrations. Consistent trend of E-R was also observed for the SC Q2W arm alone, and for mucosal healing at Week 52. These results are presented further in Section 15.3.4.

Figure 1. Probability of Clinical Remission at Week 52 for All Randomized Patients (SC Q2W and IV Q8W Combined) by Vedolizumab Exposure (Study SC-3027)



Source: Applicant's exposure response analysis report, Figure 8

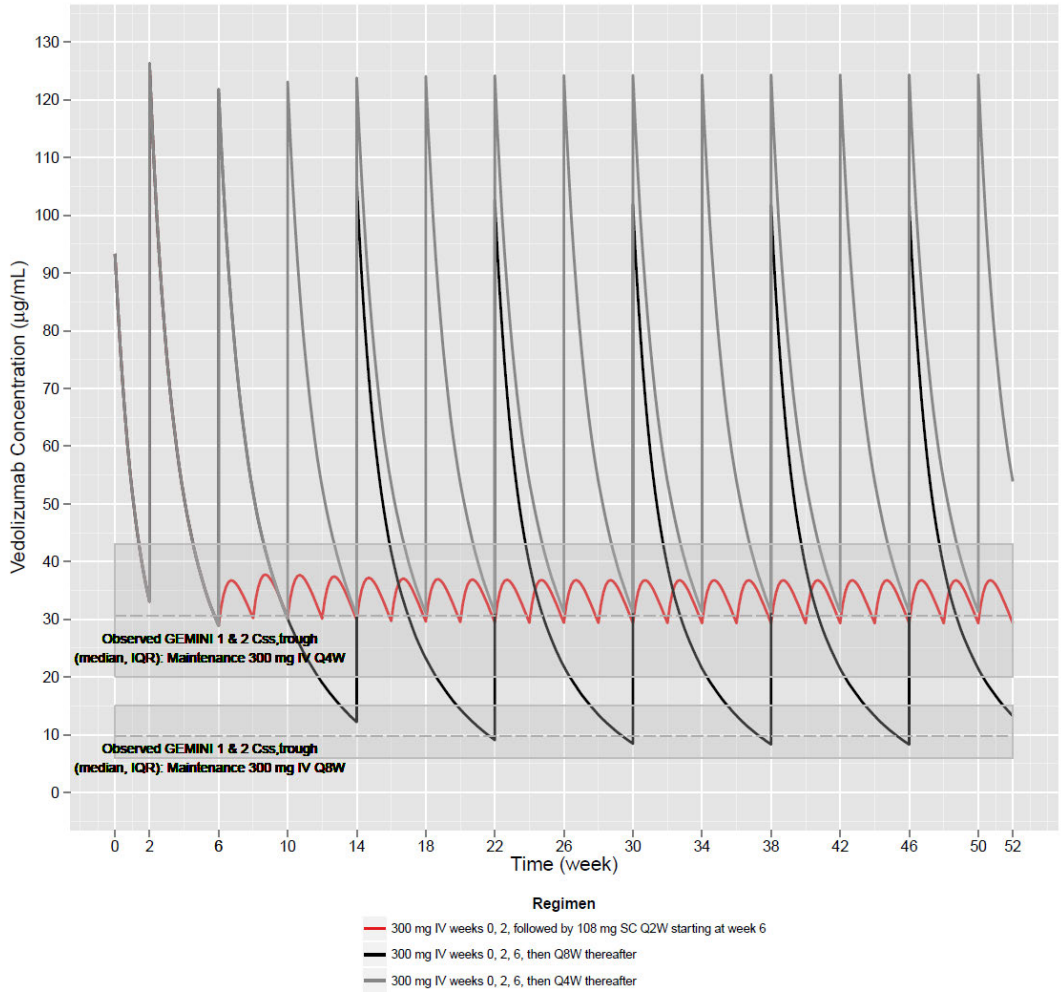
6.3.2.2. *Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes. The proposed vedolizumab 108 mg Q2W SC dosing regimen is appropriate for adult UC patients who switch from IV infusion to SC injection in the maintenance phase of treatment. The proposed dosing regimen is supported by PK, efficacy and safety results in study SC-3027 which evaluated Vedolizumab SC 108 mg Q2W starting at Week 6 following two 300 mg IV infusions at Week 0 and Week 2.

Phase 3 Dose Selection Rationale

The Applicant used population PK simulation results to support the phase 3 dose selection. The vedolizumab population PK model for the IV product was updated with SC data and the updated model was used to simulate and compare the concentration-time profiles following different SC and IV maintenance regimens. The simulated PK profiles are depicted in Figure 2. The simulated steady state average (Cavg,ss) and trough (Ctrough) concentrations are summaried in Table 7. Based on the simulation results, the 108 mg SC Q2W regimen is expected to have similar Cavg,ss to those with the 300 mg IV Q8W regimen, and have similar Ctrough to those with the 300 mg IV Q4W regimen.

Figure 2. Simulated Median Vedolizumab Concentration-Time Profiles following Different IV and SC Vedolizumab Maintenance Dosing Regimens



The solid lines represent the expected (median) concentration vs. time profile. The simulation results are overlaid and compared to the median and interquartile range (IQR) of *Css,trough* observed in the GEMINI 1 and two studies (C13006 and C13007) for maintenance regimens of 300 mg IV every 4 or 8 weeks.
Source: Applicant's Population PK SC report, Appendix B.

Table 7. Simulated Steady State Average and Trough Vedolizumab Concentrations for Different Maintenance Regimens

	Median (95% PI)	
Regmen	**$C_{avg,ss}$ (µg/mL)**	**$C_{trough,ss}$ (µg/mL)**
300 mg IV Weeks 0, 2, followed by 108 mg SC QW starting at Week 6	69.5 (41.6, 93.2)	66.9 (39.1, 90.1)
300 mg IV Weeks 0, 2 followed by 108 mg SC Q2W starting at Week 6	34.0 (20.3, 45.9)	29.3 (15.9, 40.3)
300 mg IV Weeks 0, 2, 6 then IV Q4W thereafter	61.0 (36.5, 81.8)	31.3 (12.6, 47.0)
300 mg IV Weeks 0, 2, 6 then IV Q8W thereafter	29.8 (17.8, 40.3)	8.31 (2.26, 14.0)

Source: Applicant's Population PK SC Report, Appendix B and Appendix C.

PK Comparison Between the Proposed SC Regimen and the Approved IV Regimen in Phase 3 Study

The observed mean ± SD vedolizumab serum trough concentrations at steady state (Week 46) were 35.8 ± 15.2 µg/mL with SC dosing regimen which was approximately 3-fold of the concentrations with the IV infusion dosing regimen (Table 8). The observed PK results were generally consistent with the predicted results from the PK simulations.

Table 8. Observed Trough Vedolizumab Concentration at Steady State (Week 46) From SC Phase 3 Study in UC Patients (SC-3027)

	Vedolizumab Trough Concentration (µg/mL)		
	Induction IV + Vedolizumab IV 300 mg Q8W (N=54)	**Induction IV + Vedolizumab SC 108 mg Q2W (N=106)**	**Induction IV + Placebo (N=56)**
n	41	76	23
Mean (SD)	12.0 (6.4)	35.8 (15.2)	0
Median (min, max)	10.4 (1.8, 26.3)	36.4 (6.4, 76.4)	0

Source: Applicant's Summary of Clinical Pharmacology Studies, Table 2.b

Switching Point From IV to SC Maintenance Regimen

In study SC-3027, the SC maintenance dosing regimen was initiated at a specific time point of Week 6 following two IV infusions at Week 0 and Week 2. However, the proposed dosing regimen is to initiate SC regimen at (b) (4) next scheduled IV infusion, following two or more IV infusions. Given this discrepancy, the Applicant provided additional justification to support the proposed dosing regimen upon Agency's information request.

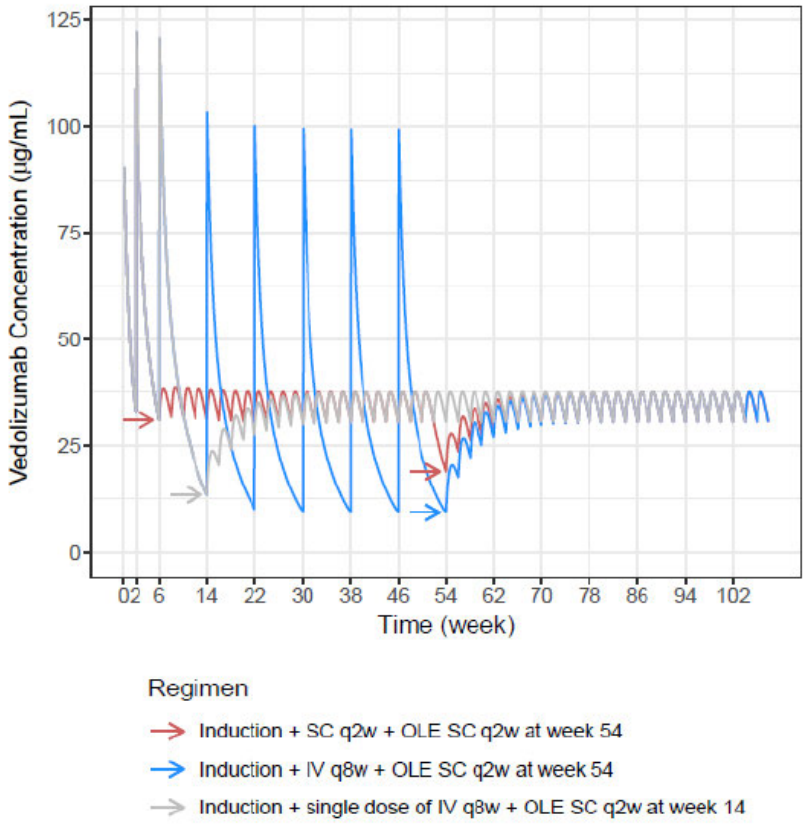
PK simulation was conducted using the final population PK model to predict the PK profiles following difference IV→SC switching scenarios (Figure 3). The results suggest that the steady state vedolizumab concentration is reached immediately following IV→SC switch at Week 6 (the dosing regimen evaluated in study SC-3017). If the IV→SC switch occurs at any scheduled IV infusion after Week 6, it would take approximately 10 to 12 weeks to re-achieve steady state. Although the Ctroughs are maintained greater than those under IV Q8W, the Cavgs would be lower during the 10-12 weeks period to re-achieve steady state. Based on reviewer's simulation using the final population PK model, initiating SC regimen 3 weeks following an IV maintenance

dose would allow vedolizumab concentrations to reaches steady-state immediately. See section 15.3.5 for more information.

The applicant also provided data from patients who completed 52 weeks of treatment in Study SC-3027 and rolled over to Study SC-3030, to show the efficacy was generally maintained following transitioning to SC regimen 8 weeks after the last IV dose (Figure 4). However, the interpretation of this result is limited by the small number of subjects (N=35) and that Study SC-3030 is an uncontrolled, open-label study.

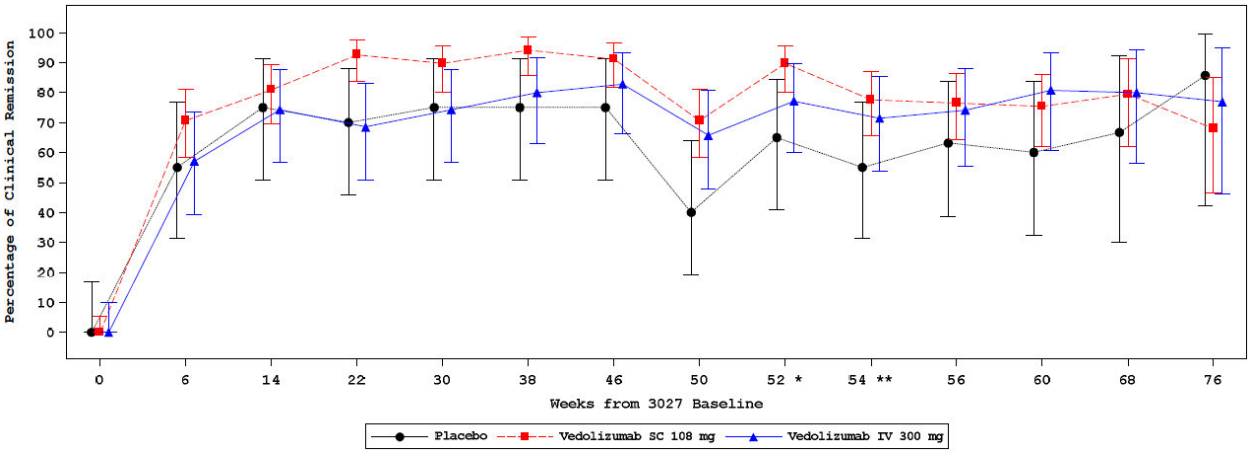
Based on totality of evidence, we recommend that the IV→SC switching can be initiated at 3-4 weeks but no later than 8 weeks (the next scheduled IV infusion) after the last IV infusion. The IV→SC switching should be initiated after at least two IV infusions. The specific IV→SC switching time for product labeling should be further discussed with the Applicant in a future BLA resubmission.

Figure 3. Simulated Vedolizumab Concentration-Time Profiles Following Different IV and SC Regimens



Note: Arrows indicate the time at which dosing switches to SC Q2W. Source: Applicant's Response to Agency Information Request dated November 4, 2019, Figure 1.

Figure 4. Proportion of Study SC-3030 UC Subjects With Clinical Remission Over Time Among Study SC-3027 Randomized Completer Subjects for Long-Term Combined Efficacy (FAS-UC)



Source: Applicant's Response to Agency Information Request dated November 4, 2019, Figure 3.

6.3.2.3. *Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?*

No. A dose adjustment or management strategy for subpopulations based on intrinsic factors is not necessary.

No clinically meaningful effect on the PK of vedolizumab was identified for age, sex, race, IBD diagnosis (UC or CD), and injection/administration site based on Applicant's updated population PK analysis using data from the phase 3 IV and SC programs. Baseline body weight and albumin were identified as potentially clinically important predictors of vedolizumab clearance. However, the impact of these factors was not considered to be clinically meaningful to require an alternative dosing regimen. See Section 15.3 for additional details of the population PK analysis and covariate analysis results.

6.3.2.4. *Are there clinically relevant drug interactions, and what is the appropriate management strategy?*

It is unknown at this time whether there are any clinically relevant drug-drug interactions as the Applicant has not provided information about the drug interaction potential for vedolizumab.

Because monoclonal antibodies are not metabolized by CYP450 enzymes, conventional drug-drug interaction studies for small molecule drugs are not considered necessary for vedolizumab. However, patients with inflammatory bowel disease have elevated levels of pro-inflammatory cytokines which can suppress the expression of some cytochrome P450 (CYP) enzymes. The suppression of the CYP enzymes could be normalized upon the disease improvement following treatment with vedolizumab. As a result, the exposure of CYP

substrates could be reduced when the disease condition is improved and the levels of pro-inflammatory cytokines are normalized.

The Applicant is currently conducting a drug-drug interaction clinical study based on the approved IV dosing regimen (recommended under PMC #2719-20 in the original BLA approval letter) in subjects with moderate-to-severe CD and UC. Results from this ongoing drug interaction study will be used to assess the potential for drug interaction upon the disease improvement following treatment with vedolizumab. As the proposed SC dosing regimen has lower Cmax and similar Cverage concentations and has been shown to result in similar efficacy results as the IV maintenance regimen, to conduct additional drug interaction studies for the proposed SC product is not necessary at this time.

6.3.2.5. *What are the drug tolerance levels of the immunogenicity assays? Does the performance of the immunogenicity assay related to drug tolerance affect the assessment of the immunogenicity incidences of vedolizumab?*

The applicant used electrochemiluminescence (ECL)-based bridging immunoassays for the assessment of anti-vedolizumab antibodies (AVA) and neutralizing AVA in the phase 1 clinical studies (SC-1017, -1018, -1021, and -1022) and phase 3 clinical study SC-3027. The assay sensitivity and drug tolerance levels are summarized in Table 9. In the Phase 3 study SC-3027, the mean Ctrough at steady state was 35.8 ug/mL, which sugget that the drug concentrations in the immunogenicity samples would interfer the AVA assay for detection of ADA<10 ng/mL and would not interfere AVA detection when AVA levels are >500 ng/mL. The relatively low drug concentrations in the phase 1 studies do not appear to interfere with AVA detection even at low AVA concentration of 10 ng/mL. Note that the applicant has not characterize the drug tolerance level at AVA concentration of 100 ng/mL as recommended by the FDA guidance.

The AVA incidences by clinical studies are summarized in Table 10. It is noted that the AVA incidences across the phase 1 PK studies were much higher than the AVA incidences reported in the phase 3 study SC-3027. The differences in AVA incidences between phase 1 and phase 3 studies could be explained by the drug tolerance level of the ECL-based AVA assay. Due to the high steady state trough concentraions in the phase 3 study, the AVA assay could only detect high titer AVA (e.g., high AVA concentrations) in an immunogenicity sample. Note that in the placebo arm (subjects who received 2 doses of vedolizumab during induction and were randomized to placebo during maintenance), the immunogenicity rate for AVA was 30.4% (17/56) and 12 of the 17 AVA positive subjects had neutralizing antibodies, which confirmed the "washout" period with decreased drug concentrations would result in much higher AVA incidences in the phase 3 trial. Overall, the reported AVA incidences in patients who received vodolizumab SC or IV treatment in the maintenance treatment period of the phase 3 study are likely underestimated.

Table 9. Sensitivity and Drug Tolerance Levels of Immunogenicity Assays for Detecting Binding (ADA) and Neutralizing Antidrug Antibodies (NAb) Against Vedolizumab in This Current Submission

Assays	Sensitivity	Drug Tolerance	Referenced concentrations of vedolizumab in clinical trials
AVA assay	3.9 ng/mL	**5 ug/mL** of vedolizumab (using 10 ng/mL of rabbit anti-vedolizumab positive control); **50 ug/mL** of vedolizumab (using 500 ng/mL of rabbit anti-vedolizumab positive control);	In Phase 1 studies, the highest concentrations were approximately 5-6 ug/mL. In the Phase 3 study SC-3027, the mean Ctrough at steady state was 35.8 ug/mL
NAb assay	31.3 ng/mL	**5 ug/mL** of vedolizumab (using 80 ng/mL of rabbit anti-vedolizumab positive control); **50 ug/mL** of vedolizumab (using 250 ng/mL of rabbit anti-vedolizumab positive control);	

Source of data: Summary of Clinical Pharmacology Studies and the Applicant's assay validation reports

Table 10: Incidences of Anti-Vedolizumab Antibodies (AVA) Across the Clinical Studies

Studies	Study Aims	Overall Subjects	AVA Positive Subjects	Percentage of AVA Positive Subjects
SC-1017	Phase 1 PK comparability study to compare PK of SC injection via PFS or PFS+NSD (small sample size)	24	13	54%
SC-1018	Phase 1 PK comparability study to compare PK of SC injection via PFS or PFS+NSD (large sample size)	102	56	55%
SC-1021	Phase 1 PK comparability study to compare PK of SC injection via PFS or PFS+AI (small sample size)	24	13	54%
SC-1022	Phase 1 PK comparability study to compare PK of SC injection via PFS or PFS+AI (large sample size)	204	125	61%
SC-3027	Phase 3 efficacy study on UC patients	383 (comed with immunomodulator)	7	1.8%
		298 (non-comed with immunomodulator)	30	10%

Source: Reviewer's analysis results of immunogenecity incidences in phase 1 and phase 3 studies

7. Sources of Clinical Data and Review Strategy

Table 11. Clinical Studies

Trial ID Design*	Treatment/ Sample Size	Endpoint/Analysis	Top-Line Results
Study SC-3027 A 52-week MC trial with a 6-wk open-label induction phase and a 46-week R, DB, double dummy treatment period for those had clinical response.	N randomized: vedolizumab (VDZ) SC + placebo IV Q8W =106 VDZ IV + placebo SC Q2W =54 Placebo SC Q2W and IV Q8W =56	Primary endpoint: clinical remission, defined as a complete Mayo score of ≤2 points with no individual subscore >1 point. Analysis: Cochran-Mantel-Haenzel (CMH) test stratified by randomization strata: (1) concomitant use of oral corticosteroids, (2) clinical remission status at Week 6, and (3) previous TNF-α antagonist failure or concomitant immunomodulator use.	The adjusted difference on the primary endpoint by the CMH method between the vedolizumab SC group (46.2%; 49/106) and placebo (14.3%; 8/56) was statistically significant with p<0.001 (33.5%; 95% CI, [20.7%, 46.3%]).
Study SC-3030 Ongoing 52-week open label extension study from parent studies SC-3027 and SC-3031	Patients with UC or CD who completed the maintenance phase (Week 52) received vedolizumab SC 108 mg Q2W Patients with UC or CD who withdrew early received vedolizumab SC 108 mg QW Patients with UC or CD who did not achieve clinical response at week 6 , but did at week 14 received vedolizumab SC 108 mg QW	Safety evaliuations including evaluation of adverse events	Ongoing safety study; no formal statistical analyses
SC-1017 Phase 1, open-label, randomized, parallel-group, pilot study	24 Healthy Volunteers	To compare the PK of a single dose of VDZ SC 108 mg administered as PFS + NSD vs PFS (PK)	

Trial ID Design*	Treatment/ Sample Size	Endpoint/Analysis	Top-Line Results
SC-1018 Phase 1, open-label, randomized, parallel-group study	102 Healthy Volunteers	To compare the PK of a single dose of VDZ SC 108 mg administered as PFS + NSD vs PFS (PK)	
SC-1021 Phase 1, open-label, randomized, parallel-group, pilot study	24 Healthy Volunteers	To compare the PK of a single dose of VDZ SC 108 mg administered as PFS + AI vs PFS (PK)	
SC-1022 Phase 1, open-label, randomized, parallel-group study	204 Healthy Volunteers	To compare the PK of a single dose of VDZ SC 108 mg administered as PFS + AI vs PFS (PK)	
SC-13010 Phase 1, open-label, single-dose study	42 Healthy Vounteers	To determine the bioavailability of vedolizumab when administered by SC and IM injection. (PK)	

Source: Reviewer's table summarizing submission contents
Abbreviations: MC: multicenter, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, Q2W: once every two weeks, Q8W: once every eight weeks.

7.1. Review Strategy

Efficacy evaluation is focused on the single phase 3 study (SC-3027) described above and the prespecified comparison between vedolizumab SC arm and the placebo arm.

Safety data on UC patients followed past Week 52 in open-label extension study SC-3030 are also summarized where relevant in the safety section below.

8. Statistical and Clinical and Evaluation

8.1. Review of Individual Trials Used to Support Efficacy

8.1.1. Study SC-3027

Trial Design

Study SC-3027 was entitled "A phase 3, randomized, double-blind, placebo-controlled study, with a vedolizumab IV reference arm, to evaluate the efficacy and safety of vedolizumab subcutaneous as maintenance therapy in subjects with moderately to severely active ulcerative colitis who achieved clinical response following open-label vedolizumab intravenous therapy."

The study included a 4-week screening period; a 6-week open-label vedolizumab IV induction phase; and a 46-week, randomized, double-blind, double-dummy, placebo-controlled maintenance phase, which included vedolizumab SC, vedolizumab IV, and placebo treatment arms. A vedolizumab IV group was included during the maintenance phase to provide a reference arm but was not intended for formal statistical testing.

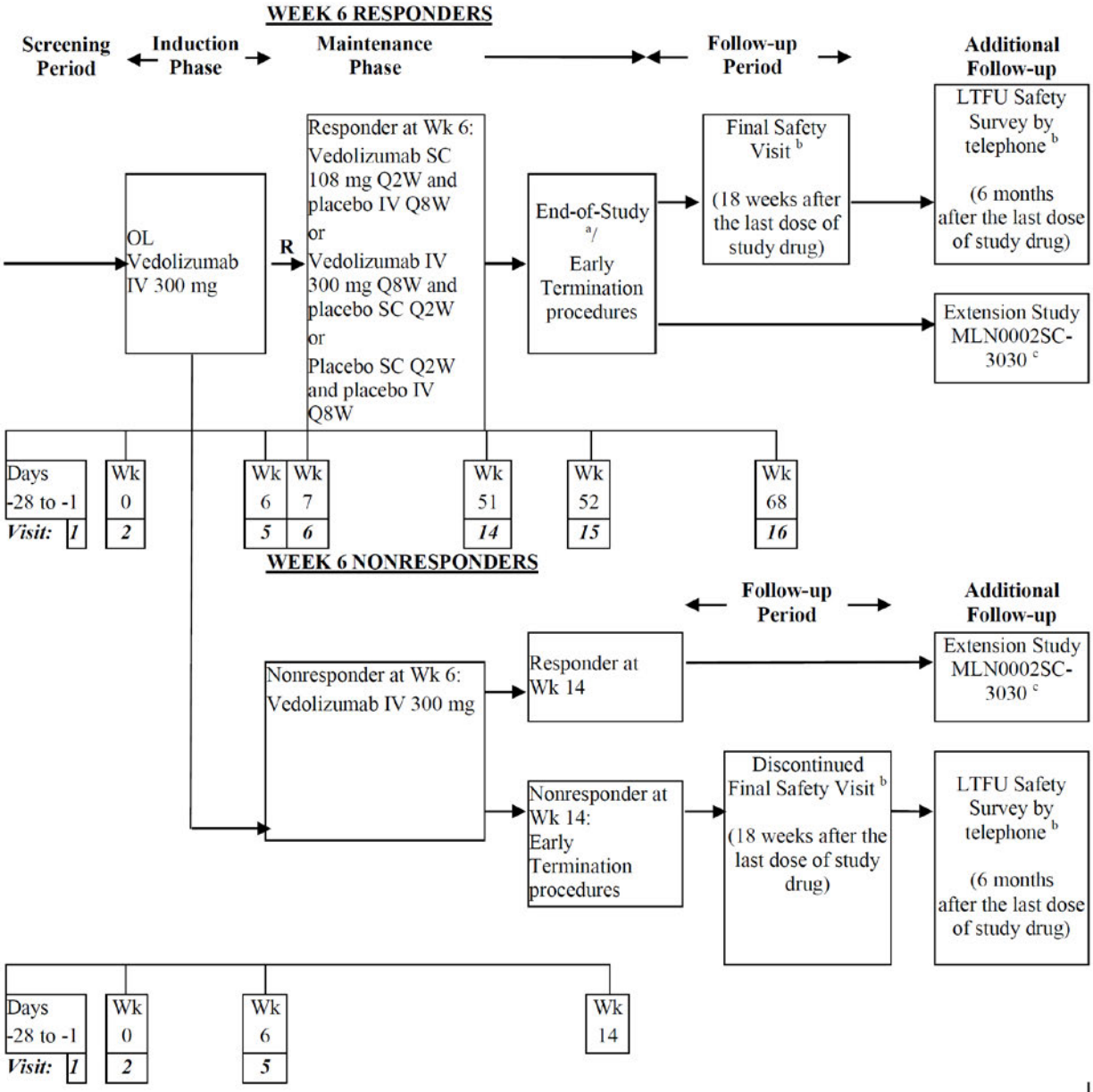
All enrolled subjects received open-label vedolizumab IV 300 mg infusions at Weeks 0 and 2. Subjects underwent assessment at Week 6 (including endoscopy to generate the Mayo score). Clinical response was defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. Subjects with clinical response at Week 6 were randomly assigned in a ratio of 2:1:1 to:

- Injections of vedolizumab SC 108 mg Q2W and placebo IV infusions Q8W,
- Infusions of vedolizumab IV 300 mg Q8W and placebo SC injections Q2W.
- Placebo SC injections Q2W and placebo IV infusions Q8W.

Randomization was stratified by the following 3 factors: concomitant use of oral corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonists failure or concomitant immunomodulator use. Baseline is defined as the last nonmissing measurement prior to or on the date of the first dose of study drug (Study Day 1). A concomitant medication was defined as a medication that was ongoing as of Day 1, started on or after Day 1 and within 127 days after the last dose of study drug.

Subjects who completed Week 52 or discontinued due to disease worsening after Week 6 or need for rescue medications after Week 14 were eligible to participate in the OLE study (SC-3030). Subjects who did not achieve clinical response at Week 6 and were not randomized, received a third open-label infusion of vedolizumab IV 300 mg at Week 6 and were assessed for clinical response by partial Mayo score (PMS) at Week 14. Subjects who achieved clinical response by Week 14 (PMS) were eligible to enroll into OLE Study SC-3030.

Figure 5. SC-3027 Study Design



IV: intravenous; LTFU: long-term follow-up; OL: open-label; OLE: open-label extension; Q2W: once every 2 weeks; Q8W: once every 8 weeks; R: randomization; SC: subcutaneous.
[a] Subjects who consent to participate in the extension study (MLN0002SC-3030; SC-3030) may begin extension study dosing after end-of-study visit procedures have been completed at the Week 52 visit.
[b] Subjects who do not enter the OLE study (SC-3030) (including early terminators and Week 14 nonresponders) will complete the final safety visit 18 weeks after their last dose of study drug and participate in a follow-up safety survey by telephone 6 months after the last dose of study drug.
[c] Visit 1 of OLE Study SC-3030 is within 4 weeks of completing Week 52 (Visit 15) procedures. Subjects not randomized into the maintenance phase (Week 6 nonresponders) who respond at Week 14 on vedolizumab IV 300 mg are also eligible for entry into the OLE study.

Source: Study CSR Figure 9.a

Study Endpoints

Primary Endpoint as Proposed by Applicant

Proportion of subjects with clinical remission, defined as a full Mayo score of ≤2 points and no individual subscore >1 point at Week 52.

While this endpoint is not consistent with the most current Agency recommendation (which now recommends use of a modified version fo the Mayo score, excluding the physician global assessment (PGA)), for this program, the Division agreed that using the same primary endpoint definition that was utilized in the phase 3 studies which supported IV formulation approval made sense, so that results in the label for the 2 formulations are shown on the same endpoint.

Secondary Efficacy Endpoints as Proposed by Applicant

1. Proportion of subjects with "mucosal healing", defined as Mayo endoscopic subscore of ≤1 point, at Week 52.

   This study design estimates the proportion of patients with "mucosal healing" at Week 52 in Week 6 responders. The Division does not accept the term mucosal healing as defined here, given that true healing of the mucosa involves not only improvement of the gross appearance, but also normalization of inflammation as assessed by histopathology. The term mucosal healing is used as defined by the applicant in the results below, but for future labeling consideration, this endpoint should be described as "improvement in endoscopic appearance of mucosa."

2. Proportion of subjects with "durable clinical response", defined as clinical response at Weeks 6 and 52, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

   This study design does not allow for direct estimation of the proportion of patients with clinical response at both Week 6 and Week 52, given that randomization occurred at Week 6 and was conditional on clinical response. Furthermore, there is no comparison group for an evaluation of the probability of being a responder at both Weeks 6 and 52 given that there was no control group during the induction period. The endpoint analyzed by the Applicant evaluates the proportion of patients who maintained response at Week 52 among patients who were responders at Week 6 of the open-label phase.

3. Proportion of subjects with "durable clinical remission", defined as clinical remission based on complete Mayo score at Weeks 6 and 52.

   Similarly to the "durable clinical response," direct estimation of the percentage of patients achieving remission at both Week 6 and Week 52 is not feasible, and there is no control group for such an evaluation. Given the study design, it is possible to evaluate remission rates at Week 52 in the subpopulation of remitters at Week 6, i.e. the proportion of

patients who stayed in remission at Week 52. The Applicant's analysis actually calculates the proportion of remitters at both Week 6 and Week 52 in Week 6 responders, which is not interpretable. See further discussion in section: Efficacy Results – Secondary and other relevant endpoints.

4. Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission based on complete Mayo score at Week 52.

   Analogous to the remark to the proposed primary endpoint, this endpoint estimates the proportion of Week 52 remitters who discontinued oral corticosteroids at Week 52 among the population of patients who used oral corticosteroids at Baseline (Week 0) and were responders at Week 6.

Exploratory Endpoints

Alternative Clinical Remission (recommended by FDA written response dated May 15, 2015, which is consistent with FDA UC draft guidance published in 2016) is the proportion of subjects with clinical remission at Week 6 and at Week 52 based on alternative definition of clinical remission, defined in 3 different ways:

1. Definition 1: Stool Frequency subscore =0; Rectal Bleeding subscore =0 and endoscopy subscore =0 or 1 (modified so that a score of 1 does not include friability),
2. Definition 2: Stool Frequency subscore =0 or 1 and a prespecified specific change of 1 or more from Baseline and rectal Bleeding subscore =0; and Endoscopy subscore =0 or 1 (modified so that a score of 1 does not include friability).
3. Definition 3: either definition 1 or 2

Statistical Analysis Plan

Analysis Populations/Sets

The primary analyses population was the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of study drug in the maintenance phase. Subjects in this set were analyzed according to the treatment they were randomized to receive. The FAS was used for the efficacy analysis with exception of corticosteroid-free remission, which was based on a subset of the FAS subjects with baseline concomitant oral corticosteroid use.

Safety Analysis Set

The applicant defined 3 safety analysis populations.

SAF- all subjects who were randomized to the maintenance phase and received at least 1 dose of study drug (SC placebo or SC vedolizumab) (placebo or vedolizumab) drug in the maintenance portion. Subjects in this set were analyzed according to the treatment that was actually received.

SAF-I included all subjects who received at least 1 induction dose, but were not randomized to maintenance phase (because this application focuses on the safety and efficacy of the SC formulation, which these patients were not eligible to receive, this subset is not a focus of the safety review).

SAF-C included both SAF and SAF-I.

Primary Statistical Analyses Method

Cochran-Mantel-Haenzel (CMH) test stratified by randomization strata at a 2-sided alpha level of 0.05. Nonremitter imputation was used for missing data at Week 52. The comparison of vedolizumab IV arm versus placebo arm was considered exploratory and was not included in the multiplicity control procedure.

Secondary efficacy endpoints were analyzed in a similar way to the primary efficacy endpoint. Mucosal healing at Week 52, "durable clinical response" and "durable clinical remission" were analyzed for the FAS subjects. Corticosteroid-free remission at Week 52 was analyzed in a subset of the FAS subjects with baseline concomitant oral corticosteroid use. All secondary endpoints were analyzed using CMH tests for risk differences, stratified by randomization stratification factors.

Multiplicity Control Procedure

A hierarchical approach was used to control the overall Type I error rate at 0.05 level for the comparison between vedolizumab SC and placebo arms for the primary and secondary endpoints. The statistical inference for the first secondary endpoint of mucosal healing will only be performed if the primary endpoint, proportion of subjects with clinical remission at Week 52, is statistically significant ($p<0.05$). The second secondary endpoint of "durable clinical response" will only be tested if the first secondary endpoint is statistically significant ($p<0.05$). Similarly, the third secondary endpoint of "durable clinical remission" will only be tested if the second secondary endpoint is statistically significant ($p<0.05$), and the fourth secondary endpoint of corticosteroids-free clinical remission will only be tested if the third secondary endpoint is statistically significant ($p<0.05$).

Mayo Score Calculation Methods

In the primary analysis, the patient reported components of the Mayo score were calculated following the method utilized in the prior vedolizumab IV studies (Studies C13006 and C13008) that were used to support approved labeling in 2014. Stool frequency and rectal bleeding subscores were derived from an eDiary completed by the subject 7 days before a study visit. These subscores were calculated using the eDiary in the following order:

1. The score from the 3 most recent days before the actual day of the study visit were averaged and rounded to the nearest integer.

2. If diary entries from the 3 days were not available, the scores from the 2 most recent entries were averaged and rounded to the nearest integer.
3. If fewer than 2 days of diary data were available, the subject was categorized as a nonresponder and the subscore was considered missing.

A sensitivity analysis for the primary endpoint of clinical remission was also conducted using Mayo score calculated in accordance with the 2016 FDA draft UC guidance. For postscreening visits, the patient-reported components of the Mayo score were calculated as the sum of the 3 most recent consecutive nonmissing results divided by 3. For subjects who did not have 3 consecutive days of nonmissing eDiary data but had at least 4 days of data available in the last 7-day period before the visit, the nonmissing scores from the total number of available days in the last 7-day period were averaged. If fewer than 3 consecutive days or 4 days of eDiary data in the last 7-day period were available, the subscore was considered missing and the subject was categorized as a nonresponder.

Missing Data Handling Approaches

Missing data for dichotomous endpoints was handled using the nonresponder imputation method. Sensitivity analysis was conducted to assess the impact of dropouts for different missing mechanisms using a hybrid approach where discontinuation due to adverse event (AE) or lack of efficacy was imputed as nonresponder (under MNAR) and other discontinuation/missing was imputed using multiple imputation in each treatment arm (under MAR) for primary and all secondary efficacy endpoints and subgroup analysis by prior anti-TNF status. For details of multiple imputation refer to Section 7.8.6 of the statistical analysis plan.

Sensitivity Analyses

Sensitivity analyses were planned for the primary endpoint and secondary endpoints using data imputed by the hybrid method, Mayo score calculated per FDA draft guidance and partial Mayo score.

Protocol Amendments

There were 5 protocol amendments to the original study protocol (dated February 26, 2015) through February 16, 2018. The amendments did not have major impact on the interpretability of the safety or efficacy results. For details, refer to Section 15.1.4

8.1.2. Study SC-3030

Study SC-3030 is an ongoing year-long OLE study (which included eligible patients from parent studies SC-3027 and SC-3031) to determine the long-term safety and efficacy of vedolizumab SC patients with UC and CD. The study is intended to collect long-term safety data for vedolizumab SC dosing to complement the safety data gathered from Study SC-3027 in UC subjects and

Study SC-3031 in CD subjects. Patients were eligible to be enrolled in Study SC-3030 from the groups listed below (which include the respective doses):

- Patients with UC or CD who completed the maintenance phase (Week 52) received vedolizumab SC 108 mg Q2W
- Patients with UC or CD who withdrew early from the maintenance phase due to disease worsening or need for rescue medications received vedolizumab SC 108 mg QW
- Patients with UC or CD who did not achieve a clinical response at Week 6, but after receiving a third vedolizumab IV infusion at Week 6, achieved a clinical response at Week 14, received vedolizumab SC 108 mg Q2W

The safety data from this uncontrolled study is supportive in nature and is described within the safety section below, as UC patients from study SC-3030 contributed safety data to the safety population described as “Pool 1 UC ” (refer to 8.2.1).

8.1.3. Study Results

Compliance With Good Clinical Practices

The Applicant attests that study 3027 and 3030 were conducted in accordance with Good Clinical Practice.

Financial Disclosure

Four investigators reported significant financial relationships to Takeda. This included 1 instance of research support, and 3 investigators who receive speaker fees in excess of $25,000 per year. Given that 141 Investigators participated (103 enrolled 1 or more subjects), this does not represent a substantial portion of the investigators. Details in appendix.

Patient Disposition

A total of 614 subjects were screened for enrollment in the study and 383 subjects were enrolled into the open-label induction phase. Subject disposition for all enrolled subjects during the induction phase refers to clinical study report (CSR) Table 10.a. A total of 30 subjects (7.8%) discontinued the induction phase for various reasons with pretreatment event/adverse event (PTE/AE) (30.0%) or lack of efficacy (30.0%) being the most frequent reasons.

Of the 383 subjects who received at least one dose of vedolizumab IV induction treatment, 143 failed to achieve a clinical response at Week 6 and were not randomized into the maintenance phase. Of these 143 subjects, 114 (79.7%) exhibited a clinical response at Week 14 and could opt to enroll in Study SC-3030. Out of the 215 subjects who achieved a clinical response at Week 6, five subjects were not randomized into the maintenance phase. In addition, the

Applicant reported site investigators misclassified six nonresponders as responders at Week 6. In total, 216 subjects were randomized into the maintenance phase including 210 out of 215 Week 6 responders and the six nonresponders misclassified as responders by site error.

Table 12 summarizes subject disposition of the 216 randomized subjects into the maintenance phase in the FAS by treatment group (placebo: 56 subjects; vedolizumab SC: 106 subjects; and vedolizumab IV: 54 subjects). In the maintenance phase, only 37.5% of the placebo subjects completed the study at Week 52, compared with 71.7% and 75.9% of subjects in the vedolizumab SC and vedolizumab IV treatment groups at Week 52, respectively. The most frequent reason for discontinuation across all treatment groups was lack of efficacy, which was highest in the placebo group (50%) compared with 17% and 11.1% for vedolizumab SC and vedolizumab IV, respectively. AEs leading to discontinuation occurred in 8.9% of placebo group, 4.7% in the vedolizumab SC group, and 3.7% in the vedolizumab IV group.

Table 12. Subject Disposition, Maintenance Phase (Full Analysis Set)

Subject Disposition	PBO N=56 n (%)	VDZ SC 108 mg N=106 n (%)	VDZ IV 300 mg N=54 n (%)	Total N=216 n (%)
Completed study drug in maintenance phase	21 (37.5)	77 (72.6)	41 (75.9)	139 (64.4)
Prematurely discontinued study drug in maintenance phase	35 (62.5)	29 (27.4)	13 (24.1)	77 (35.6)
Reason for discontinuing study drug in maintenance phase				
Pretreatment event/adverse event	5 (8.9)	5 (4.7)	2 (3.7)	12 (5.6)
Significant protocol deviation	0	1 (0.9)	1 (1.9)	2 (9.3)
Lost to follow-up	0	0	0	0
Voluntary withdrawal	1 (1.8)	1 (0.9)	4 (7.4)	6 (27.8)
Study termination	0	0	0	0
Pregnancy	0	1 (0.9)	0	1 (0.5)
Lack of efficacy	28 (50.0)	18 (17.0)	6 (11.1)	52 (24.1)
Leukopenia or lymphopenia	0	0	0	0
Other	1 (1.8)	3 (2.8)	0	4 (1.9)

Source: Adapted from CSR Table 10.c, verified by the reviewer

Protocol Violations/Deviations

Study-specific significant protocol deviations are summarized in Table 13. The study specific significant protocol deviation categories were predefined to be broader than those that are defined in the ICH E3 guidance. Of the 216 FAS subjects, 110 subjects (50.9%) had at least one study- specific significant protocol deviation (23, 58, and 29 subjects from the placebo, vedolizumab SC, and vedolizumab IV groups, respectively). Of these, 24 subjects (11.1%) had entry criteria violations, 77 subjects' (39.6%) procedures did not perform in accordance with the protocol, which included missing laboratory work or physical examinations at a study visit, and 30 subjects (13.9%) had study medication temperature excursions that occurred outside of clinic visits.

Table 13. Significant Protocol Deviations (FAS)

Type of Deviation	PBO N=56 n (%)	VDZ SC 108 mg N=106 n (%)	VDZ IV 300 mg N=54 n (%)	Total N=216 n (%)
Subjects with ≥1 significant protocol deviation	23 (41.1)	58 (54.7)	29 (53.7)	110 (50.9)
Entry criteria	2 (3.6)	14 (13.2)	8 (14.8)	24 (11.1)
Concomitant medication	1 (1.8)	1 (0.9)	2 (3.7)	4 (1.9)
Procedure not performed per protocol	17 (30.4)	37 (34.9)	23 (42.6)	77 (35.6)
Study medication	3 (5.4)	22 (20.8)	5 (9.3)	30 (13.9)
Withdrawal criteria	1 (1.8)	1 (0.9)	1 (1.9)	3 (1.4)

Source: CSR Table 10.e

The Applicant reported that 215 subjects achieved a clinical response at Week 6. Only 210 out of the 215 clinical responders at Week 6 were randomized to maintenance phase. Together with six nonresponders mis-classified as responder by site investigators, there were 216 subjects randomized into maintenance phase. A sensitivity analysis was conducted to evaluate the impact on the primary endpoint. For details of the sensitivity analysis refer to Table 20 in the efficacy section.

The Applicant reported that, after unblinding, it was discovered that stratification factors were incorrectly applied to some subjects during randomization for the maintenance phase. This issue was caused by investigative sites incorrectly entering values for some variable such as remission status or prior TNF-α antagonist failure into Interactive Web Response System (IWRS). A sensitivity analysis showed that it did not impact the results of the study. However, this CSR did not provide details on the site errors, the consequent mis-classification on stratification factors, or specific method and result of the sensitivity analysis. It was not clear which version of the information on stratification factors, with or without site errors, was used for the primary analysis and secondary analyses according to the CSR.

The Agency issued three information requests to the Applicant and obtained the information needed to verify the primary efficacy results, and to evaluate the impact of the misclassified factors caused by site errors. According to the IR response submitted on August, 13, 2019, the originally submitted efficacy data was based on IWRS with site errors on stratification factors, and the rederived efficacy dataset, ADaM: ADMAYO2B, had no site errors and was the Electronic Data Capture (EDC) of patient's electronic case report form (eCRF).

Table 14 summarizes the inconsistency in stratification factors in IWRS data with site errors and the rederived ADaM: ADMAYO2B without site errors. Of the 216 subjects in the FAS, a total of 79 unique subjects (36.6%) were mis-stratified in IWRS based on a retrospective comparison

with the data collected on eCRF in the EDC system, the patient or investigator-reported Mayo Score components data collected by (b) (4)), or the endoscopy data collected by (b) (4)). Of note, subjects (b) (6) appeared to be mis-stratified in more than one category in IWRS.

For analysis results using the corrected stratification information, refer to Table 20 in the subsection on Efficacy Results – Primary Endpoint.

Table 14. Summary of Inconsistency in Stratification Information in Data Used by the Site (IWRS) Versus EDC Efficacy Data (ADaM: ADMAYO2B)

Stratification Factors	IWRS	ADMAYO2B[a]	Description (by Treatment)[b]
Clinical Remission at Week 6 (Yes/No)[c]	Yes	No	54 subjects (Placebo=15, SC=26, IV=13)
	No	Yes	11 subjects (Placebo=5, SC=4, IV=2)
Concomitant Use of Oral Corticosteroid (Yes/No)[d]	Yes	No	6 subjects (Placebo=3, SC=2, IV=1)
	No	Yes	8 subjects (Placebo=1, SC=3, IV=4)
Previous TNF- α antagonist failure or concomitant immunomodulators use (Yes/No)[e]	Yes	No	2 subjects (SC=2)
	No	Yes	4 subjects (Placebo=1, SC=2, IV=1)

Source: Table 3.a of Applicant's IR response dated August 13, 2019 for IR issued on July 30, 2019, verified by the reviewer
[a] Rederived stratification factors in ADMAYO2B.xpt (submitted on August 1, 2019) were derived based on prior/concomitant medication data
as collected in the EDC system based on eCRF, the patient or investigator-reported Mayo Score components collected by (b) (4), and the endoscopy data collected by (b) (4)
[b] Subject counts listed in each stratification factor category are not mutually inclusive. Subjects (b) (6) appeared in more than one category.
[c] Yes = Clinical Remitter at Week 6 as collected in IWRS or derived in ADMAYO2B; No = Clinical nonremitter at Week 6 in IWRS or derived in ADMAYO2B.xpt.
[d] Yes = with oral Corticosteroid Use at the time of randomization as collected in IWRS or derived in ADMAYO2B; No = without oral Corticosteroid Use at the time of randomization as collected in IWRS or derived in ADMAYO2B.xpt.
[e] Yes = previous TNF-α antagonist failed or with immunomodulator use at Week 0 as collected in IWRS or derived in ADMAYO2B.xpt; No = TNF-α naïve and without immunomodulator use at Week 0 as collected in IWRS or derived in ADMAYO2B.

Table 15 provides a breakdown of Week 6 clinical responder and remitter by different data sources. A sensitivity analysis was conducted based on EDC data (based on eCRF) to evaluate the impact of mis-classification of stratification. The analysis result was consistent with the primary efficacy result which reported a higher proportion of Week 52 remitters in Week 6 clinical responders randomized to the vedolizumab arm relative to those randomized to placebo (Table 20).

Table 15. Breakdown of Week 6 Clinical Responder and Remitter by Different Data Sources

Source	Placebo N=56	VDZ SC 108 mg N=106	VDZ IV 300 mg N=54
Week 6 clinical remitters			
Study sites (IWRS)[a]	25	47	24
ADMAYO2 (EDC: ADaM)[b]	15	25	13
ERT data (SDTM.QS)[c]	15	25	13
Week 6 clinical responders			
Study sites (IWRS)[a]	56	106	54
ADMAYO2 (ADaM)[b]	56	103	51
ERT data (SDTM.QS)[c]	56	**102**	**52**

Source: Created by reviewer based on Tables 3.d and 3.e of IR response dated August 13, 2019
[a]Clinical response and remission status at Week 6 were determined by study sites at the time of randomization.
[b]Clinical response and remission status at Week 6 were derived at analysis and reporting stage verified against EDC data based on eCRF.
[c]Clinical response and remission status at Week 6 were derived using the (b) (4) source data (mapped to SDTM.QS domain) in post hoc fashion.

Demographic Characteristics

Baseline (i.e., Week 0) demographic and baseline characteristics of the FAS population for the maintenance phase are summarized in Table 16. Overall, the FAS population had higher proportions of subjects who were white (83.8%), male (60.2%), or aged at least 35 years (58.8%). There were more nonsmokers (65.3%) and subjects with normal BMI (55.1%). Most of the subjects (87%) were enrolled at study sites outside of North America.

Majority of demographic characteristics were similar between vedolizumab SC and placebo subjects in the FAS population, except for some age, race and region categories. As compared to the placebo arm, the Vedolizumab SC arm enrolled more subjects younger than 35 years of age (57.1% vs. 48.1%), in European study sites (64.1% vs. 48.2%), and who were white (86.8% vs. 75.0%). These differences are unlikely to meaningfully impact efficacy results.

Relative to the vedolizumab IV arm, the vedolizumab SC arm had more subjects younger than 35 years of age (46.2% vs. 35.2%), and less subjects who were overweight (36.8% vs. 63%) or obese (8.5% vs. 24.1%). Difference in body mass index could affect efficacy, however, given that the comparison of IV to placebo was included only for assay sensitivity, this identified imbalance does not impact the interpretability of the data comparing SC to Placebo, in primary support of the efficacy of the SC regimen.

Table 16. Demographic and Baseline Characteristics in FAS for Maintenance Phase

Demographic and Baseline Characteristics	PBO N=56	VDZ SC 108 mg N=106	VDZ IV 300 mg N=54	Total N=216
Age (years)				
Mean (SD)	39.4 (11.70)	38.1 (13.12)	41.6 (14.11)	39.3 (13.05)
Median (min, max)	37.0 (21, 66)	36.0 (18, 69)	40.5 (18, 68)	38.0 (18, 69)
Age categories, n (%)				
<35 years	21 (37.5)	49 (46.2)	19 (35.2)	89 (41.2)
≥35 and <65 years	32 (57.1)	51 (48.1)	32 (59.3)	114 (52.8)
≥65 years	3 (5.4)	6 (5.7)	4 (7.4)	13 (6.0)
Male, n (%)	34 (60.7)	65 (61.3)	31 (57.4)	130 (60.2)
Race, n (%)				
Asian	13 (23.2)	14 (13.2)	5 (9.3)	32 (14.8)
White	42 (75.0)	92 (86.8)	47 (87.0)	181 (83.8)
BMI (kg/m^2)				
Mean (SD)	24.7 (5.9)	24.1 (4.8)	26.2 (4.9)	24.8 (5.2)
Median (min, max)	23.9 (14.1, 51.1)	23.6 (17.0, 41.0)	26.5 (16.3, 35.3)	24.0 (14.1, 51.1)
BMI categories, n (%)				
≥25	24 (42.9)	39 (36.8)	34 (63.0)	97 (44.9)
≥30	7 (12.5)	9 (8.5)	13 (24.1)	29 (13.4)
Smoking classification, n (%)				
Current smoker	0	11 (10.4)	10 (18.5)	21 (9.7)
Ex-smoker	18 (32.1)	25 (23.6)	11 (20.4)	54 (25.0)
Geographic region, n (%)				
North America	9 (16.1)	9 (8.5)	10 (18.5)	28 (13.0)
Europe	35 (48.2)	68 (64.1)	31 (57.4)	126 (58.3)
Asia/Africa/Australia	13 (23.2)	16 (15.1)	6 (11.1)	35 (16.2)

Source: Adapted from CSR Table 11.c on Page 83, verified by the reviewer
FAS: full analysis set; PBO: placebo; VDZ: vedolizumab; IV: intravenous; SC: subcutaneous; BMI: body mass index.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline UC disease characteristics of the FAS population are summarized in Table 17. Nearly 62% of subjects had severe UC (i.e., Mayo score of 9 to 12), 81.9% of subjects had baseline fecal calprotectin levels over 500 µg/g, and most subjects had left-sided colitis (42.1%) or pancolitis (35.6%).

Durations of UC were similar in the placebo and vedolizumab SC treatment arms with median duration of 5.3 and 5.9 years, respectively. Baseline disease activity, as assessed by the complete Mayo score, was similar between the vedolizumab SC and the placebo arms, as was the category of baseline fecal calprotectin.

Vedolizumab IV arm had more subjects with severe UC (68.5%) at baseline relative to the vedolizumab SC arm (56.6%).

Table 17. Baseline UC Disease Characteristics (FAS)

Baseline Disease Characteristics	PBO N=56	VDZ SC 108 mg N=106	VDZ IV 300 mg N=54	Total N=216
Duration of UC (years)				
Mean (SD)	7.4 (7.1)	8.0 (6.2)	8.2 (6.0)	7.9 (6.4)
Median (min, max)	5.3 (0.6, 30.3)	5.9 (0.6, 29.8)	6.8 (0.5, 30.9)	5.9 (0.5 30.9)
Duration of UC categories, n (%)				
<1 year	5 (8.9)	6 (5.7)	1 (1.9)	12 (5.6)
≥1 to <3 years	14 (25.0)	16 (15.1)	10 (18.5)	40 (18.5)
≥3 to <7 years	16 (28.6)	37 (34.9)	16 (29.6)	69 (31.9)
≥7 years	21 (37.5)	47 (44.3)	27 (50.0)	95 (44.0)
Baseline disease activity, n (%)				
Severe (Mayo score=9 to 12)	36 (64.3)	60 (56.6)	37 (68.5)	133 (61.6)
Categorical baseline fecal calprotectin categories, n (%)				
>500 µg/g	44 (78.6)	87 (82.1)	46 (85.2)	177 (81.9)
Missing	0	4 (3.8)	2 (3.7)	6 (2.8)
Disease localization, n (%)				
Proctosigmoiditis	7 (12.5)	15 (14.2)	7 (13.0)	29 (13.4)
Left-sided colitis	24 (42.9)	46 (43.4)	21 (38.9)	91 (42.1)
Extensive colitis	4 (7.1)	7 (6.6)	7 (13.0)	18 (8.3)
Pancolitis	21 (37.5)	37 (34.9)	19 (35.2)	77 (35.6)
Prior UC therapy history				
TNF-α antagonist use (or failure)	20 (35.7)	40 (37.7)	24 (44.4)	84 (38.9)
Corticosteroids only	22 (39.3)	28 (26.4)	21 (38.9)	71 (32.9)
Corticosteroids and immunomodulators	32 (57.1)	71 (67.0)	32 (59.3)	135 (62.5)

Source: Adapted from CSR Tables 11.c, 11.e, 11.f and 11.i, verified by the reviewer

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Of the 216 subjects in the FAS population, treatment compliance while patients remained in the study was comparable across the treatment groups (90.2%, 92.9%, and 90.1% for placebo, vedolizumab SC, and vedolizumab IV, respectively (Study SC-3027 CSR Table 15.1.14.2).

Diary compliance for all subjects while they remained in the study was similar across treatment groups, as exhibited by the mean percentages of expected entries that were completed 95.6%, 94.5%, and 95.6% for placebo, vedolizumab SC, and vedolizumab IV, respectively. Most of the subjects across all groups were ≥90% compliant with the electronic diary (eDiary) entries (Study SC-3027 CSR Table 11.j).

The usage of concommitent drugs during the maintenance phase was similar across three arms (Table 18).

Of the 105 sites that randomized subjects into the maintenance phase in this study, 2 sites were closed by the Applicant because of noncompliance. A total of 24 subjects participated in the study at these 2 sites (15 subjects in the open-label induction phase, 2 placebo subjects, and 7 vedolizumab SC subjects). These subjects were included in the primary analysis (FAS); however,

a sensitivity analysis was also done in which the subjects from these sites were excluded. The results of this sensitivity analysis were consistent with the primary analysis results (the results are available in the applicant's CSR).

Table 18. Concommitent Medications in Maintenance Phase (FAS)

Medications	PBO N=56	VDZ SC 108 mg N=106	VDZ IV 300 mg N=54	Total N=216
Subjects with ≥1 concomitant medication	52 (92.9)	98 (92.5)	47 (87.0)	197 (91.2)
Corticosteroids	28 (50.0)	54 (50.9)	27 (50.0)	109 (50.5)
5-aminosalicylic acids	44 (78.6)	85 (80.2)	44 (81.5)	173 (80.1)
Immunomodulators	18 (32.1)	36 (34.0)	17 (31.5)	71 (32.9)

Source: Adapted from CSR Table 11.i, verified by the reviewer

Efficacy Results: Primary Endpoint

The primary efficacy results on Week 52 clinical remission are summarized in Table 19 in the FAS population. The prespecified primary analysis found significantly more clinical remitters in the vedolizumab SC arm (46.2%, 49/106) as compared to the placebo arm (14.3%, 8/56) among Week 6 clinical responders with an adjusted treatment difference of 32.3% (95% CI: 19.7%, 45%) and a p-value<0.001.

The vedolizumab IV arm showed a similar positive treatment effect over the placebo arm with an adjusted treatment difference of 27.9% (95% CI: 12.3%, 43.5%).

This efficacy section focuses on the primary comparison between subjects randomized to the vedolizumab SC arm and placebo arm, since the vedolizumab IV arm has been approved in 2014 and serves as a reference arm with no prespecified formal comparison to other treatment arms in this study.

Table 19. Clinical Remission at Week 52 (FAS)

Clinical Remission	PBO N=56	VDZ SC 108 mg N=106	VDZ IV 300 mg N=54
Number (%) of subjects achieving clinical remission at Week 52	8 (14.3)	49 (46.2)	23 (42.6)
Adjusted difference in remission rates, vedolizumab vs. placebo		32.3	27.9
95% CI [b]		(19.7, 45.0)	(12.3, 43.5)
P-value, vedolizumab vs. placebo [c]		<0.001	<0.001

Source: Adapted by the reviewer based on Study SC-3027 CSR Table 11.m
FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha; VDZ: vedolizumab.
All subjects with missing data for determination of endpoint status were categorized as nonresponders.
[a] Clinical remission was defined as a complete Mayo score of ≤2 points and no individual subscore >1 point. The Mayo score was calculated on weekly diary data with at least 2 days diary per week.
[b] The 95% CI of the adjusted difference was based on the normal approximation method, or the exact method if the number of remissions in either treatment group was ≤5.

[c] The p-values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization strata (concomitant TNF-α antagonist failure or concomitant immunomodulator use) or Fisher's Exact test if the number of remissions in either treatment group was ≤5.

A sensitivity analysis was conducted to evaluate the potential impact of misclassification in the stratification factors on the analysis of the primary endpoint. The CSR reported analysis results on the primary endpoint using stratification data as randomized (i.e., IWRS data), which contained site errors during randomization (i.e., patients were dispositioned into wrong strata). The sensitivity analysis used data free of site errors on randomization stratification factors (i.e., correct data source) that were provided in response to Agency information requests.

Both analyses on the primary endpoint found consistently higher proportions of vedolizumab SC subjects achieving clinical remission than placebo subjects at Week 52 with reported p-values <0.001 (Table 20). The analyses in the table below used complete Mayo Score based on the prespecified primary calculation method: nonmissing weekly diary data with at least two days diary per week and nonresponder imputation for missing weekly data.

Table 20. Sensitivity Analysis Results on the Primary Endpoint to Address Missclassification in the Stratification Factors

Type of Analysis	Placebo n (%) N=56	VDZ SC n (%) N=106	Treatment Difference[a] % (95% CI)	P-value[a]
Primary analysis based on misclassified stratification factors that were used to stratify randomization	8 (14.3)	49 (46.2)	32.3 (19.7, 45.0)	<0.001
Sensitivity analysis based on actual stratification factors	8 (14.3)	49 (46.2)	33.5 (20.7, 46.3)	<0.001

Source: created by reviewer
[a]P-value was based on CMH method adjusting for stratification factors, or the exact method if the number of remitters in either treatment group is <=5. The 95% CI for the adjusted treatment difference was based on normal approximation.

Additional sensitivity analyses were conducted to evaluate the robustness of the primary efficacy results in the three aspects described below. For each aspect, we conducted two versions of comparison between treatement arms, one adjusted by the mis-classified stratification factors that were used for randomization and another adjusted by the actual stratification factors.

1. To investigate the impact of different calculation methods for the Mayo score on the primary endpoint, we conducted sensitivity analyses based on the Mayo Score calculated by FDA draft guidance recommendations (at least three consecutive days or four diary days per week to be considered a non-missing week). The results were consistent with the primary efficacy results (reported in CSR table 11.n).

2. When using the partial Mayo score instead of the complete Mayo score for the primary comparison, this sensitivity analysis found similar results as the primary analysis (CSR Table 15.2.8.2.2).
3. After removing the non-compliant study sites from the FAS population, the findings were consistent with the primary analysis results (CSR Tables 15.2.1.1.3 and 15.2.1.1.4).

Furthermore, we also conducted additional sensitivity analyses to evaluate the potential effect of missing data on the efficacy conclusions. The dropout rate was much higher in the placebo arm (62.5%) than in the vedolizumab SC arm (27.4%). The applicant conducted a sensitivity analysis of week 52 clinical remission based on data imputed by hybrid imputation method and the results were consistent with the primary results (CSR Table 15.2.1.3). However, this analysis evaluates only one alternative missing data assumption and does not comprehensively evaluate the space of plausible missing data assumptions. To cope with the high and imbalanced dropout rates in this study, we conducted additional tipping point sensitivity analyses to investigate the robustness of the primary result. If at least 20% of the dropouts (7/35) in the placebo arm would be responders (assuming that all dropouts in the vedolizumab SC arm were nonresponders), statistical significance for the comparison of Week 52 remitters between the two arms would be lost (p-value of 0.072). The Week 52 remitter rate in the vedolizumab SC arm would still be 19.4% higher in comparison to the placebo arm (26.8%). Although the number of responders needed to flip the significance does not seem high, it is notable that 80% of the dropouts in placebo arm were due to lack of efficacy. This additional sensitivity analysis provides some additional support for the robustness of the results for vedolizumab SC, especially in the context of efficacy having been previously established for vedolizumab IV.

The dropout rate was much higher in the placebo arm (62.5%) than in the vedolizumab SC arm (27.4%). The applicant conducted a sensitivity analysis of week 52 clinical remission based on data imputed by hybrid imputation method and the results were consistent with the primary results (CSR Table 15.2.1.3). However, this analysis evaluates only one alternative missing data assumption and does not comprehensively evaluate the space of plausible missing data assumptions. To cope with the high and imbalanced dropout rates in this study, we conducted additional tipping point sensitivity analyses to investigate the robustness of the primary result. If at least 20% of the dropouts (7/35) in the placebo arm would be responders (assuming that all dropouts in the vedolizumab SC arm were nonresponders), statistical significance for the comparison of Week 52 remitters between the two arms would be lost (p-value of 0.072). The Week 52 remitter rate in the vedolizumab SC arm would still be 19.4% higher in comparison to the placebo arm (26.8%). Although the number of responders needed to flip the significance does not seem high, it is notable that 80% of the dropouts in placebo arm were due to lack of efficacy. This additional sensitivity analysis provides some additional support for the robustness of the results for vedolizumab SC, especially in the context of efficacy having been previously established for vedolizumab IV.

Subgroup Analyses

In all subgroups analyzed, the proportion of subjects in clinical remission at Week 52 favored vedolizumab SC relative to placebo. Figure 7 in the Appendices illustrates the adjusted treatment differences and the corresponding 95% CIs.

Efficacy Results: Secondary and Other Relevant Endpoints

Secondary Endpoints

The secondary efficacy endpoint results for this study are summarized in Table 21. Statistically significant treatment differences favoring vedolizumab SC treatment over placebo was observed for rates of "mucosal healing" at Week 52 (vedolizumab SC: 56.6%; placebo: 21.4%, p<0.001) and clinical response at Week 52 (vedolizumab SC: 64.2%; placebo: 28.6%, p<0.001) in Week 6 induced clinical responders (Applicant used the term durable clinical response).

The third secondary endpoint analyzed by the Applicant was percentage of clinical remitters at both Week 6 and Week 52 in Week 6 clinical responders (Applicant used the term durable clinical remission for this endpoint in the CSR). The proportion of patients that met this definition was 15.1% (16 of 106 subjects) in the vedolizumab SC group and 5.4% (3 of 56 subjects) in the placebo group. The p-value for the comparison of the third secondary endpoint was 0.076 for a treatment difference of 9.7% (95%CI: -6.6%, and 25.7%).

Since the third secondary endpoint was not statistically significant, the fourth secondary endpoint, corticosteroid-free remission at Week 52 in patients who used corticosteroids at baseline and were clinical responders at Week 6, was not formally tested according to the prespecified hierarchical multiple testing procedure. Corticosteroid-free remission was achieved in 28.9% (13 of 45 subjects) in the vedolizumab SC group and 8.3% (2 of 24 subjects) in the placebo group, with a treatment difference of 20.6% (95%CI, -4.5%, 43.7%).

Discussion of Applicant's Secondary Endpoints

The Applicant proposed the same key secondary endpoint definitions as those used and included in 2014 vedolizumab IV labeling. However, the definitions and calculations of durable clinical response and durable clinical remission were difficult to interpret and could lead to confusion, since randomization occurred at Week 6, and Week 6 response/remission was not induced by the investigated drug, vedolizumab SC. Furthermore, there is no comparison group for an evaluation of the probability of being a responder at both Weeks 6 and 52 given that there was no control group during the induction period. For the current study design, all efficacy endpoints should clarify in which population the endpoints were evaluated.

FDA proposed secondary analysis of maintaining clinical remission at Week 52.

The design of Study SC 3027 allows to evaluate the proportion of patients who maintained remission at Week 52 in the subset of randomized patients who were Week 6 clinical remitters. FDA thinks that this analysis would be clinically relevant and should replace the Applicant's "durable clinical remission" analysis. We conducted such analyses using the EDC dataset free of site errors (errors on stratification factors) and the IWRS dataset including site errors. Table 22 reported a significant treatment effect of vedolizumab SC relative to placebo regardless of whether the analysis stratified by the missclassified randomization stratification factors or the actual factors. When using the actual stratification factors (free of site errors), the vedolizumab SC arm had a significantly higher percentage of Week 6 remitters who were able to maintain the remission status at Week 52, with a difference of 40.8% (95% CI: 12.2%, 69.3%), than the placebo arm (p-value of 0.013).

Overall, both the vedolizumab IV arm and vedolizumab SC arm had similar efficacy results on secondary endpoints and exploratory analyses of alternative clinical remission definition endpoints. Due to the Agency's complete response to this submission, further evaluation of the potential upcoming resubmission and communication with the Applicant are warranted.

Table 21. Study SC-3027 Secondary Efficacy Endpoints Reported by Applicant (FAS)

Secondary Efficacy Endpoint	PBO N=56	VDZ SC 108 mg N=106	VDZ IV 300 mg N=54
"Mucosal healing" at Week 52 in Week 6 responders, n (%)	(21.4)	60 (56.6)	29 (53.7)
Adjusted difference, vedolizumab vs. placebo		35.7	32.2
95% CI [a]		(22.1, 49.3)	(15.7, 48.7)
P-value, vedolizumab vs. placebo [b]		<0.001	<0.001
Clinical response at Week 52 in Week 6 responders, n (%)	16 (28.6)	68 (64.2)	39 (72.2)
Adjusted difference, vedolizumab vs. placebo		36.1	44.5
95% CI [a]		(21.2, 50.9)	(28.3, 60.6)
P-value, vedolizumab vs. placebo [b]		<0.001	<0.001
Clinical remission at both Week 6 and Week 52 in Week 6 responders, n (%)	3 (5.4)	16 (15.1)	9 (16.7)
Difference, vedolizumab vs. placebo		9.7	11.3
95% CI [a]		(-6.6, 25.7)	(-7.1, 29.9)
P-value, vedolizumab vs. placebo [b]		0.076	0.071
Corticosteroid- free clinical remission[c], n (%)	2 (8.3)	13 (28.9)	6 (28.6)
Difference, vedolizumab vs. placebo		20.6	20.2
95% CI[d]		(-4.5, 43.7)	(-9.8, 47.8)
P-value, vedolizumab vs. placebo [e]		0.067	0.121

Source: created by reviewer based on Summary of clinical efficacy Table 2.b, SC-3027 CSR Table 15.2.2.1.1 (mucosal healing), 15.2.2.2.1 (durable clinical response), 15.2.1.1.1 (durable clinical remission), and 15.2.2.3.1 (corticosteroid-free remission).
[a] The 95% CI of the difference was based on the normal approximation method, or the exact method if the number of events in either treatment group was ≤5.
[b] The p-values were obtained using a stratified CMH test by randomization strata (concomitant use of corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure or concomitant immunomodulator use) or Fisher's Exact test if the number of events in either treatment group was ≤5.

[c] Corticosteroid-free remission, defined as subjects using oral corticosteroids at Week 6 (determined by IWRS at time of randomization) who have discontinued oral corticosteroids and were in clinical remission based on the complete Mayo score at Week 52. PBO: N = 24; VDZ SC: N = 45; VDZ IV: N = 21
[d] The 95% CI of the difference was based on the exact method.
[e] The p-values were obtained using Fisher's Exact test because the number of subjects in one of the treatment groups being compared was ≤5.

Table 22. Results on Clinical Remission at Week 52 in Week 6 Remitters

Type of Data Used for Analyses	Placebo n/N (%)	VDZ SC n/N (%)	Treatment Difference[a] % (95% CI)	P-value[a]
EDC data with no site errors (using actual stratification factor)	3/15 (20)	16/25 (64)	40.8 (12.2, 69.3)	0.013
IWRS data with site errors (using misclassified factor that was used to stratify randomization)	5/25 (20)	27/47 (57.4)	37.9 (17.7, 58.1)	0.002

Source: created by reviewer
[a]P-value was based on CMH method adjusting for two stratification factors (concomitant use of corticosteroids, and previous TNF-α antagonist failure or concomitant immunomodulator use), or the exact method if the number of remitters in either treatment group is <=5. The 95% CI for the adjusted treatment difference was based on normal approximation.

Exploratory Endpoints

The proportion of subjects in clinical remission was greater with vedolizumab SC over placebo (p<0.001) among Week 6 clinical responders in all three exploratory analyses using the alternative definitions in accordance with the FDA draft UC guidance (CSR Table 11.y). The difference between vedolizumab SC and placebo was generally similar to the results of the primary endpoint analysis.

Other reported exploratory analyses results also supported treatment effect of vedolizumab over placebo from difference perspectives. For details refer to CSR Section 11.4.1.4.

Data Quality and Integrity

The efficacy data was ready to be analyzed at submission. There was no significant data quality and integrity issue identified during this review.

Overall, the CSR described and reported efficacy analyses related information with various ambiguities and some inconsistency, such as no specifics on which Mayo score calculation methods was used and/or which type of missing data imputation was used, whether the data was free of site errors, and to what degree the site errors affected the efficacy results, etc., and different number of the same clinical remitters in different tables. The review team issued five IRs to obtain clarifications, and to request additional data including site errors and Applicant's evaluation on impact of site errors to the efficacy analyses.

8.1.4. Assessment of Efficacy Across Trials

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Based on the submission by the Applicant, vedolizumab SC demonstrated efficacy as compared to placebo by the percentage of remitters, meeting the primary endpoint, the alternative clinical remission endpoints, and two out of four key secondary endpoints. The findings of sensitivity analyses coping with missing data using different imputation approaches, different calculation methods of Mayo score and data sources with or without site errors were consistent with the primary efficacy results and demonstrated efficacy in the vedolizumab arm relative to the placebo arm, thereby, further supporting demonstration of efficacy of vedolizumab for the treatment of moderate to severe UC in adults.

The efficacy data from this trial support approval. The application will receive a CR action, for reasons unrelated to the clinical efficacy and safety profile. If the approvability issues are adequately addressed in a future resubmission, decisions on labeling will be based on further evaluation of the updated submission and communication with the applicant.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review will focus on pivotal Study SC-3027 with additional analyses from an integrated population which the Applicant defined as “Pool 1” (patients randomized to vedolizumab SC in Study SC-3027 and patients (with UC) in extension Study SC-3030 who were previously enrolled in Study SC-3027. The primary aim of analyses in Pool 1 is to assess for rare events that may require a longer duration of follow-up to detect.

The applicant described three safety analysis populations (described above in section 8.1.1 Safety Analysis Set). The safety review of Study SC-3027 data focuses on SAF population (patients who received at least 1 dose of blinded treatment in the maintenance phase). The data from SAF-I and SAF-C populations place more weight on exposure to IV induction therapy, the safety profile of which is already well characterized.

Throughout the review, for brevity, maintenance dosing is referred to by the treatment patients were randomized to at Week 6 (IV, SC or placebo). In all cases, all of these patients had previously received vedolizumab IV induction for the first 6 weeks (therefore more accurate arm description is IV/IV, IV/SC, or IV/placebo). Many of the safety evaluations conducted in the SAF population involve calculations of incidence proportions that include events that occurred during the induction period. This approach compares risks between IV induction/SC maintenance and IV induction/placebo maintenance treatment regimens and has the limitation

that it could potentially underestimate adverse effects of vedolizumab SC maintenance therapy as compared to placebo maintenance therapy. Select addditional analyses were conducted focusing on only adverse events occurring during the maintenance period and are described below.

8.2.2. Review of the Safety Database

Overall Exposure

Vedolizumab IV is an approved and marketed product, and the known safety profile of the IV formulation is considered relevant and informative to the safety database, given the similarity in PK profile noted from SC or IV administration. Taking this into account, the overall exposure in the current submission to the SC formulation listed below (for the maintenance of UC) appears adequate.

Study SC-3027

- 106 subjects with UC received at least 1 dose of vedolizumab SC during the maintenance phase
- Mean duration of exposure was 439 days in the vedolizumab SC group, 437 days in the vedolizumab IV group, and 396 days in the placebo group

Pool 1 (UC)

- 303 subjects with UC had received at least 1 dose of vedolizumab SC at the time of the data cut
- Mean duration of exposure was 421 days, and on average, subjects received 24 injections
- Vedolizumab SC exposure was ≥6 months in 269 subjects, ≥12 months in 193 subjects, and ≥24 months in 13 subjects

Adequacy of Safety Database

The number of subjects exposed to the SC formulation exceeds the recommended minimum number of patients per ICH E1A guidance and the overall safety of vedolizumab (combined IV and SC) is well established as describe above.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Regarding safety, there were no major concerns about data quality and integrity. Refer to the section above (Patient Disposition) for detailed description of site misclassification and

stratification errors. Despite these limitations, the collected safety data appears adequate. Narrative summaries for individual subjects with serious adverse events (SAEs) and AEs of special interest were provided and reviewed.

Categorization of Adverse Events

Medical Dictionary for Regulatory Activities version 21.0 was used for coding treatment-emergent adverse events (TEAEs) in the vedolizumab SC studies and data pools. When this reviewer deemed it necessary to combine similar preferred terms into one term to facilitate a more accurate analysis, this was performed and subsequent analysis of AEs reflect these groupings. Refer to appendix (Table 29) for details of recoding of AEs.

Routine Clinical Tests

Clinically relevant tests were collected at appropriate time intervals including laboratory tests (e.g., chemistry, hematology, antivedolizumab antibodies, fecal calprotectin), vital signs, weight, height, 12 lead electrocardiograms (ECGs) and endoscopy. These safety assessment methods and time intervals were reasonable for the studied population and indication that was investigated.

8.2.4. Safety Results

Deaths

There were no deaths reported in the UC population. There was one death reported in the CD population of a patient who underwent a surgical procedure and subsequently developed a pulmonary embolism. As this is a known surgical/hospitalization complication, it appears unrelated to study treatment.

Serious Adverse Events

In Study SC-3027, a total of 11%(23/216) of patients reported an SAE during the study. The frequency of SAEs was generally similar across all treatment groups 11% (6/56) in placebo, 9% (10/106)in vedolizumab SC, 13% (7/54) in vedolizumab IV. The overall highest incidence 5% (10/216) of SAEs was reported in the gastrointestinal disorders SOC and occurred in placebo patients more frequently 9%(5/56) than in the vedolizumab SC 4%(4/106) or vedolizumab IV 2%(1/54) groups. UC was the most common SAE (4%) reported. As would be expected, the frequency of UC was higher in the placebo group than in either of the vedolizumab groups. The only other SAE reported with a frequency of >1% was anemia, with a similar incidence between the vedolizumab SC and placebo groups (1.9% (2/106) and 1.8% (1/56) respectively). Both patients in vedolizumab SC group had SAE of anemia recorded initially after 155 or 163 days in the study. Both received treatment for anemia (transfusion of PRBC in one; IV iron in the other) with resolution of anemia after eight days in one patient and 45 days in the other patient (although resolution was within 1-2 days following transfusion/iron). Concomitant medications

included mesalazine for both and one patient had a history of iron deficient anemia. These AEs were reported as serious due to brief hospital stays. Similarly, the placebo patient was admitted on two separate occasions (Days 54 and 166) for transfusion of PRBC.

The incidence of SAEs in other SOCs was low (<2%). No particular type of infection/ infestations was reported in ≥1% of patients in any treatment group. In addition, no SAEs of nasopharyngitis, upper respiratory tract infection, or pneumonia were reported. In the vedolizumab SC group, peritonitis and tonsillitis were reported with frequencies of 1% each (one patient each) and anal abscess occurred in one patient in the vedolizumab IV group. Although none of these infections appeared in the placebo group, it is difficult to draw conclusions from only one occurrence. In addition, anal abscess was seen in the vedolizumab IV pivotal trials, tonsillitis is a frequent infection seen in the general population, and the patient with peritonitis (also with SAEs of acute abdomen and large intestine perforation) had a colonoscopy with polyp removal the one day prior See Table 23 below for comparison and listing of the specific SAEs

Table 23. Study SC-3027 Serious TEAEs by SOC and PT

Table 12.p Serious TEAEs by SOC and PT (SAF)

Primary SOC PT	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)	Total N = 216 n (%)
Subjects with at least 1 SAE	6 (10.7)	10 (9.4)	7 (13.0)	23 (10.6)
Blood and lymphatic system disorders	1 (1.8)	2 (1.9)	0	3 (1.4)
Anaemia	1 (1.8)	2 (1.9)	0	3 (1.4)
Cardiac disorders	0	1 (0.9)	0	1 (0.5)
Tachycardia	0	1 (0.9)	0	1 (0.5)
Gastrointestinal disorders	5 (8.9)	4 (3.8)	1 (1.9)	10 (4.6)
Colitis ulcerative	5 (8.9)	3 (2.8)	1 (1.9)	9 (4.2)
Acute abdomen	0	1 (0.9)	0	1 (0.5)
Large intestine perforation	0	1 (0.9)	0	1 (0.5)
Hepatobiliary disorders	0	0	1 (1.9)	1 (0.5)
Cholelithiasis	0	0	1 (1.9)	1 (0.5)
Infections and infestations	0	3 (2.8)	0	3 (1.4)
Anal abscess	0	1 (0.9)	0	1 (0.5)
Peritonitis	0	1 (0.9)	0	1 (0.5)
Tonsillitis	0	1 (0.9)	0	1 (0.5)
Injury, poisoning and procedural complications	0	1 (0.9)	3 (5.6)	4 (1.9)
Craniocerebral injury	0	0	1 (1.9)	1 (0.5)
Clavicle fracture	0	0	1 (1.9)	1 (0.5)
Scapula fracture	0	0	1 (1.9)	1 (0.5)
Ligament rupture	0	0	1 (1.9)	1 (0.5)
Road traffic accident	0	0	1 (1.9)	1 (0.5)
Facial bones fracture	0	1 (0.9)	0	1 (0.5)
Jaw fracture	0	1 (0.9)	0	1 (0.5)
Lumbar vertebral fracture	0	0	1 (1.9)	1 (0.5)
Rib fracture	0	0	1 (1.9)	1 (0.5)
Investigations	1 (1.8)	0	0	1 (0.5)
Blood creatine phosphokinase increased	1 (1.8)	0	0	1 (0.5)
Psychiatric disorders	0	0	1 (1.9)	1 (0.5)
Major depression	0	0	1 (1.9)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0	0	2 (3.7)	2 (0.9)
Pulmonary sarcoidosis	0	0	1 (1.9)	1 (0.5)
Pneumothorax	0	0	1 (1.9)	1 (0.5)

Source: CSR Study SC-3027 Table 12.p pg 174 (results verified by reviewer). Analysis is conducted in SAF population, and includes events that occurred in Induction or Maintenance, grouped by Maintenance treatment arm.

SAE in Pool 1:

In Pool 1, treatment-emergent serious adverse events were reported by 10% (31/303) of patient-subjects (10%). UC and anemia were the only SAEs reported in ≥3% (10/303) of patients. Other SAEs were appendicitis in two patients (1%) and tachycardia, large intestine

polyp, rectal polyp, acute abdomen, large intestine perforation, anal abscess, peritonitis, tonsillitis, spinal compression fracture, glomerulonephritis rapidly progressive and cough reported in one patient (0.3%) each. One patient-reported SAEs of facial bones fracture and jaw fracture due to a road traffic accident. Once again, if is difficult to draw conclusions from only one occurrence and there did not appear to be any safety signal. All of the above SAEs with the exception of pneumothorax occurred during the maintenance phase of the study, which is not surprising given the 46-week duration of maintenance the six weeks of induction)versus.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study SC-3027, the overall incidence of AEs leading to study discontinuation was 6% (12/216). Of these 12 patients, ten discontinued because of UC disease worsening or exacerbation. As would be expected, this incidence was higher in the placebo group than in either vedolizumab group (placebo: 9% (5/56); vedolizumab SC: 4% (4/106); vedolizumab IV: 2% (1/54)) Of the remaining two subjects who discontinued study medication, one patient (vedolizumab IV group) discontinued due to injuries sustained in a road traffic accident. The other patient (vedolizumab SC group) discontinued due to a severe, nonserious AE of increased liver enzymes, See Liver Enzyme Elevation/Liver Injury section below for further details.

In Pool 1, a total of 4% (11/303) patients discontinued from the studies included in Pool 1 because of a TEAE. UC and anemia were the most common reasons for discontinuation; these were reported by six patients (UC), one patient (anemia), and one patient (both UC and anemia). Other discontinuations were due to TEAEs of increased alanine aminotransferase, increased gammaglutamyl transferase, and increased blood alkaline phosphatase (all in one patient); B-cell lymphoma and diffuse large B-cell lymphoma (both reported in one patient); and rapidly progressive glomerulonephritis (one patient).

Significant Adverse Events

In Study SC-3027, 5% (11/216) of the patients had AEs that were classified as severe. All of these patients were already included in the SAEs above and/or discontinuations with the exception of one patient with elevated creatine phosphokinase (CPK) (vedolizumab SC group), one patient with UC exacerbation (vedolizumab SC group). The CPK elevation occurred in a 19-year-old male patient who developed this lab abnormality on Day 112 of treatment. The etiology of the CPK elevation was unclear from the information provided in the narrative (from Romania); however, the patient remained in the study without any dose adjustment and the AE resolved five days later (see also CPK discussion below).

Similarly, the patient with UC exacerbation remained in the study without any dose adjustment and the AE resolved.

Treatment-Emergent Adverse Events and Adverse Reactions

Table 24. Common AEs Seen in 3% or More and with Greater Frequency on Treatment (SC or IV) Than Placebo, Study 3027 (Including Open-Label Induction and Maintenance Events),

Adverse Event	Placebo N=56	IV N=54	SC N=106
Upper respiratory tract infection	2 (4%)	2 (4%)	10 (9%)
Anemia	3 (5%)	5 (9%)	9 (8%)
Injection site reaction	0 (0%)	0 (0%)	6 (6%)
Arthralgia	1 (2%)	4 (7%)	6 (6%)
Abdominal pain	3 (5%)	3 (6%)	5 (5%)
Abnormal Liver Enzymes	0 (0%)	4 (7%)	2 (2%)
Rash	2 (4%)	4 (7%)	3 (3%)
Bronchitis	0 (0%)	2 (4%)	3 (3%)
Eczema	0 (0%)	0 (0%)	3 (3%)
Hypertension	0 (0%)	0 (0%)	3 (3%)
Noncardiac chest pain	0 (0%)	0 (0%)	3 (3%)
Edema peripheral	0 (0%)	0 (0%)	3 (3%)
Pneumonia	1 (2%)	1 (2%)	3 (3%)
Blood creatine phosphokinase increased	1 (2%)	3 (6%)	1 (1%)
Leukopenia	0 (0%)	2 (4%)	0 (0%)
Gastroesophageal Reflux Disease	0 (0%)	2 (4%)	1 (1%)

Source: reviewer's analysis of ADAE dataset. Analysis included safety population (SAF)- (patients who received were randomized into maintenance and who received at least one dose of maintenance study drug (PC or placebo), includes treatment-emergent events that occurred in induction or maintenance, (period 1 or 2), by actual period 2 treatment, reviewer's coded AE terms.

In Study SC-3027, the majority of most common AEs observed in any treatment group were consistent with what was seen in the pivotal trials for the vedolizumab IV formulation.[7] Notable exceptions were blood creatine phosphokinase increased (highest in vedolizumab IV at 6% (3/54) vs. 1% (2/106) and 2% (1/56) in vedolizumab SC and placebo respectively), anemia (highest in vedolizumab IV group at 9% (5/54), although frequency in all treatment groups was similar at 5% (13/54) and 8% (91/106) for placebo and vedolizumab SC respectively) and leukopenia (seen only in vedolizumab IV group 4% (2/54)). Relevant details regarding CPK AEs are provided in Table 25 and discussed below.

- The placebo patient's AE was severe and also considered an SAE as patient was hospitalized for UC exacerbation (and CPK elevation), concomitant medication prior to UC exacerbation was dicloxacillin sodium monohydrate). - unclear in narrative why CPK was elevated, this resolved and dose was not changed (although patient discontinued study secondary to lack of efficacy
- The vedolizumab SC patient's AE was not considered SAE, dose wasn't changed and CPK elevation resolved
- The three patients in vedolizumab IV group had mild/moderate elevations, no dose was changed and all elevations resolved, (There were no narrative summaries available for these mild/moderate AEs). It is unclear what caused the CPK elevations in this study; however

[7] i.e. UC, upper respiratory infection, nasopharyngitis, arthralgia, abnormal liver enzymes, rash

these were all foreign young patients who could have exercised a great deal, participated in a heavy activity, sustained an injury or another scenario that would affect muscle enzymes levels. This occurrence is not uncommon in the general population (often times these abnormal lab value are not detected because blood is not taken for evaluation).

Table 25. Study SC-3027 Details of Six CPK Elevations by Patient

Patient Number	Placebo N=56	IV N=54	SC M=106	Intensity	Days	Age/Sex/Location	Maximal CPK elevation (U/L)
(b) (6)	1	0	0	Severe SAE	209–213	29 yo male Denmark	8028U/L on day 209
	0	1	0	Moderate	273–288	28 yo female/Poland	1635U/L on day 273
	0	0	1	Severe	112–117	19 yo male/Romania	7734U/L on day 112
	0	2	0	Mild Moderate	208–266 248–355	32 yo female/Russia	1552U/L on day 208 2656U/L on day 348
	0	1	0	Moderate	160–195	26 yo male/Ukraine	4109U/L on day 160

Source: reviewer's analysis of ADAE dataset and narrative summaries

In future, consideration should be given to potentially including in the labeling "elevated CPK" as a less common adverse reaction that was noted in the clinical trial.

In addition, noncardiac chest pain, peripheral edema, eczema and hypertension were seen solely in the vedolizumab SC group. These AEs meet the threshold for "common AEs" per the current labeling (3% or greater), and could be considered for inclusion in revised labeling. However, given the small size of this study, relative to the initial IV formulation studies that supported initial approval, these events occurred in a small number of patients 3% (3/106), and therefore the precision around these estimates is low and their potential clinical significance is uncertain. Reassuringly, although a small number of patients experienced AE of hypertension, there was no other data (from analysis of changes in VS parameters) to support a major effect of the drug on blood pressure overall. Mean change in systolic and diastolic BP at Week 52 compared to baseline was small and comparable across all three arms. Of the 3 subjects with AE of hypertension reported, 2/3 had very small changes from baseline (5-15mm Hg) and none of the three demonstrated a clear trend of increasing blood pressures over the duration of treatment.

Given the SC administration, injection site reactions were solely seen in the vedolizumab SC group at 6% (6/106) as would be expected. These are discussed further in section 8.2.5.1 below.

In addition, because the main aim of the trial was to demonstrate safety and efficacy of the SC arm, we also assessed the maintenance period of the trial separately, to better assess AEs specific to the SC arm. Table 26 below shows the AEs that occurred in 5% or more patients during the maintenance period of Study SC- 3027, and in greater proportion in either vedolizumab arm than placebo. The analysis is limited to those events occurring in treatment period 2 (where patients who had clinical response to vedolizumab IV were transitioned to either SC, placebo, or continued IV treatment. Overall the demonstrated profile appears similar to the common AEs already noted in the approved label for the IV formulation. Notable differences include that anemia and abnormal liver function tests (when using reviewer grouped terms) were seen with increased frequency compared to Applicant's analysis of the trial overall and the current label. Hepatoxicity is already a labeled risk (including warning in section 5) and the cases of increased liver enzymes are discussed further in this review below. The rate of anemia was highest in the SC arm of this trial at 6% (6/106) vs. 4% in both IV and placebo arms (2/54 and 2/56 respectively. It is unclear why the SC treatment arm had a slightly higher percentage of anemia. It is not surprising that anemia occurred in this trial in a UC population UC is a chronic disease that can cause blood loss in the stool leading to iron deficiency, inadequate nutritional intake due to GI symptoms, and/or anemia of chronic disease which is commonly reported in IBD patients. Therefore this small difference in number of patients with documented anemia is unlikely to be drug related.

Table 26. Most Common Treatment-Emergent AEs Maintenance Period (≥5%) in SC/IV

Adverse Events	Placebo N=56	IV N=54	SC N=106
Colitis ulcerative	18 (32%)	6 (11%)	15 (14%)
Nasopharyngitis	10 (18%)	8 (15%)	10 (9%)
Anemia	2 (4%)	2 (4%)	6 (6%)
Upper respiratory tract infection	2 (4%)	2 (4%)	7 (7%)
Injection site reaction	0 (0%)	0 (0%)	6 (6%)
Arthralgia	0 (0%)	3 (6%)	5 (5%)
Rash	2 (4%)	4 (7%)	3 (3%)
Abnormal liver enzymes	0 (0%)	3 (6%)	2 (2%)
Blood creatine phosphokinase increased	1 (2%)	3 (6%)	1 (1%)
Urinary tract infection	2 (4)	4 (7%)	0 (0%)

Source: reviewer's analysis of ADAE dataset. Analysis limited to events occurring in treatment period 2 (maintenance period).

Laboratory Findings

Vedolizumab IV is known to cause elevations in some liver function tests. In Study SC-3027,there were several patients who had mildly elevated liver enzymes but none led to dose changes or study discontinuation. There was one patient with markedly elevated liver enzymes. See Liver Enzyme Elevation/Liver Injury below.

Anemia is associated with the underlying disease of UC and is often associated with iron deficiency as described above. AEs of anemia occurred with slightly greater frequency on

treatment than placebo, as already described above. It is unclear why there is some disparity between treatment groups, however, it is a small amount. No clinically relevant differences between the treatment groups in mean changes from baseline were observed for any hematology or chemistry parameter.

In Pool 1, some patients had thrombocytosis and leukocytosis. Secondary thrombocytosis is commonly associated with anemia and leukocytosis could be secondary to multiple causes including infection or inflammation. However, there were no clinical sequalae associated with these lab abnormalities. (The CPK elevations observed were discussed above).

There were fluctuations throughout the 52-week study in many lab parameters (including leukocytes, lymphocytes, eosinophils, etc.) however, these did not lead to any clinically meaningful outcomes.

Vital Signs

In Study SC-3027, in general, no clinically relevant findings were noted regarding mean changes from baseline for vital signs, including blood pressure, pulse, respiratory rate, temperature, and body weight. In pool 1, abnormal vital signs were reported in some patients, however, there were no other associated symptoms, the abnormalities were not regarded as clinically relevant and none led to study discontinuation.

Electrocardiograms (ECGs)

There were no abnormal clinically significant changes in ECG after treatment with vedolizumab SC.

QT

A thorough QT study was not performed in support of this application since it was submitted previously with the original vedolizumab IV approval. Review of the submitted ADEG data (ECG dataset) identified no postbaseline abnormal ECGs that were reported as clinically significant. Submitted data was limited to summary of interpretation of ECG (normal, abnormal not clinically significant, abnormal clinically significant). However, given that the larger prior vedolizumab IV studies and previously conducted TQT study with this molecule did not identify concerns, this limited summary data is considered adequate.

Immunogenicity

Immunogenicity evaluation encompassed assessment of antidrug antibodies and their potential impact of efficacy and PK (described in clinical pharmacology section above 6.3.2), as well as clinical sign/symptoms of immune related reactions, including local injection site reactions, and potential systemic immune reactions, both of which are described in the sections below under Adverse Events of Special Interest.

8.2.5. Analysis of Submission-Specific Safety Issues

Since this is a subcutaneous administration of vedolizumab, injection site reactions are a submission specific safety issue. This is in addition to AEs of special interest for vedolizumab that include: hypersensitivity reactions, progressive multifocal leukoencephalopathy (PML), malignancies, infections, and liver injury.

8.2.5.1. *Injection Site Reactions*

In Study SC-3027, site reactions were more common in patients administered vedolizumab SC (10% (10/106) than vedolizumab IV (2%(1/54) or placebo (0%). All injection site reactions except two were of mild severity (two were moderate), and none were serious or resulted in discontinuation or change in the dosing regimen. In addition, most of the reactions were observed multiple times in the same patient. There were three patients who had between 10 and 21 reactions (10,13 and 21) and the remaining patients had one, two or three reactions. See Table 27 below. Notable is that the earliest injection reaction occurred at Day 48, with the majority of reactions occurring after Day 150. The applicant assessed relationship between injection site reaction and AVA status, however, given the limitations of the AVA assay utilized, these data are not considered reliable or informative.

Table 27. Number of Injection Site Reactions Per Patient (Study 3027)

SUBJID	Vedolizumab IV	Vedolizumab SC
(b) (6)	0	21
	0	13
	0	2
	0	1
	0	2
	0	3
	0	2
	1	0
	0	2
	0	10

Source: reviewer's analysis of ADAE dataset

In Pool 1, injection site reactions occurred in 4% (12/303) of patients. Similarly, all injection site reactions were nonserious and of mild or moderate severity with a few patients having many reactions but most others having one to three. Injection site reactions do not appear to have negatively impacted tolerability, as none of the events resulted in discontinuation or required change in dose regimen, and all were resolved at the time of last follow-up. Given the SC route of administration, the presence of injection site reactions is an expected AE. See Table 28 for Study SC-3030 (UC patients during extension period).

Table 28: Study SC-3030 Injection Site Reactions by Severity

Unique SUBJID	(b) (6)	Mild	Moderate
MLN0002SC-3027		3	0
MLN0002SC-3027		1	0
MLN0002SC-3027		10	0
MLN0002SC-3027		3	0
MLN0002SC-3027		0	1
MLN0002SC-3027		2	0
MLN0002SC-3027		1	0
MLN0002SC-3027		2	0
MLN0002SC-3027		1	0
MLN0002SC-3027		1	0
MLN0002SC-3027		12	0
MLN0002SC-3027		0	4

Source: Reviewers table adapted via JMP from Applicant datasets

8.2.5.2. *Hypersensitivity Reactions*

In Study 3027, the overall incidence of hypersensitivity AEs[8] was 12% (25/216) These AEs were more common in vedolizumab-treated than placebo-treated subjects, but comparable between the vedolizumab SC and IV groups (15% 16/106 and 13% (7/54), respectively). All hypersensitivity reactions were reported as nonserious and of mild or moderate severity with no anaphylaxis or severe allergic reaction and none of these AEs led to discontinuation of treatment. Similarly, in Pool 1, the incidence of hypersensitivity reactions was 13% (39/303).

8.2.5.3. *PML*

Natalizumab, a currently approved integrin antagonist, is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis and Crohn's Disease. As a result, integrin antagonists in development (including vedolizumab) have been required to include thorough PML risk identification and minimization programs in their clinical trials and ensure that premarketing patient drug exposure is sufficient to assess the risk for PML before drug approval. Therefore, despite the postulation that vedolizumab may have a more gut specific mechanism of action, PML is included as an Adverse Event of Special Interest.

There were no cases of PML in the vedolizumab SC development program to date for both UC and CD indications. However, there was one case of PML identified in the postmarketing setting of vedolizumab IV. See below in Expectations on Safety in the Postmarket Setting.

[8] Includes anaphylactic/anaphylactoid shock conditions, angioedema, and hypersensitivity

8.2.5.4. *Malignancies/Neoplasms*

In Study SC-3027, one patient in the vedolizumab IV group reported basal cell carcinoma under the right eye, 56 days after starting study drug. No action was taken with the study drug, and the subject recovered from the AE on Day 181 (after 126 days) and continued study medication as planned. This patient enrolled on concomitant azathioprine, which is known to increase the risk of skin cancers.

An additional subject was diagnosed with rectal adenocarcinoma during the open-label induction period. This was considered related to long-standing UC disease. The patient was not eligible for maintenance study, and went on to undergo colectomy. Additional follow-up data is not available.

In Pool 1 (all Study SC-3030), there were three patients who had four TEAEs in this category.

- One patient developed a melanocytic nevus on his chest 129 days after the first dose of study drug. The nevus was resected on the same day, and the event was considered recovered. The treatment was not changed in response to this event.
- A 62-year-old male developed diffuse large B-cell and Grade 3B follicular lymphoma 69 days after the first dose of study drug. The study treatment was withdrawn in response to this event. The subject was recovering at the time of the data cut. Concomitant medications included colecalciferol, pravastatin and cough and cold preparations.
- One patient developed a benign neoplasm of skin on the right thigh on the day of the first dose of study drug. Given the timing this is considered unrelated to study drug. The patient recovered in 46 days. The study treatment was not changed in response to this event.

In the UC vedolizumab SC clinical program, the frequency of malignancies or neoplasms appears to be low with the majority of neoplasms being skin and only one case of B-cell lymphoma. In general, immunosuppressant drugs are known to increase the risks of malignancies. The possible risk of malignancy associated with vedolizumab has not been fully characterized to date, given then these events may have long (years) latency period. A PMR was issued at the time of the IV formulation approval to conduct a prospective, observational cohort study of vedolizumab vs. other agents for inflammatory bowel disease, with primary outcome of serious infection, and secondary outcomes including PML, malignancy and specific infections (including GI and upper respiratory). This study is ongoing, with the first summary safety report (2.5 year follow-up interim databased lock, after 50% of enrolled subjects have completed at least 1 year of treatment) is expected in October 2020.

8.2.5.5. *Infections*

In Study SC-3027, the number of patients who reported infections in each group was (52% 29/56), 43% (46/106), and 63% (34/54) in the placebo, vedolizumab SC, and vedolizumab IV groups, respectively). The most frequent AEs were in the HLT of upper respiratory tract infections and occurred in 29%(16/56) of placebo, 22% (23/106) of vedolizumab SC, and 24% (13/54) of vedolizumab IV subjects. Other HLTs of infections with an overall frequency of >2% included lower respiratory tract and lung infections, abdominal and gastrointestinal infections (4%), urinary tract infections (3%), viral infections (2%), and dental and oral soft tissue infections (2%) See Table 31 in Section 15.1 for further details. However, the limited number of total patients with these infections precludes clinically meaningful analysis across various groups.

In the vedolizumab SC group, the most common preferred terms of infections were nasopharyngitis (9%) and upper respiratory tract infections (7%). Nasopharyngitis occurred in 9% (10/106) on vedolizumab SC, 24% (13/54) on vedolizumab IV and 18% (10/56) on placebo. Upper respiratory tract infection was reported in 7%, 11% and 4% of patients on vedolizumab SC, vedolizumab IV and placebo respectively. Urinary tract infection occurred in in 1% (1/106) on vedolizumab SC, 7% (4/54) on vedolizumab IV and 4% (2/56) on placebo. In addition, there were no opportunistic infections reported in any treatment group.

Although there may be some numerical differences between treatment groups regarding the type of infection, there is no clear trend to suggest that infection risk is increased with vedolizumab SC or vedolizumab IV. In addition, a difference in frequency of specific type of infection would not be expected with an IV versus SC formulation of vedolizumab given the similarity PK demonstrated. See Tables 31 and 32 in Section 15.1.2 for details regarding specific infections.

In Pool 1, infections were reported in 105 patients (35%). The most frequent infections were also nasopharyngitis reported in 31 subjects (10%) followed by upper respiratory tract infections reported in 21 subjects (7%). Other infections reported in ≥2% of subjects included bronchitis, gastroenteritis, influenza and pharyngitis all (2-3%). Most of the infections are commonly seen in a general population and also consistent with what would be expected in a UC patient population. There were no opportunistic infection reported, thus, the UC patient population pooled here did not appear to be at increased risk of developing an opportunistic infection, though the small size of the study limits conclusions that can be drawn regarding rare events. See Section 15.1.2 for a list of infections which occurred in <1% of patients.

In summary, patients treated with vedolizumab are at increased risk for developing infections. The most commonly reported infections in previous clinical trials which occurred at a rate

greater in vedolizumab IV than placebo involved the upper respiratory and nasal mucosa. The infections observed in the vedolizumab SC program appear consistent with this.

8.2.5.6. *Liver Injury*

The current prescribing information contains a warning regarding liver injury. Liver injury was assessed as an AESI of special interest in this program, and was defined as including any of the following events:

- Cholestasis and jaundice of hepatic origin
- Hepatic failure, fibrosis and cirrhosis, and other liver damage–related conditions
- Hepatitis, noninfectious
- Liver related investigations, signs and symptoms
- Liver infections

In Study SC-3027, there were 10 patients who reported a total of 19 AEs that were flagged for possible liver injury. The AE severity ranged, with 3 patients having one or more AEs rated as "severe" intensity, though none were reported as SAE. A single patient (described below) required study drug discontinuation. Six patients experienced events within the induction period, and five had events within the maintenance period (thus one experienced both). The onset ranged from 1 day to 436 days on treatment. These events are consistent with the known risk of liver injury which is already labeled. None of the TEAEs were serious. The incidence of this AESI was 4% in the vedolizumab SC group, 9% in the vedolizumab IV group and 0% in placebo group. Among those who entered the maintenance trial, this AESI affected 7% (4/54) patients were randomized to vedolizumab IV and 2% (2/106) in SC. Therefore overall, the risk of liver injury related to SC vedolizumab does not appear any greater than that known to be associated with IV.

A single case required study drug discontinuation (description follows). The remaining patients improved or resolved without intervention.

A 40-year-old man, who received SC vedolizumab reported increased alanine aminotransferase (ALT) of 52 U/L (normal range 10 to 40 U/L), GGT of 435 U/L (normal range 10 to 49 U/L) and alkaline phosphatase of 249 U/L (normal range 43 to 115 U/L) 14 days after being on study medication. The patient continued to have fluctuating levels of ALT, GGT, aspartate aminotransferase (AST) and alkaline phosphatase until Day 210 when the subject developed worsening of ALT, GGT, and alkaline phosphatase that led to study drug discontinuation. The total bilirubin remained within normal limits (<18.81 µmol/L) throughout most of the study, and was above normal (23.43 µmol/L) at Week 14 only. The ALT and bilirubin levels resolved at the Week 68 follow-up visit. However, GGT and alkaline phosphatase had not completely resolved to within normal limits at this visit. See Section 15.1.3 for Additional Cases of Liver Enzyme Elevation.

Elevation of liver function tests is an established risk of treatment with vedolizumab IV. Thus, the above liver function abnormalities are consistent with the known safety profile of vedolizumab. Refer to Section 15.1.3 for shift tables of ALT, AST, bilirubin and Alkaline Phosphatase.

8.2.6. Safety Analyses by Demographic Subgroups

In Study SC-3027, a safety analysis based on age (≥65 or <65) or based on race would not be a meaningful analysis because over 94% of the safety analysis population was of age < 65 and the vast majority (84%) were white. The study was comprised of 60% (130/216) males and 40% (86/216) females. A total of 23 patients experienced an SAE which occurred in 12% (16/130) of males[9]; 8% (7/86) of females[10] This information is limited to draw definitive conclusions regarding differential safety by gender, but no obvious worrisome difference was identified.

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

Limited data on vedolizumab SC use during pregnancy and fetal outcomes became available as a result of unplanned pregnancies in study subjects. Patients were withdrawn from clinical studies as soon as pregnancy was known, and all pregnancies were to be followed to outcome.

A total of four pregnancies were reported by patients participating in the vedolizumab SC clinical studies.

Two patients had voluntary termination of their pregnancies, one patient had a intrauterine gestational sac and yolk sac but no fetal pole was appreciated by ultrasound; no further information was available on this patient. One patient became pregnant after three months of treatment with vedolizumab (six weeks IV and six weeks SC). She gave birth to a healthy infant at 38 ½ weeks. Later, on an unknown date, the child was diagnosed with neonatal jaundice and suspicion of hip dysplasia. However, the details of the clinical course and outcome were not available.

[9] 7 SC, 5 IV and 4 placebo

[10] 3 SC, 3 IV, 2 placebo

In addition, according to the Applicant, two studies evaluating the presence of vedolizumab in breast milk were recently published. In these studies, the authors concluded that vedolizumab is excreted into breast milk at low concentrations.

Available information on the safety of vedolizumab IV in pregnancy is already included in the current label in Section 8 and no changes to this portion of the label were proposed based on the additional pregnancies that occurred in the vedolizumab SC trial.

Pediatrics and Assessment of Effects on Growth

No pediatric data or assessments of growth was submitted with this application. The current label for IV Entyvio (vedolizumab) states the following:

> "Safety and effectiveness of Entyvio in pediatric patients have not been established."

However, this application triggers the Pediatric Research Equity Act therefore postmarketing studies of vedolizumab SC in pediatric patients 2-17 years will be required upon approval. There is an agreed upon initial Pediatric Study Plan (iPSP) for vedolizumab SC (received July 31, 2015) on file outlining a plan to assess pediatric patients ages 2-17 (consistent with current precedent that ages <2 are waived in pediatric IBD programs).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose (accidental overdose or intentional overdose) in the submitted application. The potential for abuse, withdrawal and rebound with vedolizumab have not been evaluated in clinical studies, but risk is not suspected based on mechanism of action. There were no reports of abuse in the clinical trial setting.

8.2.7. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting

There is no postmarketing experience with vedolizumab SC. However, given the similarity and shared mechanism of action between vedolizumab SC and vedolizumab IV, the postmarketing safety experience with vedolizumab SC would be expected to be comparable to that of vedolizumab IV. According to a recent Periodic Benefit-Risk Evaluation Report for vedolizumab, overall, 7,439 healthy volunteers and patients have been enrolled in the company-sponsored clinical trials with approximately 6,376 have receiving active treatment with vedolizumab. The global postmarketing patient exposure to vedolizumab since its initial launch in 2014 is estimated to be approximately 336,400 patient-years. No new safety or efficacy concerns were identified.

There was one postmarketing case of PML which was reported in a HIV-positive patient who was being treated with vedolizumab IV for CD. The case history was evaluated by the Applicant as well as by an Independent Adjudication Committee of experts with experience in PML. This evaluation determined that the most likely explanation for the patient's development PML was HIV infection in the setting of a prolonged history of immunosuppressant treatment. This determination seems reasonable since in addition to the above rationale, it is a well-established fact that HIV positivity with decreased CD4 count is an independent risk factor for development of PML. A supplement to update the label to acknowledge this single case is currently under review.

8.2.8. 120-Day Safety Update

The 120-day Safety Update was reviewed wherein the Applicant included updated data collected in the ongoing Study SC-3030 through a cut-off of February 1, 2019 (original submission had a cut-off date of May 31, 2018). Pool 1 now included 304 patients (as opposed to 303 in original submission). There did not appear to be a difference in the most common AEs between the original submission and the 120-day safety update with UC, nasopharyngitis, URI, anemia and arthralgia being the most frequent adverse events reported. Included in the submission was a brief listing of the latest AESIs. The events described seemed consistent with what has been observed for vedolizumab IV and in the clinical studies for vedolizumab SC. In summary, according to the data provided in the 120-Day Safety Update, there does not appear to be any change to the vedolizumab SC safety profile.

8.3. Conclusions and Recommendations

The efficacy and safety of vedolizumab SC injection were demonstrated in study 3027. Results on the primary and first two key secondary endpoints were statistically significant, and results were considered robust on sensitivity analyses.

The safety profile of vedolizumab SC was characterized in this study and appears comparable to the safety profile of the IV formulation of vedolizumab, which has substantial clinical information (both pre and postapproval) available to reference.

The product could be recommended for approval, on the basis of the efficacy and safety data from this trial, if the outstanding approvability issues (relating to product quality and device) are adequately rectified in the future.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was convened for this application.

10. Pediatrics

During the current review cycle, this application will receive a Complete Response action; therefore, final decisions regarding pediatrics are deferred at this time.

With this submission the Applicant requested a deferral of pediatric studies for patients birth to 2 years of age, citing studies are impossible or highly impracticable. The Division agrees.

The Applicant also submitted a deferral request for pediatric studies for patients 2 to 17 years of age, citing that the adult studies are complete and the product is ready for approval.

The Applicant has an agreed iPSP on file (dated July 23, 2015).

11. Labeling Recommendations

Because of the recommended CR Action, labeling negotiations were deferred.

Upon resubmission, the following issues require further discussion and negotiation with Applicant:

1) Dosing and Administration: Consider recommending that initial SC switch occur at 3-4 weeks after last IV infusion (refer to section 6.3.2.2 and 15.3.5 for additional details), (b) (4)

2) Adverse Reactions: Results of reviewer conducted analyses including recoded AE terms have not been communicated to the Applicant for verification and further negotiation. Additional discussion regarding elevation of CPK, peripheral edema, and other AEs not previously included in Section 6 at the time of IV approval are warranted (see Table 24 and Table 26 and related discussion in safety review above).

3) Clinical Studies: Further discussion regarding which endpoints to include (b) (4) (b) (4) as well as the description of the "durable clinical remission" endpoint (defined by clinical remission at both Week 6 and 52 in week 6 responders) is warranted. See discussion of this issue in Section 8.1.3 above under "Discussion of Applicant's Secondary Endpoints."

12. Risk Evaluation and Mitigation Strategies

No new safety signals were identified during this review that would warrant initiation of risk evaluation mitigation strategies.

13. Postmarketing Requirements and Commitment

Given the application will receive a CR action, postmarketing requirements and commitments were not negotiated during the review cycle. If the application is resubmitted after adequately addressing the approvability issues identified, postmarketing required studies under the Pediatric Research Equity Act will be issued. An additional PMC to assess immunogenicity with an adequate assay should also be considered.

14. Deputy Director for Safety / Designated Signatory Authority (DGIEP) Comments

I agree with the conclusions and recommendation of the review team for a CR action for this application, as outlined in this review and in the action letter.

15. Appendices

15.1. Clinical Appendices (safety and efficacy)

15.1.1. Adverse Event Recoding

Table 29. Adverse Event Recoding

Count	Old Values (40/233)		New Values (13/206)
9	Abdominal pain	▼	Abdominal pain
3	Abdominal pain upper		
1	Abdominal pain lower		
6	Alanine aminotransferase increased	▼	Abnormal liver enzymes
3	Blood alkaline phosphatase increased		
2	Aspartate aminotransferase increased		
2	Gamma-glutamyltransferase increased		
2	Hyperbilirubinaemia		
1	Hepatic function abnormal		
16	Anaemia	▼	Anaemia
3	Haemoglobin decreased		
2	Iron deficiency anaemia		
4	Bronchitis	▼	Bronchitis
1	Bronchitis chronic		
9	Cough	▼	Cough
1	Productive cough		
5	Gastroenteritis	▼	Gastroenteritis
1	Gastroenteritis rotavirus		
1	Gastroenteritis viral		
1	Gastrointestinal viral infection		
6	Haemorrhoids	▼	Haemorrhoids
1	Haemorrhoids thrombosed		
21	Headache	▼	Headache
1	Cluster headache		
1	Migraine		
27	Injection site reaction	▼	Injection site reaction
3	Injection site erythema		
2	Injection site swelling		
2	Peripheral swelling	▼	Oedema peripheral
1	Oedema peripheral		
6	Rash	▼	Rash
1	Rash generalised		
1	Rash papular		
1	Rash pruritic		
1	Rash pustular		
1	Rash vesicular		
2	Respiratory tract infection viral	▼	Respiratory tract infection
1	Respiratory tract infection		
18	Upper respiratory tract infection	▼	Upper respiratory tract infection
1	Viral upper respiratory tract infection		

Source: reviewer table showing regrouping of reported AEDECOD terms utilized in primary safety analysis.

15.1.2. Details of infections

Table 30.Listing of Infectons Reported in Study SC-3027 (Maintenance Phase) by Recoded Term

Recoded Terms	Placebo N=56	Placebo %	Vedo IV N=54	Vedo IV %	Vedo SC N=106	Vedo SC%
Adenoviral conjunctivitis	0	0%	0	0%	1	1%
Anal abscess	0	0%	0	0%	2	2%
Bronchitis	0	0%	2	4%	2	2%
Campylobacter infection	0	0%	1	2%	0	0%
Ear infection	0	0%	0	0%	1	1%
Eye infection	1	2%	0	0%	0	0%
Folliculitis	1	2%	0	0%	0	0%
Gastroenteritis	2	4%	2	4%	3	3%
Gingivitis	1	2%	0	0%	0	0%
Herpes zoster	0	0%	0	0%	1	1%
Influenza	1	2%	1	2%	2	2%
Nasopharyngitis	10	18%	13	24%	10	9%
Oral fungal infection	1	2%	0	0%	0	0%
Oral herpes	1	2%	0	0%	2	2%
Paronychia	0	0%	1	2%	0	0%
Periodontitis	0	0%	0	0%	1	1%
Peritonitis	0	0%	0	0%	1	1%
Pharyngitis	1	2%	0	0%	2	2%
Pilonidal cyst	1	2%	0	0%	0	0%
Pneumonia	1	2%	2	4%	2	2%
Pulpitis dental	0	0%	0	0%	1	1%
Respiratory tract infection	0	0%	1	2%	1	1%
Rhinitis	0	0%	1	2%	0	0%
Sinusitis	3	5%	0	0%	1	1%
Tonsillitis	1	2%	0	0%	1	1%
Tooth abscess	0	0%	0	0%	2	2%
Tracheitis	0	0%	0	0%	1	1%
Upper respiratory tract infection	2	4%	6	11%	7	7%
Urinary tract infection	2	4%	4	7%	1	1%
Viral infection	1	2%	0	0%	1	1%
Vulvovaginal mycotic infection	1	2%	0	0%	0	0%

Source: : Adapted via JMP from Applicant's ADAE dataset

Table 31.Listing of Infections Reported in Study SC-3027(Maintenance Phase) by High Level Term

AEHLT	Placebo N=56	Placebo %	Vedo IV N=54	Vedo IV %	Vedo SC N=106	Vedo SC%
Abdominal and gastrointestinal infections	1	2%	2	4%	5	5%
Adenoviral infections	0	0%	0	0%	1	1%
Bacterial infections NEC	1	2%	0	0%	0	0%
Campylobacter infections	0	0%	1	2%	0	0%
Dental and oral soft tissue infections	1	2%	0	0%	4	4%
Ear infections	0	0%	0	0%	1	1%
Fungal infections NEC	2	4%	0	0%	0	0%
Herpes viral infections	1	2%	0	0%	3	3%
Infections NEC	0	0%	0	0%	1	1%
Influenza viral infections	1	2%	1	2%	2	2%
Lower respiratory tract and lung infections	1	2%	3	6%	5	5%
Pseudomonal infections	0	0%	1	2%	0	0%
Rotaviral infections	1	2%	0	0%	0	0%
Skin structures and soft tissue infections	2	4%	0	0%	1	1%
Tinea infections	0	0%	0	0%	1	1%
Upper respiratory tract infections	16	29%	13	24%	23	22%
Urinary tract infections	2	4%	4	7%	1	1%
Viral infections NEC	2	4%	1	2%	2	2%

Source: Adapted via JMP from Applicant's ADAE dataset

Specific Infections Occurring in Pool 1 Patients

In Pool 1, infections reported in ≥1% of patients included anal abscess, herpes zoster, oral herpes, pneumonia, respiratory tract infection, sinusitis, tooth abscess, and urinary tract infection. Other infections listed below were reported in <1% patients:

- Adenoviral conjunctivitis, angular cheilitis, appendicitis, Clostridium difficile infection, conjunctivitis, ear infection, diverticulitis, empyema, folliculitis, fungal skin infection, gastroenteritis viral, gastrointestinal viral infection, gingivitis, herpes virus infection,

laryngitis, periodontitis, peritonitis, pharyngitis streptococcal, pulpitis dental, rhinitis, salmonellosis, tinea pedis, tinea versicolour, tooth infection, tonsillitis, tracheitis, trichophytosis, viral infection, viral upper respiratory tract infection, and vulvovaginal mycotic infection.

15.1.3. Details on Liver Injury Evaluation

Additional cases of liver enzyme elevation

A 25-year-old man, reported two AEs of hyperbilirubinemia while receiving SC vedolizumab. These included a total bilirubin of 58.15 µmol/L on Day 389 and 54.39 µmol/L on Day 436 AST and ALT were within the normal range on these days and throughout the study. The subject was continued on the study medication.

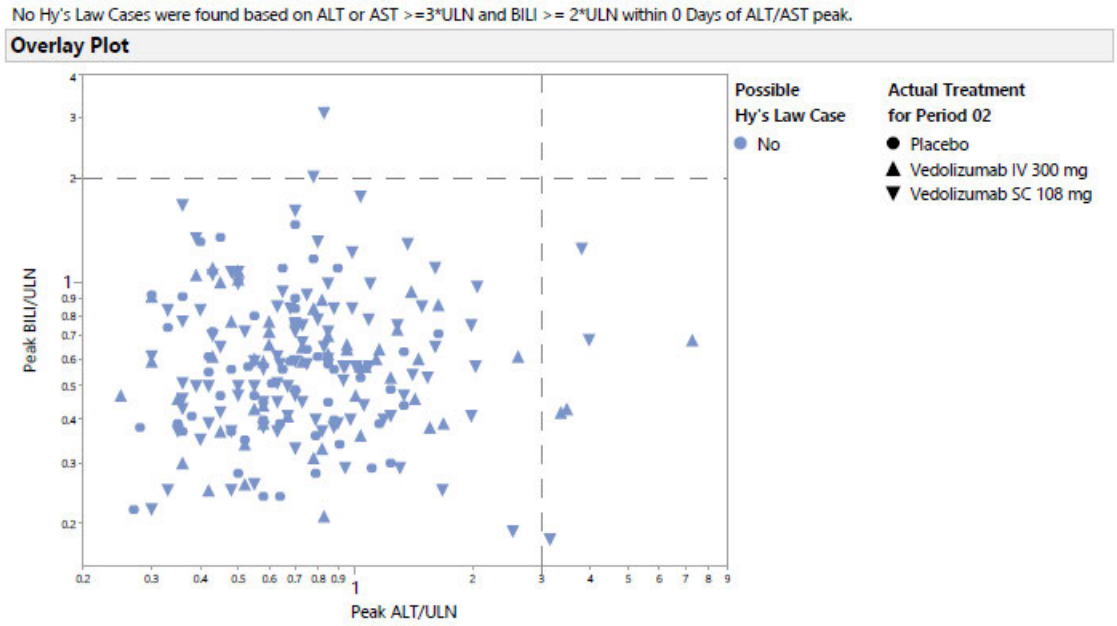
A 19-year-old man who received IV vedolizumab, developed moderate increase in ALT (292 U/L) during the induction phase. These levels normalized by Week 14 and remained within normal levels for the remainder of the study.

While on IV vedolizumab two patients reported mild elevations of ALT and AST and one patient reported mild elevation of alkaline phosphatase. In all three of these cases, the total bilirubin remained within normal limits throughout the study. One additional patient reported cholelithiasis, which was also considered mild.

While on SC vedolizumab, one patient had mild elevation of ALT and another patient had a mild "liver disorder" (not further clarified) that occurred during screening and resolved Day 1 of treatment.

In Pool 1, four patients (1%) reported five liver injury AESIs. These AEs included gamma-glutamyl transferase increased (three AEs), hyperbilirubinemia (one AE) and alanine aminotransferase increased (one AE) One event of alanine aminotransferase increased and one event of gamma-glutamyl transferase increased were severe (same patient as above) and the remaining three events were mild in intensity. None of the events were serious. No cases of Hy's law abnormalities were reported.

Figure 6. Hy's Law Screening Plot



Source: reviewer's analysis, Hy's law plot, JMP clinical 6.0, based upon applicant's submitted ADLB datasets

Table 32. ALT Shift Analysis, Study 3027

	Actual Treatment for Period 02					
	Placebo		Vedolizumab IV 300 mg		Vedolizumab SC 108 mg	
ALT Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	56	100.0%	50	92.6%	100	94.3%
Between 2x and 5x ULN	0	0.0%	3	5.6%	6	5.7%
Between 5x and 10x ULN	0	0.0%	1	1.9%	0	0.0%
All	56	100.0%	54	100.0%	106	100.0%

Source: reviewer's analysis, using JMP clnical 6.0, applicant's submitted ADLB datasets

Table 33. AST Shift Analysis, Study 3027

	Actual Treatment for Period 02					
	Placebo		Vedolizumab IV 300 mg		Vedolizumab SC 108 mg	
AST Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	52	92.9%	50	92.6%	102	96.2%
Between 2x and 5x ULN	4	7.1%	4	7.4%	4	3.8%
All	56	100.0%	54	100.0%	106	100.0%

Source: reviewer's analysis, using JMP clnical 6.0, applicant's submitted ADLB datasets

Table 34. Bilirubin Shift Analysis, Study 3027

	Actual Treatment for Period 02					
	Placebo		Vedolizumab IV 300 mg		Vedolizumab SC 108 mg	
BILI Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	56	100.0%	54	100.0%	104	98.1%
Between 2x and 5x ULN	0	0.0%	0	0.0%	2	1.9%
All	56	100.0%	54	100.0%	106	100.0%

Source: reviewer's analysis, using JMP clnical 6.0, applicant's submitted ADLB datasets

Table 35. Alkaline Phosphatase Shift Analysis, Study 3027

	Actual Treatment for Period 02					
	Placebo		Vedolizumab IV 300 mg		Vedolizumab SC 108 mg	
ALP Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	56	100.0%	52	96.3%	104	98.1%
Between 2x and 5x ULN	0	0.0%	2	3.7%	1	0.9%
Between 5x and 10x ULN	0	0.0%	0	0.0%	1	0.9%
All	56	100.0%	54	100.0%	106	100.0%

Source: reviewer's analysis, using JMP clnical 6.0, applicant's submitted ADLB datasets

15.1.4. Protocol Amendments

There were 5 protocol amendments to the original study protocol (dated February 26, 2015) through February 16, 2018. This section summarized efficacy related protocol changes below.

Protocol Amendment 1, dated November 10, 2015, updated the protocol regarding inclusion of further exploratory objectives and endpoints as follows.

1) Adding exploratory objectives and endpoints to gather alternative remission and
2) corticosteroid-free status data.
3) Making minor clarifications to the inclusion/exclusion criteria to assist the correct selection of participating subjects.
4) Adding a Product Complaints section to clarify the process for reporting product complaints during the study.

Protocol Amendment 2, dated February 10, 2016, was to update the protocol regarding inclusion of a benefit risk assessment. Other changes with this amendment were to:

1) Add 2 exploratory endpoints (proportion of subjects with clinical response at ≥80% study visits, including the final visit and proportion of subjects with clinical remission at ≥80% study visits, including the final visit, respectively) to Section 5.2.4.

2) Modify language about unblinding in Section 8.4 to clarify the requirements on investigator unblinding.

Protocol Amendment 3, dated May 12, 2016, was to update the protocol to include additional information for clarification. Other changes with this amendment were to:

1) Clarify the endpoint text to correctly assign the 2 definitions of clinical remission.
2) Add exploratory endpoints:
    a. Proportion of subjects with clinical response (by partial Mayo score) at ≥60% study visits, including the final visit.
    b. Proportion of subjects with clinical response (by partial Mayo score) at ≥80% study visits, including the final visit.
    c. Proportion of subjects with hypersensitivity reactions by positive AVA.
3) Correct Exclusion Criterion #24 by including the screening time point to exclude a subject because of a positive PML subjective symptom checklist.
4) Remove Exclusion Criterion #26 (subject has received any nonbiologic therapies for UC not listed under Permitted Medications and Treatments) as it was a repeat of Exclusion Criterion #4.
5) Clarify Exclusion Criterion #12 (evidence of active or latent tuberculosis)
6) Clarify Exclusion Criterion #29 (subject unable to attend all study visits or comply with study procedures) to include the caregiver.
7) Update text in Section 7.3.1 (Permitted Medications and Treatments) concerning stable doses of permitted medications. Information about the need for rescue medications was also added to this section.
8) Update the schedule of assessments. The schedule of study procedures was split into 2 separate tables for the induction phase and the maintenance phase, respectively.

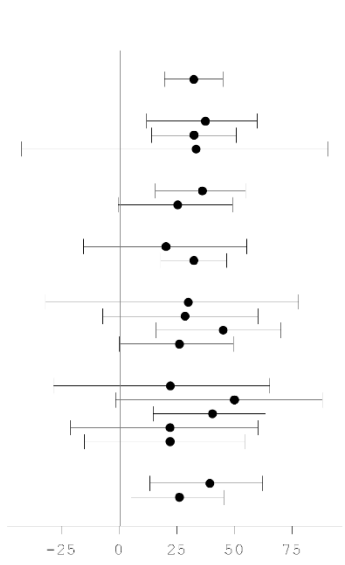
Protocol Amendment 4, dated July 26, 2016, was to clarify the infectious disease Exclusion Criterion #11 about hepatitis and Exclusion Criterion #12 about tuberculosis. Exclusion Criterion #11 included a note that allowed HBV immune subjects to be included. In addition, a histological endpoint (proportion of subjects with a change in histology from baseline to Week 52) was added.

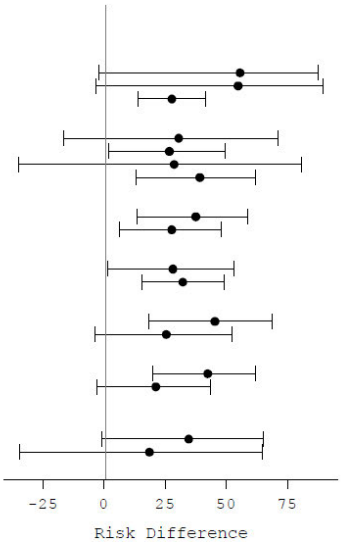
Protocol Amendment 5, dated September 28, 2016: This amendment applied to Japan sites only. The primary change in this amendment was to extend the visit window from -3 days to -5 days for Week 6a, as close as possible to the beginning of the evaluation period, to adjust for clinical practice in Japan.

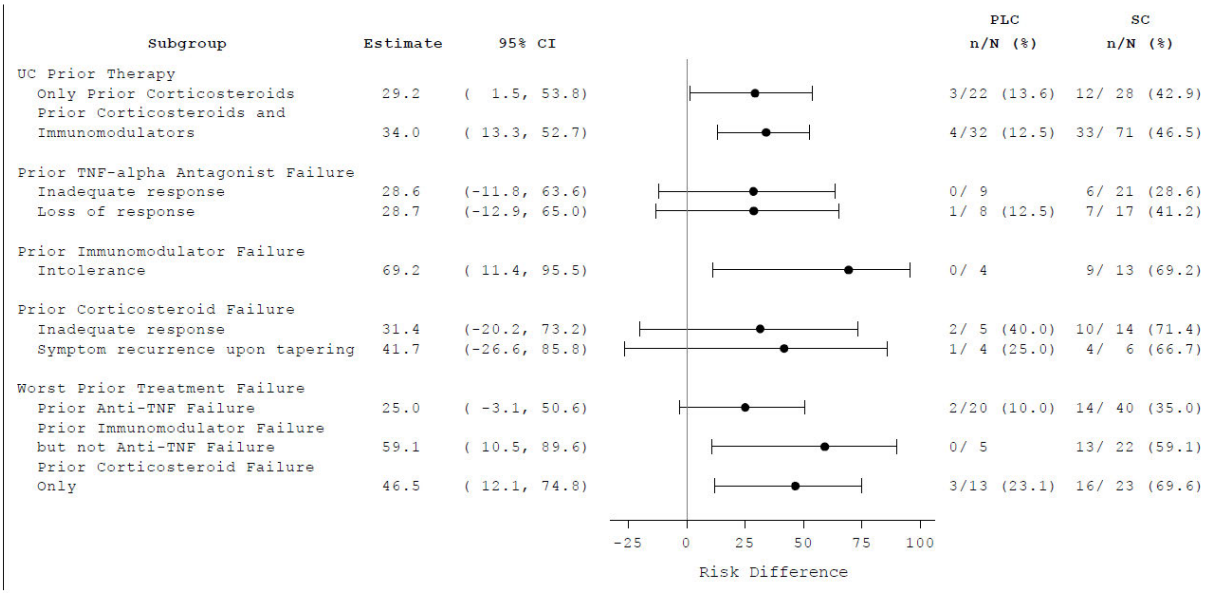
15.1.5. Subgroup Analyses on the Primary Endpoint

Figure 7. Forest Plot for Subgroup Analyses of Clinical Remission at Week 52 (FAS)

Subgroup	Estimate	95% CI	PLC n/N (%)	SC n/N (%)
Overall	32.3	(19.7, 45.0)	8/56 (14.3)	49/106 (46.2)
Age				
< 35 years	37.4	(11.9, 60.0)	2/21 (9.5)	23/ 49 (46.9)
>= 35 years to < 65 years	32.4	(14.1, 50.8)	6/32 (18.8)	24/ 51 (47.1)
>= 65 years	33.3	(-42.1, 90.5)	0/ 3	2/ 6 (33.3)
Gender				
Male	36.1	(15.7, 54.7)	5/34 (14.7)	33/ 65 (50.8)
Female	25.4	(-0.3, 49.3)	3/22 (13.6)	16/ 41 (39.0)
Race				
Asian	20.3	(-15.5, 55.3)	2/13 (15.4)	5/ 14 (35.7)
White	32.4	(18.2, 46.6)	6/42 (14.3)	44/ 92 (47.8)
Duration of UC				
< 1 year	30.0	(-31.8, 77.9)	1/ 5 (20.0)	3/ 6 (50.0)
1 - <3 years	28.6	(-7.1, 60.2)	3/14 (21.4)	8/ 16 (50.0)
3 - <7 years	45.1	(16.1, 70.1)	1/16 (6.3)	19/ 37 (51.4)
>= 7 years	26.1	(0.2, 49.6)	3/21 (14.3)	19/ 47 (40.4)
Geographic Region				
North America	22.2	(-28.5, 65.4)	2/ 9 (22.2)	4/ 9 (44.4)
Western / Northern Europe	50.0	(-1.7, 88.1)	0/ 6	5/ 10 (50.0)
Central Europe	40.5	(14.7, 63.4)	2/19 (10.5)	26/ 51 (51.0)
Eastern Europe	22.1	(-21.2, 60.1)	2/ 8 (25.0)	8/ 17 (47.1)
Africa / Asia / Australia	22.1	(-15.1, 54.3)	2/13 (15.4)	6/ 16 (37.5)
Baseline Disease Activity				
Moderate	39.3	(13.3, 62.1)	3/20 (15.0)	25/ 46 (54.3)
Severe	26.1	(5.3, 45.4)	5/36 (13.9)	24/ 60 (40.0)
Baseline Fecal Calprotecin				
<= 250 ug/g	55.6	(-2.4, 87.3)	0/ 5	5/ 9 (55.6)
> 250-<=500 ug/g	54.8	(-3.3, 89.5)	2/ 7 (28.6)	5/ 6 (83.3)
> 500 ug/g	27.7	(13.7, 41.6)	6/44 (13.6)	37/ 87 (42.5)
Disease Localization				
Proctosigmoiditis	30.5	(-16.7, 70.9)	3/ 7 (42.9)	11/ 15 (73.3)
Left Sided Colitis	26.6	(1.8, 49.6)	3/24 (12.5)	18/ 46 (39.1)
Extensive Colitis	28.6	(-35.3, 80.6)	0/ 4	2/ 7 (28.6)
Pancolitis	39.1	(12.9, 61.9)	2/21 (9.5)	18/ 37 (48.6)
Clinical Remission at Week 6				
Yes	37.4	(13.2, 58.8)	5/25 (20.0)	27/ 47 (57.4)
No	27.6	(6.3, 47.6)	3/31 (9.7)	22/ 59 (37.3)
Prior TNF-alpha Antagonist Therapy				
Failure	28.1	(1.3, 52.9)	1/19 (5.3)	13/ 39 (33.3)
Naive	32.1	(15.2, 49.0)	7/37 (18.9)	36/ 67 (53.7)
Prior Immunomodulator Failure				
Yes	45.3	(18.2, 68.8)	1/17 (5.9)	22/ 43 (51.2)
No	25.4	(-3.9, 52.3)	3/16 (18.8)	15/ 34 (44.1)
Prior Corticosteroid Failure				
Yes	42.3	(19.9, 62.0)	4/28 (14.3)	30/ 53 (56.6)
No	21.1	(-3.0, 43.4)	3/26 (11.5)	15/ 46 (32.6)
Prior Immunomodulator and Anti-TNF Failure				
Yes	34.5	(-1.2, 65.1)	1/12 (8.3)	9/ 21 (42.9)
No	18.5	(-34.8, 64.8)	1/ 5 (20.0)	5/ 13 (38.5)







Source: CSR Figure 11.a, verified by reviewer
The risk difference represents the treatment difference between vedolizumab SC and placebo. If the total number of subjects in any subgroup was fewer than 10 across all 3 treatment groups, that subgroup was not presented. A difference >0 favors vedolizumab SC.
Subgroup analyse results for clinical remission at Week 52 (FAS) are provided for subgroups based on age (CSR Table 15.2.3.1.1); gender (CSR Table 15.2.3.1.2); race (CSR Table 15.2.3.1.3); duration of UC (CSR Table 15.2.3.1.4); geographic region (CSR Table 15.2.3.1.5); baseline disease activity (CSR Table 15.2.3.1.6); baseline fecal calprotectin (CSR Table 15.2.3.1.7); disease localization (CSR Table 15.2.3.1.8); clinical remission at Week 6 (CSR Table 15.2.3.1.9); prior TNF-α antagonist therapy (CSR Table 15.2.3.1.10); prior immunomodulator, corticosteroid therapy (CSR Table 15.2.3.1.11); prior therapies (CSR Table 15.2.3.1.12); prior TNF-α antagonist failure (CSR Table 15.2.3.1.13); and worst prior treatment failure (CSR Table 15.2.3.1.14).

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 3027 / 3030 (information is same for both studies)

Covered Clinical Study (Name and/or Number): 3027 / 3030 (information is same for both studies)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 Code of Federal Regulations 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (technical documents supporting OCP recommendations)

15.3.1. Bioanalytical Method Validation and In-Study Report

Serum concentrations of vedolizumab were measured using a validated enzyme-linked immunosorbent assay. The analytical range of the assay was 0.200 to 8.00 µg/mL. The validation data are summarized in Table 36. Although interday precision and accuracy was not presented, the original assay using different QCs (0.125, 0.2, 1, 6.7 µg/mL) showed that the inter-day precision and accuracy were 4.0% to 16.2% and -2.5% to 10.1%, respectively, which were within the acceptance criteria. Therefore, the validated method is acceptable. In addition, the summary of in study bioanalytical reports listed as follows showed data for these four PK comparability studies were acceptable.

Table 36. Summary of In-Study Bioanalytical Reports

Method	ELISA
Analyte	Vedolizumab
Sample volume	5 µL
Calibration range	0.2-8.0 µg/mL
QC concentrations	0.2, 0.6, 3.0, 6.7, and 8.0 µg/mL
QC intrabatch precision	5.1 to 10.7%
QC intrabatch accuracy	-2.0 to 4.4%
Stability	Benchtop stability in human serum: 26 hours at room temperature Freeze/thaw stability in human serum: 5 cycles at room temperature/-70°C Long-term storage stability in human serum: 120 days at -20°C, 765 days at -70°C
Ulcerative colitis disease Human matrix selectivity (10 lots, spiked 0.2 and 8.0 µg/mL)	89% lots tested within 100±25% recovery at 0.2 µg/mL 100% lots tested within 100±25% recovery at 8.00 µg/mL
Hemolyzed human matrix selectivity (6 lots, spiked 0.2 and 8.0 µg/mL)	Evaluated and acceptable recovery at 0.2 µg/mL and 8.0 µg/mL
Lipemic human matrix selectivity (6 lots, spiked 0.2 and 8.0 µg/mL)	Evaluated and acceptable recovery at 8.0 µg/mL. Inconclusive regarding recovery at 0.2 µg/mL
HIV-infected human matrix selectivity (10 lots, spiked 0.200 and 8.00 µg/mL)	80% of lots tested within 100±25% recovery at 0.2 µg/mL 100% of lots tested within 100±25% recovery at 8.0 µg/mL
Serum separating tube Collection matrix selectivity (10 lots, spiked 0.200 and 8.00 µg/mL)	80% of lots tested within 100±25% recovery at 0.2 µg/mL 100% of lots tested within 100±25% recovery at 8.0 µg/mL
Adalimumab* interference (40.0 µg/mL)	Evaluated and acceptable recovery at 0.2 µg/mL and 8.0 µg/mL

*Adalimumab (Humira) is the drug usually comedicated to treat Crohn's disease and ulcerative colitis.

Table 37. In Study Bioanalytical Reports for the Phase 1 PK Comparability Studies

	SC-1017	SC-1018	SC-1021	SC-1022
Standard curve CV%	1.1–5.7%	2.4–6.1%	1.5–8.5%	2.7–5.1%
QCs CV%	5.0–6.1%	6.2–8.5%	4.5–7.3%	5.9–10.8%
Incurred sample reanalysis (percentage of samples that %difference is within ±30%)	94.7%	94.6%	100%	95.0%

Immunogenecity

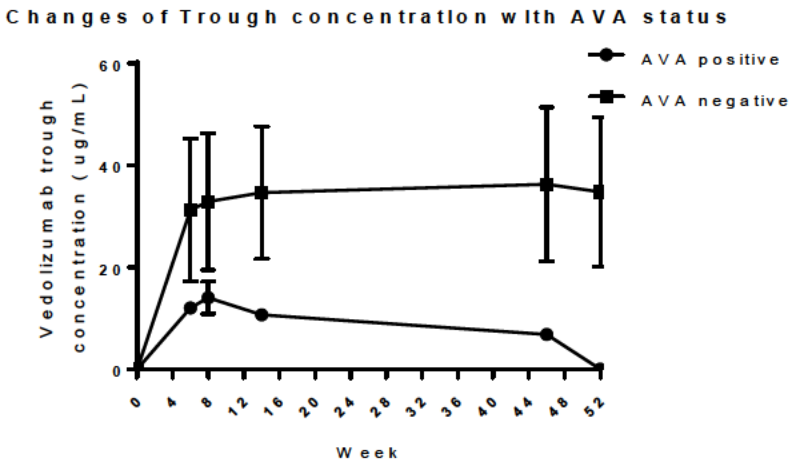
Drug Tolerance Level of the Immunogenicity Assays

See Section 6.3.2.5.

Immunogenicity Impact on PK

In Study SC-3027, the trough vedolizumab concentrations in patients who developed AVA were lower than the trough concentrations in AVA negative patients (Figure 8).

Figure 8. Vedolizumab Trough Concentrations by AVA Status in Study SC-3027



Source: Reviewer's analysis per SC-3027 clinical study report table 15.2.6.2.2.

Immunogenicity Impact on Efficacy

Patients who developed AVA were generally associated with reduced efficacy in both SC and IV treatment groups in Study SC-3027 (Table 38 and Table 39). All the 6 subjects who were AVA-positive in the SC treatment arm did not achieve clinical remission or mucosal healing at Week 52. All the 3 subjects who were AVA-positive in the IV treatment arm did not achieve clinical remission at Week 52; however, 2 of the 3 AVA-positive subjects achieved mucosal healing at Week 52.

Table 38. Clinical Remission at Week 52 by Overall AVA Status (SC-3027)

Clinical Remission (Yes/No)	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)
At least 1 nonmissing AVA sample	56	106	54
Yes			
N	8	49	23
AVA negative [a]	6 (75.0)	49 (100.0)	23 (100.0)
AVA positive [b]	2 (25.0)	0	0
Transiently positive AVA [c]	1 (12.5)	0	0
Persistently positive AVA [d]	1 (12.5)	0	0
Positive neutralizing AVA [e]	1 (12.5)	0	0
No			
N	48	57	31
AVA negative [a]	33 (68.8)	51 (89.5)	28 (90.3)
AVA positive [b]	15 (31.3)	6 (10.5)	3 (9.7)
Transiently positive AVA [c]	2 (4.2)	2 (3.5)	0
Persistently positive AVA [d]	13 (27.1)	4 (7.0)	3 (9.7)
Positive neutralizing AVA [e]	11 (22.9)	3 (5.3)	3 (9.7)

Source: Table 12.y, CSR for Study SC-3027

Table 39 Mucosal Healing at Week 52 by Overall AVA Status (SC-3027)

Mucosal Healing (Yes/No)	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)
At least 1 nonmissing AVA sample	56	106	54
Yes			
N	12	60	29
AVA negative [a]	8 (66.7)	60 (100.0)	27 (93.1)
AVA positive [b]	4 (33.3)	0	2 (6.9)
Transiently positive AVA [c]	1 (8.3)	0	0
Persistently positive AVA [d]	3 (25.0)	0	2 (6.9)
Positive neutralizing AVA [e]	2 (16.7)	0	2 (6.9)
No			
N	44	46	25
AVA negative [a]	31 (70.5)	40 (87.0)	24 (96.0)
AVA positive [b]	13 (29.5)	6 (13.0)	1 (4.0)
Transiently positive AVA [c]	2 (4.5)	2 (4.3)	0
Persistently positive AVA [d]	11 (25.0)	4 (8.7)	1 (4.0)
Positive neutralizing AVA [e]	10 (22.7)	3 (6.5)	1 (4.0)

Source: Table 12.z, CSR for Study SC-3027

Immunogenicity Impact on Safety

Due to the small number of AVA positive patients and the limitations of the ADA assay used in study SC-3027, we cannot make a definitive conclusion regarding the impact of AVA on safety of vedolizumab. In Study SC-3027, among 11 subjects who had injection site reactions while receiving vedolizumab SC, only 1 (9%) subject was positive for AVA (Table 40).

Table 40. AVA Status by Injection Site Reactions – Safety Population (SC-3027)

AEs Defined as Injection Site Reactions	Induction IV + Placebo[a] N=56	Induction IV + Vedolizumab SC 108 mg N = 106	Induction IV + Vedolizumab IV 300 mg N=54
At least 1 non-missing AVA sample	56	105	53
Yes			
N	0	11[b]	1[d]
AVA-negative	0	10 (91)[b]	1 (100)
AVA-positive (%)	0	1 (9)[b]	0
Transiently AVA-Positive	0	1 (9)[b]	0
Persistently AVA-Positive	0	0	0
Positive Neutralizing AVA	0	0	0
No			
N	56	94[c]	52
AVA-negative	40 (71)	91 (97)[c]	49 (94)
AVA-positive (%)	16 (29)	3 (3)[c]	3 (6)
Transiently AVA-Positive	2 (4)	2 (2)[c]	0
Persistently AVA-Positive	14 (25)	1 (1)[c]	3 (6)
Positive Neutralizing AVA	12 (21)	1 (1)[c]	3 (6)

Source: Summary of Clinical Pharmacology Studies, pg 55, table 4.d.

15.3.2. Individual Study Report

Study C13010

Title

Phase 1, open-label, single-dose study to determine the absolute bioavailability following SC and IM administration in healthy subjects (aged 18-60 years)

Study Date

05/31/2009—11/05/2009

Study Design

This was a phase 1 study of the absolute bioavailability of vedolizumab when administered as a SC injection and IM injection to healthy male subjects aged 18 to 60 years.

- Dose administration

  All subjects received a single dose of vedolizumab (180 mg) by SC injection, IM injection, or IV infusion (1:1:1).

- Study population

  A total of 42 subjects were enrolled (14 per dosing cohort): healthy male subjects aged 18 to 60 years with body weight of 70 to 95 kg and a body mass index (BMI) of 18 to 32 kg/m^2.

- Investigational drug

  Vedolizumab 180 mg administered by SC injection or IM injection. Lot number: IC006LA02.

  Vedolizumab 180 mg administered by IV infusion. Lot number: IC006LA02.

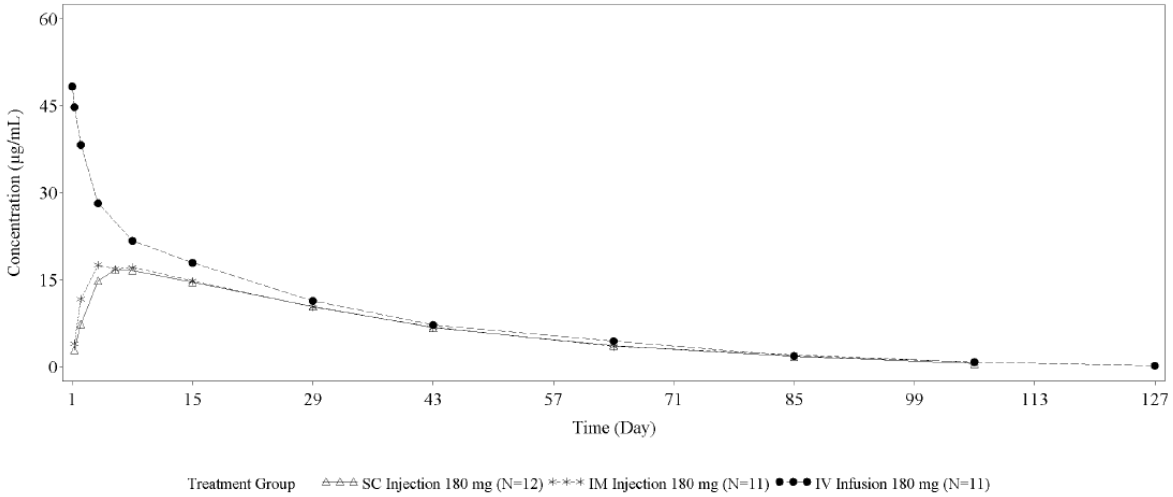
- Pharmacokinetics (PK)

  Blood specimens for the determination of serum vedolizumab concentrations were obtained as follows: 5 minutes after the end of infusion (IV group only), and 6, 24, 72, 120 (except for the IV group), 168, 336, 672, 1008, 1512, 2016, 2520, and 3024 hours after start of infusion/injection. Serum concentrations of vedolizumab were determined using a validated sandwich enzyme-linked immunosorbent assay. The absolute bioavailability of vedolizumab was calculated as the geometric mean ratio of the area under the drug concentration-time curve, extrapolated to infinity; AUC0-inf (SC injection of vedolizumab versus IV infusion of vedolizumab and IM injection of vedolizumab versus IV infusion of vedolizumab).

- Study results

  The PK profile is shown in Figure 9 and PK parameters are summarized in Table 41. Following IM and SC administration, the maximum concentrations were achieved at 5-7 days post injection. The absolute bioavailability of vedolizumab was approximately 75% following SC administration and approximately 80% following IM administration.

Figure 9. Mean Vedolizumab Serum Concentrations-Time Profiles by Treatment Group (Study C13010)



Source: CSR pg49, Figure 11-1

Table 41. Vedolizumab PK Parameters (Study C13010)

Parameter	Units	Treatment Group	n	Arithmetic Mean[a]	Standard Deviation[b]
C_{max}	µg/mL	SC Injection 180 mg	12	17.8	3.74
		IM Injection 180 mg	11	18.8	5.12
		IV Infusion 180 mg	11	48.6	6.31
T_{max}	d	SC Injection 180 mg	12	7.00[a]	3.00, 14.0[b]
		IM Injection 180 mg	11	5.00[a]	2.98, 14.0[b]
$AUC_{0\text{-}inf}$	µg*d/mL	SC Injection 180 mg	12	683	134
		IM Injection 180 mg	10	723	88.2
		IV Infusion 180 mg	11	916	165
$AUC_{0\text{-}tlast}$	µg*d/mL	SC Injection 180 mg	12	675	136
		IM Injection 180 mg	11	663	184
		IV Infusion 180 mg	11	902	171
CL[c]	L/d	SC Injection 180 mg	12	0.273	0.056
		IM Injection 180 mg	10	0.253	0.032
		IV Infusion 180 mg	11	0.205	0.052
t1/2	d	SC Injection 180 mg	12	13.0	2.58
		IM Injection 180 mg	10	15.1	2.59
		IV Infusion 180 mg	11	14.3	2.85
Vz[d]	L	SC Injection 180 mg	12	5.13	1.50
		IM Injection 180 mg	10	5.45	0.888
		IV Infusion 180 mg	11	4.25	1.41
Vss	L	IV Infusion 180 mg	11	5.77	0.852

Source: CSR pg65, Table 11g.

Study SC-101:

Title

A Phase 1, Open-Label, Randomized, Parallel Group Study to Assess the Absolute Bioavailability and Pharmacokinetics of Vedolizumab in Healthy Subjects Following Single Subcutaneous Administration

Study Date

05/20/2014—01/16/2015

Study Design

This is a single dose, parallel study. Subjects were randomly assigned in a ratio of 1:1:1:1 to 1 of 4 treatment groups (12 subjects per treatment group). Randomization was stratified by ethnicity (Japanese and non-Japanese). All subjects received study drug on Day 1. The 4 treatment groups were as follows:

- Vedolizumab IV 300 mg by infusion over approximately 30 minutes.
- Vedolizumab SC 54 mg (in prefilled syringes) by SC injection.
- Vedolizumab SC 108 mg (in prefilled syringes) by SC injection.
- Vedolizumab SC 160 mg (in prefilled syringes) by SC injection.

- Dose administration

  Different from study C13010 in which SC administration of vedolizumab were given as two 1.5 mL injections (180 mg in total, 60 mg/mL solution), the study SC-101 used a single 1 mL (or less) injection of the vedolizumab.

- Study population

  A total of 48 heathy subjects were enrolled: aged 20 to 60 years; weighing at least 45 kg (99 lbs) and with a body mass index between 18.0 and 30.0 kg/m^2 for non-Japanese subjects and between 18.0 and 28.0 kg/m^2 for Japanese subjects.

- PK and AVA sampling

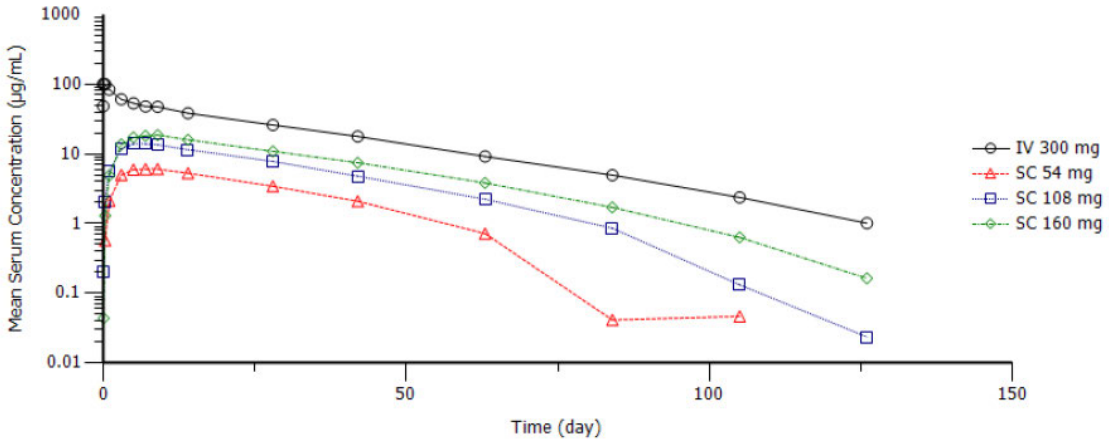
  For subjects in the vedolizumab IV group, blood samples were collected 0.25 hours (15 minutes) and 0.58 hours (35 minutes) after the start of the infusion. For subjects in both the vedolizumab IV and SC treatment groups, samples were also collected 2, 8, 24, 72, 120, and 168 hours on Day 1, and on Days 10±1, 15±1, 29±2, 43±2, 64±3, 85±3, 106±3, and Final Visit Day 127±3/ET. Blood samples for determination of AVA were collected at predose, Days 10, 29±2, 64±3, 85±3, 106±3, and 127±3/ET postdose.

- Study results

The PK profiles are shown in Figure 10 and PK parameters are summarized in

Table 42. Peak serum concentrations (C_{max}) were observed around 1 week after a single SC injection of vedolizumab SC 54, 108, or 160 mg. The bioavailability following a single SC injection of vedolizumab SC was approximately 75% at the studied doses.

Figure 10. Mean Serum Concentration-Time Profiles of Vedolizumab in Study SC-101.



Source: CSR pg61, Figure 11a.

Table 42. Summary Pharmacokinetic Parameters of Vedolizumab in Study SC-101.

Treatment Population	N	t_{max} (day)	C_{max} (µg/mL)	AUC_t (µg·day/mL)	AUC_∞ (µg·day /mL)	$t_{1/2z}$ (day)
300 mg IV						
Japanese	6	0.09 (0.02, 0.33)	116.15 (16)	2241 (15)	2265 (15)	19.8 (14)
Non-Japanese	6	0.05 (0.02, 0.33)	95.92 (20)	1972 (15)	2016 (15)	23.2 (16)
Overall	12	0.08 (0.02, 0.33)	106.03 (20)	2106 (16)	2140 (16)	21.5 (17)
54 mg SC						
Japanese	5	8.81 (7.00, 9.00)	5.82 (34)	202 (33)	212 (31)	13.3 (15)
Non-Japanese	5	5.00 (5.00, 7.00)	7.17 (19)	217 (37)	226 (34)	14.0 (35)
Overall	10	7.00 (5.00, 9.00)	6.49 (27)	209 (33)	219 (31)	13.6 (26)
108 mg SC						
Japanese	5	7.00 (5.00, 7.00)	16.76 (33)	598 (30)	611 (29)	15.4 (20)
Non-Japanese	5	8.86 (3.00, 9.06)	13.26 (20)	430 (16)	441 (17)	14.6 (18)
Overall	10	7.00 (3.00, 9.06)	15.01 (30)	514 (30)	526 (30)	15.0 (18)
160 mg SC						
Japanese	6	8.91 (7.00, 9.86)	22.88 (19)	905 (22)	921 (21)	17.3 (24)
Non-Japanese	6	8.93 (6.83, 9.27)	17.37 (36)	644 (41)	657 (40)	16.1 (15)
Overall	12	8.93 (6.83, 9.86)	20.13 (29)	775 (34)	789 (33)	16.7 (19)

Source: CSR pg65, Table 11g.

Study SC-1017

Title

A Phase 1, Open-Label, Randomized, Parallel Group Pilot Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe (PFS) Versus Prefilled Syringe in Needle Safety Device (PFS+NSD) in Healthy Subjects

Study Date

02/06/2018—07/27/2018

Study Design

This was an open-label, randomized, parallel-group, pilot study to compare the PK of a single dose of vedolizumab SC 108 mg for injection administered in 2 different device delivery presentations in healthy subjects. A minimum of 24 subjects (12 per group) were randomized to 1 of 2 device presentations (Group A or B) in a 1:1 ratio, and within each group, the subjects were randomized to injection site (abdomen, thigh, or arm) in a 1:1:1 ratio, for a total of 6 treatment combinations.

- Dose administration

  108 mg solution for injection via PFS or PFS+NSD administrations
- Study population

  The subjects were healthy male or female (nonpregnant and nonlactating) adult aged 18 to 65 years. The subject weighed >50 kg and <90 kg or had a body mass index (BMI) from 18 to 28 kg/m2.
- Investigational drug

Table 43. Investigation Drug Products in Study SC-1017

Study Drugs	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe	108 mg Solution for Injection	108 mg	SC	225628
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe in Needle Safety Device	108 mg Solution for Injection	108 mg	SC	225632

Source: CSR pg 23, Table 9c.

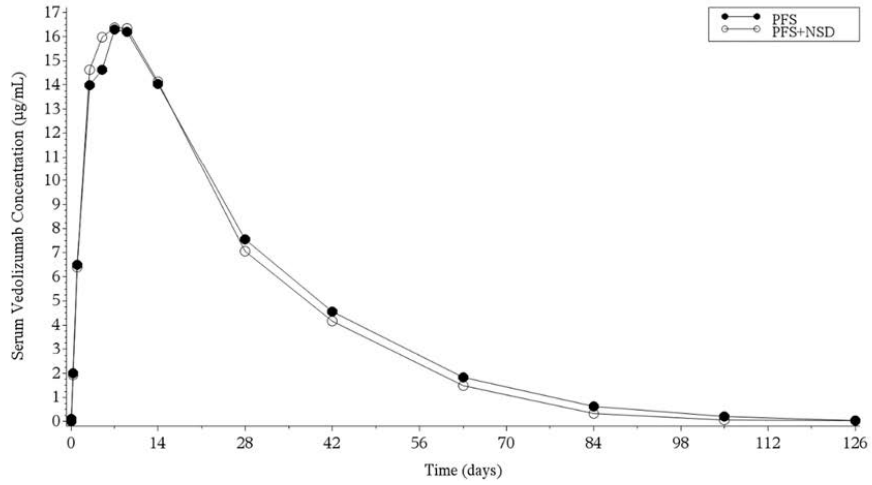
- PK and AVA sampling

  For PK analysis, blood samples for PK analyses of vedolizumab were collected beginning predose on Day 1 (within 0.5 hours before the SC injection) and then at 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10, 15, 29, 43, 64, 85, 106, and Final Visit Day 127/ET. For ADA analysis, blood samples for determination of AVA were collected at predose on Day 1 (within 0.5 hours before dosing), Days 29, 64, 85, 106, and 127/ET postdose.

- Study results

The PK profiles are shown in Figure 11, the statistical PK comparisions between PFS and PFS+NSD are summarized in Table 44, and the immunogenicity results are summarized in Table 45.

Figure 11. Mean Serum Vedolizumab Concentrations-Time Profiles (Study SC-1017)



Source: CSR pg46, Figure 11a.

Table 44. Statistical PK Comparisons Between PFS and PFS+NSD (Study SC-1017)

	PFS+NSD (Test)		PFS (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	Ratio of Geometric LSMs (%)	90% Confidence Interval (%)	Inter-subject CV%
AUC_{Week2} (µg•day/mL)	191.6	12	187.9	12	102.01	89.94 - 115.71	17.9
AUC_{last} (µg•day/mL)	480.6	12	498.9	12	96.32	79.38 - 116.88	27.8
AUC_{inf} (µg•day/mL)	500.1	12	520.6	12	96.06	79.80 - 115.62	26.6
C_{max} (µg/mL)	16.86	12	16.59	12	101.62	90.01 - 114.73	17.3

Source: CSR pg50, Table 11f.

Table 45. Summary of Overall Anti-Vedolizumab Antibody Status (Study SC-1017)

	PFS				PFS+NSD				
AVA Status	Overall N=12	Abdomen N=4	Arm N=4	Thigh N=4	Overall N=12	Abdomen N=4	Arm N=4	Thigh N=4	Total N=24
Ava Negative	7 (58)	3 (75)	1 (25)	3 (75)	4 (33)	2 (50)	1 (25)	1 (25)	11 (46)
Ava Positive	5 (42)	1 (25)	3 (75)	1 (25)	8 (67)	2 (50)	3 (75)	3 (75)	13 (54)
Transiently Positive	1 (8)	0 (0)	0 (0)	1 (25)	1 (8)	0 (0)	0 (0)	1 (25)	2 (8)
Persistently Positive	4 (33)	1 (25)	3 (75)	0 (0)	7 (58)	2 (50)	3 (75)	2 (50)	11 (46)
Neutralizing Ava Positive	3 (25)	1 (25)	2 (50)	0 (0)	7 (58)	2 (50)	3 (75)	2 (50)	10 (42)

Source: CSR p65, Table 12e.

Study SC-1018

Title

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Needle Safety Device in Healthy Subjects

Study Date

02/21/2018—09/26/2018

Study Design

A total of 102 subjects (51 per group) were randomized to 1 of 2 device presentations (Group A or B) in a 1:1 ratio, and within each group, the subjects were randomized to injection site (abdomen, thigh, or arm) in a 1:1:1 ratio, for a total of 6 treatment combinations.

- Dose administration

  108 mg solution for injection via PFS or PFS+NSD administrations

- Study population

  The subjects were healthy male or female (nonpregnant and nonlactating) adult aged 18 to 65 years. The subject weighed >50 kg and <90 kg or had a body mass index (BMI) from 18 to 28 kg/m^2.

- Investigational drug

Table 46. Investigation Drug Products in Study SC-1018

Study Drugs	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe	108 mg Solution for Injection	108 mg	SC	225629
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe in Needle Safety Device	108 mg Solution for Injection	108 mg	SC	225633

Source: CSR pg 23, Table 9c.

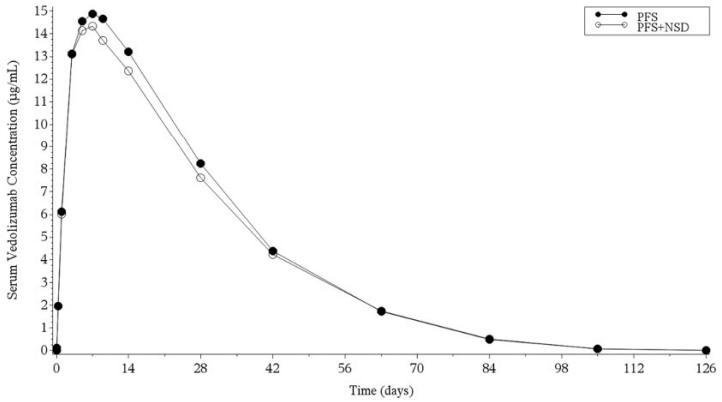
- PK and AVA sampling

  Same to study SC-1017 shown as above.

- Study results

  The PK profiles are shown in Figure 12, the statistical PK comparisions between PFS and PFS+NSD are summarized in Table 47, the impact of injection site on PK of vedolizumab is summarized in Table 48 and the immunogenicity results are summarized in Table 49.

Figure 12. Mean Serum Vedolizumab Concentrations-Time Profiles (Study SC-1018)



Source: CSR pg47, Figure 11a.

Table 47. Statistical PK Comparisons Between PFS and PFS+NSD (Study SC-1018)

	PFS+NSD (Test)		PFS (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	Ratio of Geometric LSMs (%)	90% Confidence Interval (%)	Inter-subject CV%
AUC_{last} (µg*day/mL)	470.2	50	477.5	51	98.46	90.40 - 107.23	25.5
AUC_{inf} (µg*day/mL)	491.8	49	491.0	51	100.17	92.55 - 108.41	23.5
C_{max} (µg/mL)	15.18	51	15.09	51	100.60	94.20 - 107.43	19.8

Source: CSR pg50, Table 11f.

Table 48. Effect of Injection Site on PK of Vedolizumab (Study SC-1018)

Parameter	PFS	PFS+NSD
	Overall (N=51)	
AUC_{last} (µg•day/mL)	492.6 (22.5)	455.4 (34.4)
AUC_{inf} (µg•day/mL)	504.4 (22.0)	478.4 (30.7)
C_{max} (µg/mL)	15.42 (19.9)	14.86 (24.4)
t_{max} (day)	6.986 (2.96, 13.99)	6.956 (2.95, 13.99)
$t_{½}$ (day)	13.170 ± 2.8475	13.447 ± 2.8201
CL/F (L/day)	0.2191 ± 0.047848	0.2361 ± 0.073889
V_z/F (L)	4.068 ± 0.89093	4.429 ± 1.2102
	Abdomen (N=17)	
AUC_{last} (µg•day/mL)	506.4 (23.1)	472.4 (37.1)
AUC_{inf} (µg•day/mL)	521.9 (22.5)	486.1 (36.0)
C_{max} (µg/mL)	15.46 (19.5)	15.81 (25.6)
t_{max} (day)	4.998 (2.99, 13.94)	4.997 (2.95, 9.14)
$t_{½}$ (day)	13.608 ± 3.0057	13.351 ± 2.8296
CL/F (L/day)	0.2118 ± 0.047509	0.2348 ± 0.078929
V_z/F (L)	4.075 ± 0.96765	4.346 ± 1.2301
	Arm (N=17)	
AUC_{last} (µg•day/mL)	516.8 (19.7)	434.9 (31.2)
AUC_{inf} (µg•day/mL)	527.4 (19.3)	447.7 (30.7)
C_{max} (µg/mL)	15.78 (17.6)	14.02 (27.6)
t_{max} (day)	6.986 (2.96, 9.00)	6.956 (2.97, 13.99)
$t_{½}$ (day)	13.630 ± 2.6907	12.979 ± 3.0303
CL/F (L/day)	0.2085 ± 0.042102	0.2526 ± 0.086496
V_z/F (L)	4.014 ± 0.74423	4.503 ± 1.1723
	Thigh (N=17)	
AUC_{last} (µg•day/mL)	456.7 (23.7)	458.4 (36.3)
AUC_{inf} (µg•day/mL)	466.4 (23.1)	502.6 (24.9)
C_{max} (µg/mL)	15.01 (23.2)	14.80 (19.0)
t_{max} (day)	6.997 (2.99, 13.99)	6.972 (3.00, 9.00)
$t_{½}$ (day)	12.271 ± 2.7885	14.016 ± 2.6715
CL/F (L/day)	0.2371 ± 0.051041	0.2209 ± 0.052987
V_z/F (L)	4.114 ± 0.99243	4.442 ± 1.2978

Source: CSR pg 49, Table 11e.

Table 49. Summary of Overall Antivedolizumab Antibody Status (Study SC-1018)

	PFS				PFS+NSD				
AVA Status	Overall N=51	Arm N=17	Abdomen N=17	Thigh N=17	Overall N=51	Arm N=17	Abdomen N=17	Thigh N=17	Total N=102
AVA Negative	22 (43)	9 (53)	6 (35)	7 (41)	24 (47)	10 (59)	9 (53)	5 (29)	46 (45)
AVA Positive	29 (57)	8 (47)	11 (65)	10 (59)	27 (53)	7 (41)	8 (47)	12 (71)	56 (55)
Transiently Positive	0 (0)	0 (0)	0 (0)	0 (0)	4 (8)	0 (0)	1 (6)	3 (18)	4 (4)
Persistently Positive	29 (57)	8 (47)	11 (65)	10 (59)	23 (45)	7 (41)	7 (41)	9 (53)	52 (51)
Neutralizing AVA Positive	25 (49)	7 (41)	9 (53)	9 (53)	24 (47)	7 (41)	7 (41)	10 (59)	49 (48)

Source: CSR p67, Table 12e.

Study SC-1021

Title

A Phase 1, Open-Label, Randomized, Parallel Group Pilot Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

Study Date

02/22/2018—08/13/2018

Study Design

This was an open-label, randomized, parallel-group, pilot study to compare the PK of a single dose of vedolizumab SC 108 mg for injection administered in 2 different device delivery presentations in healthy subjects. A minimum of 24 subjects (12 per group) were randomized to 1 of 2 device presentations (Group A or B) in a 1:1 ratio, and within each group, the subjects were randomized to injection site (abdomen, thigh, or arm) in a 1:1:1 ratio, for a total of 6 treatment combinations.

- Dose administration

  108 mg SC injection via PFS or PFS+AI administration

- Study population

  The 24 subjects were healthy male or female (nonpregnant and nonlactating) adult aged 18 to 65 years. The subject weighed >50 kg and <90 kg or had a body mass index (BMI) from 18 to 28 kg/m2.

- Investigational drug

Table 50. Investigation Drug Products in Study SC-1021

Study Drugs	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe	108 mg Solution for Injection	108 mg	SC	225630
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe in Autoinjector	108 mg Solution for Injection	108 mg	SC	225634

Source: CSR pg 23, Table 9c.

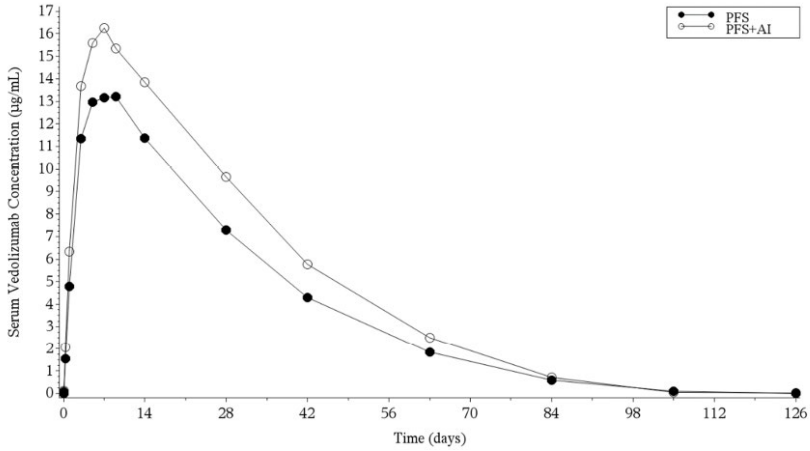
- PK and AVA sampling

  For PK analysis, blood samples for PK analyses of vedolizumab were collected beginning predose on Day 1 (within 0.5 hours before the SC injection) and then at 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10, 15, 29, 43, 64, 85, 106, and Final Visit Day 127/ET. For AVA analysis, Blood samples for determination of AVA were collected at predose on Day 1 (within 0.5 hours before dosing), Days 29, 64, 85, 106, and 127/ET postdose. AVA positive samples were further analyzed for neutralizing AVA.

- Study results

  The PK profiles are shown in Figure 13, the statistical PK comparisions between PFS and PFS+AI are summarized in Table 51, the impact of injection site on PK of vedolizumab is summarized in Table 52 and the immunogenicity results are summarized in Table 53.

Figure 13. Mean Serum Vedolizumab Concentrations-Time Profiles (Study SC-1021)



Source: CSR pg45, Figure 11a.

Table 51. Summary of Statistical PK Comparisons between PFS and PFS+AI (Study SC-1021)

	PFS+AI (Test)		PFS (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	Ratio of Geometric LSMs (%)	90% Confidence Interval (%)	Inter-subject CV%
AUC_{Week2} (µg•day/mL)	182.5	11	153.3	12	119.08	103.57 - 136.90	19.4
AUC_{last} (µg•day/mL)	562.1	11	435.0	12	129.24	107.86 - 154.86	25.3
AUC_{inf} (µg•day/mL)	594.7	11	448.0	12	132.74	111.47 - 158.07	24.4
C_{max} (µg/mL)	16.50	11	13.77	12	119.78	103.94 - 138.04	19.7

Source: CSR pg49, Table 11f.

Table 52. Effect of Injection Site on PK of Vedolizumab (Study SC-1021)

Parameter	PFS		PFS+AI
	(N=12)	Overall	(N=11)
AUC_{last} (µg•day/mL)	433.4 (38.3)		560.3 (26.3)
AUC_{inf} (µg•day/mL)	446.5 (36.2)		594.0 (23.6)
C_{max} (µg/mL)	13.70 (24.2)		16.53 (26.9)
t_{max} (day)	7.000 (2.99, 9.00)		6.999 (3.00, 9.02)
$t_{½}$ (day)	12.199 ± 2.3548		16.260 ± 2.2689
CL/F (L/day)	0.2561 ± 0.092163		0.1861 ± 0.040335
V_z/F (L)	4.345 ± 1.3028		4.316 ± 0.91100
	(N=4)	Abdomen	(N=3)
AUC_{last} (µg•day/mL)	461.6 (25.7)		612.6 (7.9)
AUC_{inf} (µg•day/mL)	469.6 (24.7)		625.2 (7.8)
C_{max} (µg/mL)	13.10 (12.6)		18.89 (15.6)
t_{max} (day)	7.000 (4.99, 8.99)		8.987 (7.01, 8.99)
$t_{½}$ (day)	12.084 ± 0.9727		14.708 ± 1.5531
CL/F (L/day)	0.2351 ± 0.055807		0.1731 ± 0.013757
V_z/F (L)	4.066 ± 0.86343		3.681 ± 0.54648
		Arm (N=4)	
AUC_{last} (µg•day/mL)	318.0 (35.1)		444.1 (14.1)
AUC_{inf} (µg•day/mL)	332.3 (31.7)		497.6 (13.1)
C_{max} (µg/mL)	11.89 (5.7)		13.42 (12.6)
t_{max} (day)	7.997 (4.99, 9.00)		6.992 (4.99, 9.02)
$t_{½}$ (day)	10.656 ± 2.8485		16.313 ± 2.8961
CL/F (L/day)	0.3365 ± 0.099757		0.2185 ± 0.028545
V_z/F (L)	5.047 ± 1.6504		5.081 ± 0.62761
		Thigh (N=4)	
AUC_{last} (µg•day/mL)	554.6 (33.8)		661.3 (29.4)
AUC_{inf} (µg•day/mL)	570.2 (31.8)		682.5 (30.4)
C_{max} (µg/mL)	16.51 (34.6)		18.43 (34.0)
t_{max} (day)	6.993 (2.99, 8.99)		5.994 (3.00, 7.00)
$t_{½}$ (day)	13.858 ± 2.0998		17.369 ± 1.7646
CL/F (L/day)	0.1966 ± 0.064401		0.1635 ± 0.047276
V_z/F (L)	3.923 ± 1.3247		4.027 ± 0.93690

Source: CSR pg48, Table 11e.

Table 53. Summary of Overall Antivedolizumab Antibody Status (Study SC-1021)

	PFS				PFS+AI				
AVA Status	Overall N=12	Abdomen N=4	Arm N=4	Thigh N=4	Overall N=12	Abdomen N=4	Arm N=4	Thigh N=4	Total N=24
Ava Negative	6 (50)	2 (50)	1 (25)	3 (75)	5 (42)	0 (0)	2 (50)	3 (75)	11 (46)
Ava Positive	6 (50)	2 (50)	3 (75)	1 (25)	7 (58)	4 (100)	2 (50)	1 (25)	13 (54)
Transiently Positive	1 (8)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Persistently Positive	5 (42)	1 (25)	3 (75)	1 (25)	7 (58)	4 (100)	2 (50)	1 (25)	12 (50)
Neutralizing Ava Positive	4 (33)	0 (0)	3 (75)	1 (25)	6 (50)	4 (100)	1 (25)	1 (25)	10 (42)

Source: CSR p63, Table 12e.

Study SC-1022

Title

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

Study Date

03/12/2018-11/13/2018

Study Design

This was an open-label, randomized, parallel-group, pilot study to compare the PK of a single dose of vedolizumab SC 108 mg for injection administered in 2 different device delivery presentations in healthy subjects. A total 204 subjects (102 per group) were enrolled in this study from 2 clinical sites.

- Dose administration

  108 mg vedolizumab SC injection via PFS or PFS+AI administration

- Study population

  The 204 subjects were healthy male or female (nonpregnant and nonlactating) adult aged 18 to 65 years. The subject weighed >50 kg and <90 kg or had a body mass index (BMI) from 18 to 28 kg/m^2.

- Investigational drug

Table 54. Investigation Drug Products in Study SC-1022

Study Drugs	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe	108 mg Solution for Injection	108 mg	SC	225631
Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC), in Prefilled Syringe in Autoinjector	108 mg Solution for Injection	108 mg	SC	225635

Source: CSR pg 24, Table 9c.

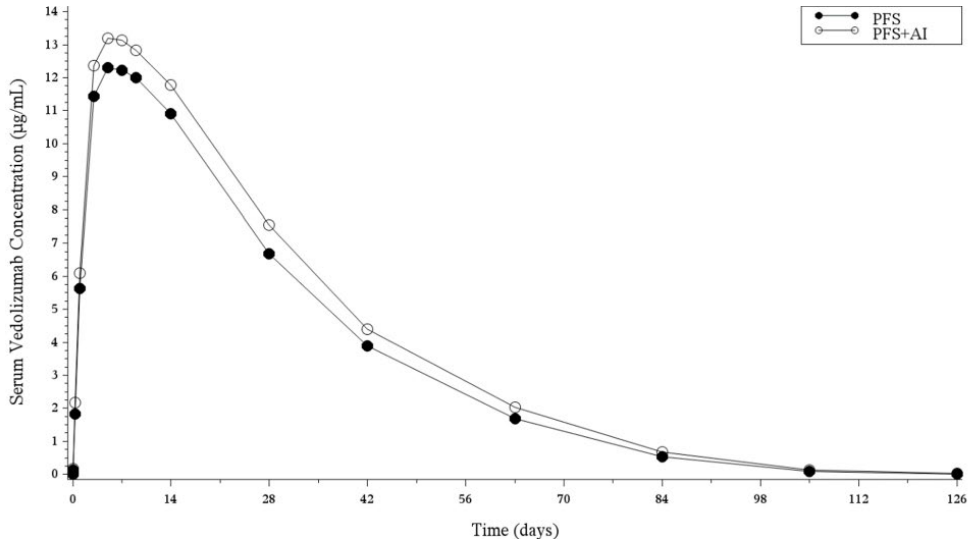
- PK and AVA sampling

  Same to the study SC-1021.

- Study results

  The PK profiles are shown in Figure 14, the statistical PK comparisions between PFS and PFS+AI are summarized in Table 55, the impact of injection site on PK of vedolizumab is summarized in Table 56 and the immunogenicity results are summarized in Table 57.

Figure 14. Mean Serum Vedolizumab Concentrations-Time Profiles (Study SC-1022)



Source: CSR pg50, Figure 11a.

Table 55. Summary of Statistical PK Comparisons Between PFS and PFS+AI (Study SC-1022)

	PFS+AI (Test)		PFS (Reference)				
Parameter	Geometric LSMs	n	Geometric LSMs	n	Ratio of Geometric LSMs (%)	90% Confidence Interval (%)	Inter-subject CV%
AUC_{last} (µg•day/mL)	441.2	97	411.0	97	107.34	99.63 - 115.65	31.9
AUC_{inf} (µg•day/mL)	465.4	96	430.0	95	108.24	101.69 - 115.21	26.3
C_{max} (µg/mL)	13.31	99	12.72	99	104.65	99.35 - 110.23	22.2

Source: CSR pg55, Table 11f.

Table 56. Effect of Injection Site on PK of Vedolizumab (Study SC-1022)

Parameter	PFS	PFS+AI
Overall		
AUC_{last} (µg•day/mL)	402.8 (38.3) [n=97]	452.3 (39.0) [n=97]
AUC_{inf} (µg•day/mL)	424.3 (35.6) [n=95]	479.8 (29.8) [n=96]
C_{max} (µg/mL)	12.60 (29.1) [n=99]	13.66 (27.6) [n=99]
t_{max} (day)	6.990 (1.00, 14.00) [n=99]	6.996 (2.98, 14.00) [n=99]
$t_{½}$ (day)	13.966 ± 3.5031 [n=96]	14.627 ± 3.5403 [n=97]
CL/F (L/day)	0.2705 ± 0.099703 [n=95]	0.2356 ± 0.081069 [n=96]
V_z/F (L)	5.166 ± 1.5752 [n=95]	4.762 ± 1.2994 [n=96]

Parameter	PFS	PFS+AI
Abdomen		
AUC_{last} (µg•day/mL)	423.2 (38.2) [n=33]	400.0 (52.6) [n=34]
AUC_{inf} (µg•day/mL)	438.1 (37.5) [n=33]	441.7 (33.4) [n=33]
C_{max} (µg/mL)	12.99 (28.4) [n=34]	13.40 (33.6) [n=34]
t_{max} (day)	6.993 (2.99, 14.00) [n=34]	6.991 (2.99, 13.99) [n=34]
$t_{½}$ (day)	14.314 ± 3.7518 [n=33]	13.548 ± 2.7865 [n=33]
CL/F (L/day)	0.2632 ± 0.10173 [n=33]	0.2590 ± 0.10370 [n=33]
V_z/F (L)	5.101 ± 1.5861 [n=33]	4.831 ± 1.2695 [n=33]
Arm		
AUC_{last} (µg•day/mL)	348.6 (41.5) [n=33]	438.2 (29.6) [n=31]
AUC_{inf} (µg•day/mL)	376.2 (37.1) [n=31]	457.7 (28.4) [n=31]
C_{max} (µg/mL)	10.96 (28.5) [n=34]	12.27 (18.7) [n=33]
t_{max} (day)	7.001 (1.00, 14.00) [n=34]	8.977 (2.99, 14.00) [n=33]
$t_{½}$ (day)	13.207 ± 3.0769 [n=31]	15.172 ± 4.7407 [n=31]
CL/F (L/day)	0.3059 ± 0.11353 [n=31]	0.2455 ± 0.074382 [n=31]
V_z/F (L)	5.505 ± 1.6204 [n=31]	5.109 ± 1.4839 [n=31]

Parameter	PFS	PFS+AI
Thigh		
AUC_{last} (µg•day/mL)	445.5 (30.2) [n=31]	531.7 (23.0) [n=32]
AUC_{inf} (µg•day/mL)	462.4 (28.9) [n=31]	547.1 (22.5) [n=32]
C_{max} (µg/mL)	14.20 (24.1) [n=31]	15.57 (23.2) [n=32]
t_{max} (day)	4.995 (2.98, 8.99) [n=31]	4.998 (2.98, 14.00) [n=32]
$t_{½}$ (day)	14.343 ± 3.6144 [n=32]	15.195 ± 2.6351 [n=33]
CL/F (L/day)	0.2430 ± 0.071330 [n=31]	0.2020 ± 0.042931 [n=32]
V_z/F (L)	4.897 ± 1.5056 [n=31]	4.356 ± 1.0413 [n=32]

Source: CSR pg52-54, Table 11e.

Table 57. Summary of Overall Antivedolizumab Antibody Status (Study SC-1022)

	PFS				PFS+AI				
AVA Status	Overall N=102	Arm N=34	Abdomen N=34	Thigh N=34	Overall N=102	Arm N=34	Abdomen N=34	Thigh N=34	Total N=204
AVA Negative	33 (32)	11 (32)	14 (41)	8 (24)	46 (45)	12 (35)	18 (53)	16 (47)	79 (39)
AVA Positive	69 (68)	23 (68)	20 (59)	26 (76)	56 (55)	22 (65)	16 (47)	18 (53)	125 (61)
Transiently Positive	8 (8)	1 (3)	3 (9)	4 (12)	6 (6)	4 (12)	1 (3)	1 (3)	14 (7)
Persistently Positive	61 (60)	22 (65)	17 (50)	22 (65)	50 (49)	18 (53)	15 (44)	17 (50)	111 (54)
Neutralizing AVA Positive	51 (50)	18 (53)	13 (38)	20 (59)	46 (45)	19 (56)	14 (41)	13 (38)	97 (48)

Source: CSR p63, Table 12e.

15.3.3. Applicant's Population Pharmacokinetics Analysis

Objectives:

To describe the PK for intravenous (IV) and subcutaneous (SC) vedolizumab in adults with inflammatory bowel disease (IBD), and quantify the effects of individual-specific covariate factors as predictors of interindividual variability in vedolizumab PK.

Results: Vedolizumab pharmacokinetic data from four clinical Phase III studies were included in the analysis (Table 58). The vedolizumab PK data set was comprised of 2085 subjects contributing a total of 18171 observations for the analysis. There were 1167 below the limit of quantification (BLQ) observations that occurred after the first dose (6% of total post-first dose observations). The breakdown of PK data by administration route was: analyzed PK concentrations (IV=16801, SC=1370), post-first dose BLQ (IV=1149, SC=18). The study population consisted of 1097 (53%) males and 988 (47%) females, with body weights ranging from 28.0–172 kg (median=68.6 kg), albumin ranging from 1.40–5.30 g/dL (median=3.80 g/dL), and ages ranging from 17.7–77.7 years (median=36.2 years). The distribution of IBD was 1119 subjects (54%) with UC and 966 subjects (46%) with CD. There were 1899 subjects (91%) with observed AVA titers that were all negative (AVASUB=negative) and 186 subjects (8.9%) with at least one observed positive AVA titer (AVASUB=positive). The distribution of races in the population was: 1788 White (86%), 241 Asian (12%), 33 Black (1.6%), 12 Other (0.6%), 8 American Indian or Alaskan Native (0.4%), and 3 Native Hawaiian or Other Pacific Islander (0.1%).

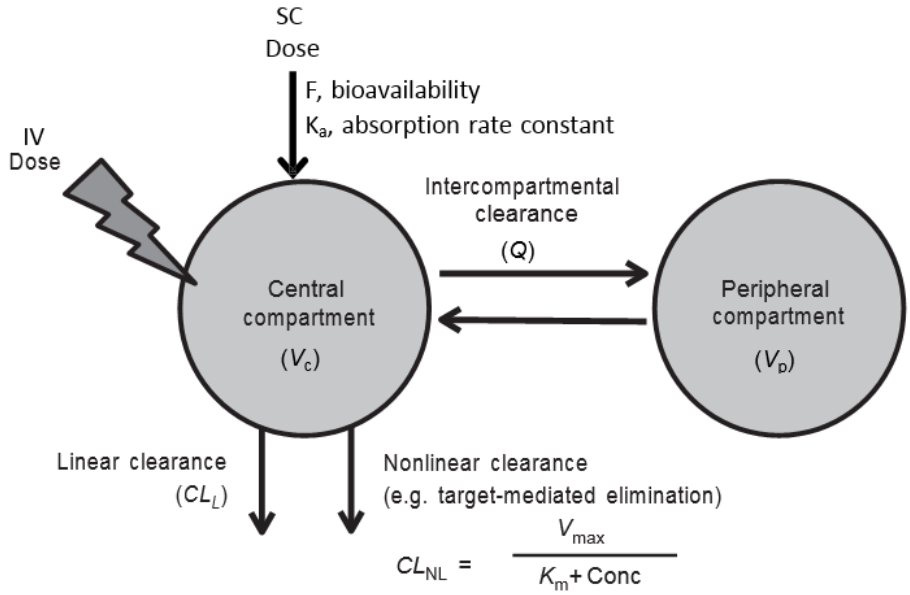
Vedolizumab PK was best described by a two-compartment model with zero order (IV infusion) and first order (SC) input and parallel linear and nonlinear elimination pathways (Figure 15). Interindividual variability was estimated for CLL, Vc, Vp, and Ka, while inter-occasion variability (IOV) was modeled on CLL. Residual random effects were described with a proportional error model. Informative priors were defined for the fixed-effect parameters Vmax, Km, Vp, Q, Ka, and F, and for the interindividual random-effect parameter on Ka. Uninformative (vague) priors were defined for the remaining fixed-effect parameters (structural PK parameters and covariate coefficients) and interindividual random-effect parameters in the model. Parameter estimates for the final model are presented in Table 59.

Table 58. Summary of Vedolizumab PK Data by Study

Study	Number of Subjects†	Analyzed PK Concentrations*	Post-First Dose BLQ Concentrations*
All studies	2085	18171 (94%)	1167 (6%)
SC-3027	375	2048 (90%)	218 (10%)
SC-3030	236	523 (93%)	39 (7%)
C13006	743	6984 (95%)	382 (5%)
C13007	966	8616 (94%)	528 (6%)

*Data presented as counts (percent of total PK concentrations by row).
Source:Applicant's population pharmacokinetics report, Table 2
Note: The low limit of quantification (LLOQ) was 125 ng/mL

Figure 15. Diagrammatic Representation of the Final Population PK Model



Source: Applicant's population pharmacokinetics report, Figure 13

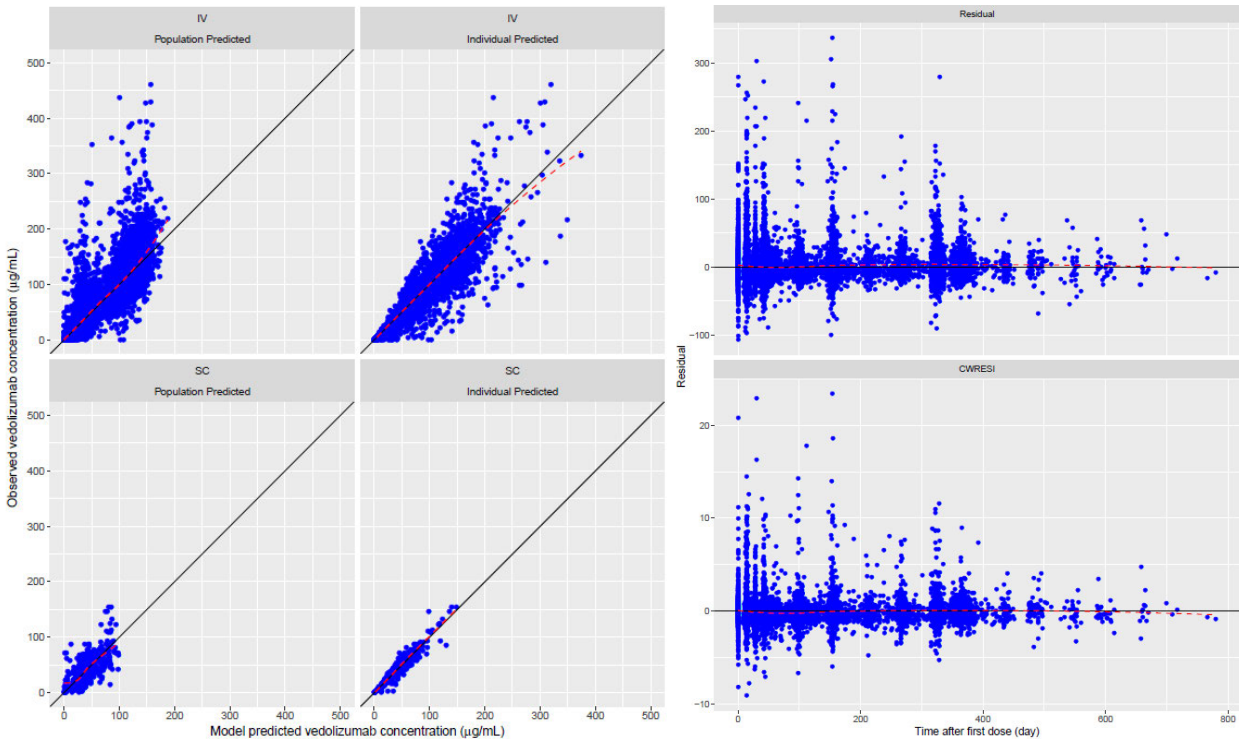
Goodness-of-fit plots are shown in Figure 16. The final population PK model was also evaluated using a posterior predictive check and visual inspection of computed normalized prediction distribution errors (NPDE).

Table 59. Final Population PK Model Parameter Estimates

Parameter	Estimate*	Bayesian 95% CDI*
AVA - CL_L (L/day)	0.169	(0.164, 0.174)
AVA + CL_L (L/day)	0.254	(0.229, 0.281)
V_c (L)	3.16	(3.09, 3.22)
V_p (L)	1.82	(1.66, 1.98)
V_{max} (mg/day)	0.211	(0.170, 0.262)
Q (L/day)	0.163	(0.150, 0.181)
K_m (µg/mL)	0.859	(0.646, 1.13)
CL_L ~ WT	0.471	(0.406, 0.531)
V_c ~ WT	0.478	(0.435, 0.521)
V_p ~ WT	1.00 Fixed	
V_{max} ~ WT	0.750 Fixed	
Q ~ WT	0.750 Fixed	
F	0.793	(0.767, 0.821)
k_a (day^{-1})	0.169	(0.111, 0.261)
CL_L ~ ALB	-1.19	(-1.29, -1.11)
CL_L ~ AVA+	0.0756	(0.0464, 0.104)
CL_L ~ Race: Asian	1.02	(0.982, 1.06)
CL_L ~ Diagnosis: CD	0.968	(0.943, 0.993)
k_a ~ Site: Thigh	0.510	(0.299, 0.882)
k_a ~ Site: Arm	0.416	(0.201, 0.921)
IIV CL_L ($\omega^2_{CL_L}$)	0.0921 (%CV = 31.1)	(0.0847, 0.100)
COV_{CL_L-Vc}	0.0357 (CORR = 0.587)	(0.0314, 0.0403)
IIV V_c (ω^2_{Vc})	0.0401 (%CV = 20.2)	(0.0362, 0.0444)
COV_{CL_L-Vp}	-0.00734 (CORR = -0.0368)	(-0.0226, 0.00739)
COV_{Vc-Vp}	0.0456 (CORR = 0.347)	(0.0325, 0.0587)
IIV V_p (ω^2_{Vp})	0.431 (%CV = 73.4)	(0.349, 0.526)
IIV k_a ($\omega^2_{k_a}$)	0.193 (%CV = 46.1)	(0.0654, 0.862)
IIV V_{max} ($\omega^2_{V_{max}}$)	0.00 Fixed	
IIV Q (ω^2_Q)	0.00 Fixed	
IIV k_m (ω^2_{km})	0.00 Fixed	
IOV CL_L ($\omega^2_{IOV\ CL_L}$)	0.0444 (%CV = 21.3)	(0.0372, 0.0533)
Res_{prop} (σ^2_{prop})	0.0319 (%CV = 17.9)	(0.0303, 0.0337)

Source: Applicant's population pharmacokinetics report, Table 8

Figure 16. Left: Observed Versus Model Predicted Vedolizumab Concentration for Final Population PK Model: Stratified by Route of Administration; Right: Residuals Versus Time After the First Dose

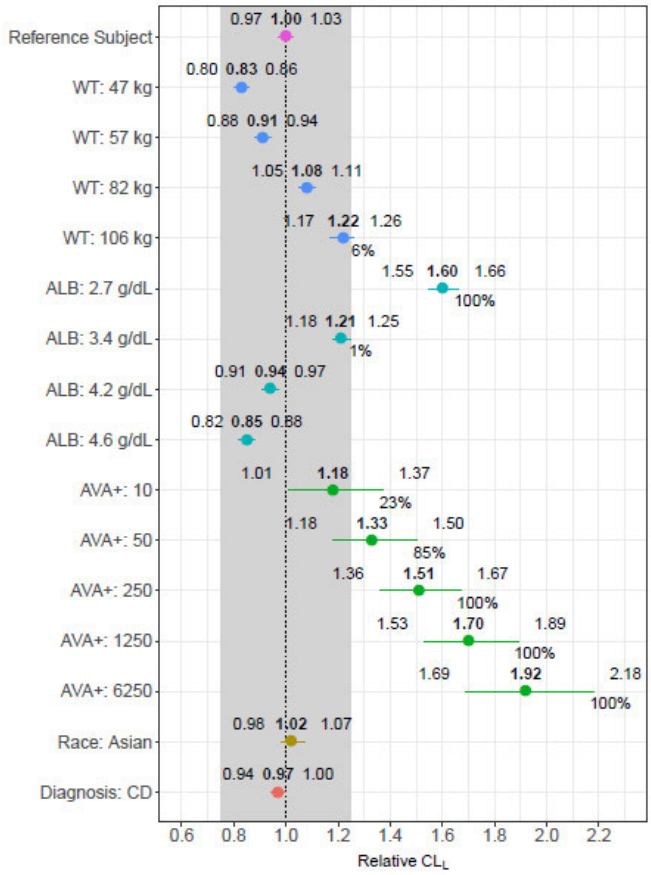


Source: Applicant's population pharmacokinetics report, Figure 14 and Figure 20

A full covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. The primary covariates of interest for the full covariate model were defined a priori. They included: body weight as a predictor of CLL, Vc, Vp, Q, and Vmax ; serum albumin as a predictor of CLL; AVA as a predictor of CLL; race (Asian vs. Non-Asian) as a predictor of CLL; IBD diagnosis (UC vs. CD) as a predictor of CLL; and injection site (abdomen, thigh, upper arm) as a predictor of Ka and F. All covariates (with the exception of race and IBD diagnosis) were time-varying.

Covariate effects on CLL were of primary interest and were evaluated via simulation using the joint posterior probability distribution of parameter samples from the Bayesian MCMC chain (Figure 17). Results from the final model indicated that body weight, albumin, and AVA were the most influential covariates, while the effects of race (Asian vs. Non-Asian) and IBD diagnosis (UC vs.CD) are unlikely to result in a clinically meaningful change in vedolizumab CLL. Based on the chosen ±25% limits, extreme values of body weight (e.g., 106 kg) and albumin (e.g., 2.7 g/dL) and a positive AVA titer (≥10) were identified as potentially clinically important predictors of CLL.

Figure 17, Covariate Effects on Vedolizumab CLL



Note: CLL relative to the typical reference subject (body weight = 70 kg, albumin = 4 g/dL, race = non-Asian, AVA = negative (titer <10), diagnosis = UC) is plotted by covariate value. Covariates were fixed to the reference values except when they were the subject of perturbation. Body weight and albumin were evaluated at the observed 5th, 25th, 75th, and 95th percentiles in the data set. Positive AVA was evaluated at titer values with the highest incidence in the data set. The closed circle represents the effect for that covariate at the median covariate parameter estimate derived from the Bayesian posterior probability distribution. The horizontal line represents the evaluation of the effect at the extremes of the posterior derived 95% CDI for that covariate parameter estimate. Median and 95% CDI values for the covariate effect are shown above the distribution. The number below the distribution denotes the percent of the distribution outside the shaded grey area. The vertical dashed line at x = 1 represents the typical reference subject, and the grey shaded region represents a parameter change of ±25% from the reference value of 1 (null effect).
Source: Applicant's population pharmacokinetics report, Figure 29

***Reviewer's Comments*:** *The goodness-of-fit plots and the visual predictive check indicate that the final population PK model is generally adequate for characterizing the PK profile of vedolizumab SC regimen in subjects with UC. As such, it is acceptable for PK simulation and generating exposure metrics (i.e. average and trough concentrations at steady state) for exposure-response analyses.*

The covariate analysis indicated that extreme values of body weight, serum albumin and a positive AVA titer (≥10) would result in potentially clinically meaningful changes in vedolizumab clearance. However, no dose adjustment based on these covariates was proposed.

15.3.4. Applicant's Exposure-Response Analysis

Objective: To characterize vedolizumab ER for Clinical Remission and Mucosal Healing at week 52 for both the IV and SC presentations

Methods:

Study 3027 (MLN0002SC-3027) data was used for the analysis. Exposure metrics included observed week 46 trough concentration (observed Ctroughss), model-predicted minimum concentration in the steady state dosing interval (model-predicted Ctroughss), and model-predicted average concentration during a steady-state dosing interval (model-predicted Cavgss). Individual, clinical and demographic covariate factors included in the analysis data set were: albumin (g/L), prior TNF-α experience (naive or failure), baseline endoscopic scores (moderate disease or severe disease), and baseline rectal bleeding scores (a score of 0 or 1, or a score of 2 or 3 at baseline).

Quartile analyses and logistic regression:

Exploratory analyses of ER were performed both within arm and on the combined set of exposures. These exploratory analyses were followed by use of logistic regression models to describe ER of combined exposure while adjusting for the set of clinical and demographic covariate factors.

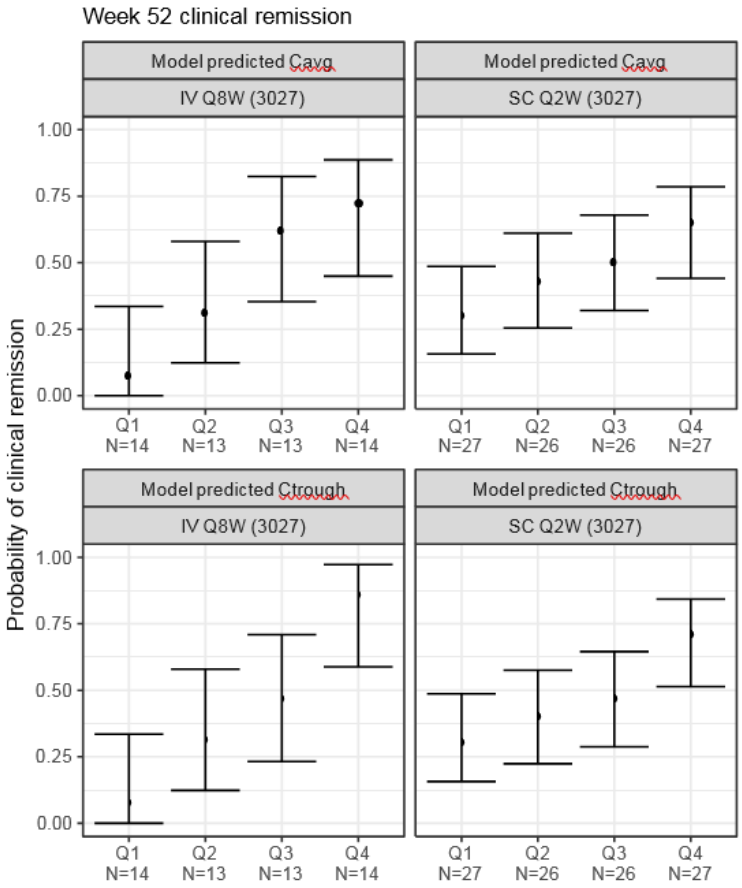
Results

Quartile analyses

To investigate ER within each arm, exposure quartiles were calculated within arm and were related to probability of week 52 clinical remission; Figure 18 shows a positive ER trend for each exposure metric within each arm. Similarly, the rate of week 52 mucosal healing per within-arm quartile of exposure is shown in Figure 19.

For week 52 clinical remission, quartile-matched response appeared similar between the IV and SC presentations with possible indication that low exposure IV (quartile 1, calculated within arm) performed worse than low exposure SC patients . Observed placebo clinical remission was 14.3% [7.2%, 26.0%] (mean, [95% CI]). Based upon quartiles of model-predicted Cavgss within the IV q8w arm, week 52 clinical remission increased from 7.14% [0.00%, 33.5%] to 71.4% [45.0%, 88.7%] while the SC q2w week 52 clinical remission, within quartiles of the SC q2w arm, increased from 29.6% [15.7%, 48.7%] to 63.0% [44.2%, 78.5%]. Likewise, when using model-predicted Ctroughss, IV q8w patient week 52 clinical remission increased from 7.1% [0.00%, 33.5%] to 85.7% [58.8%, 97.2%], while SC q2w clinical remission increased from 29.6% [15.7%, 48.7%] to 70.4% [51.3%, 84.3%].

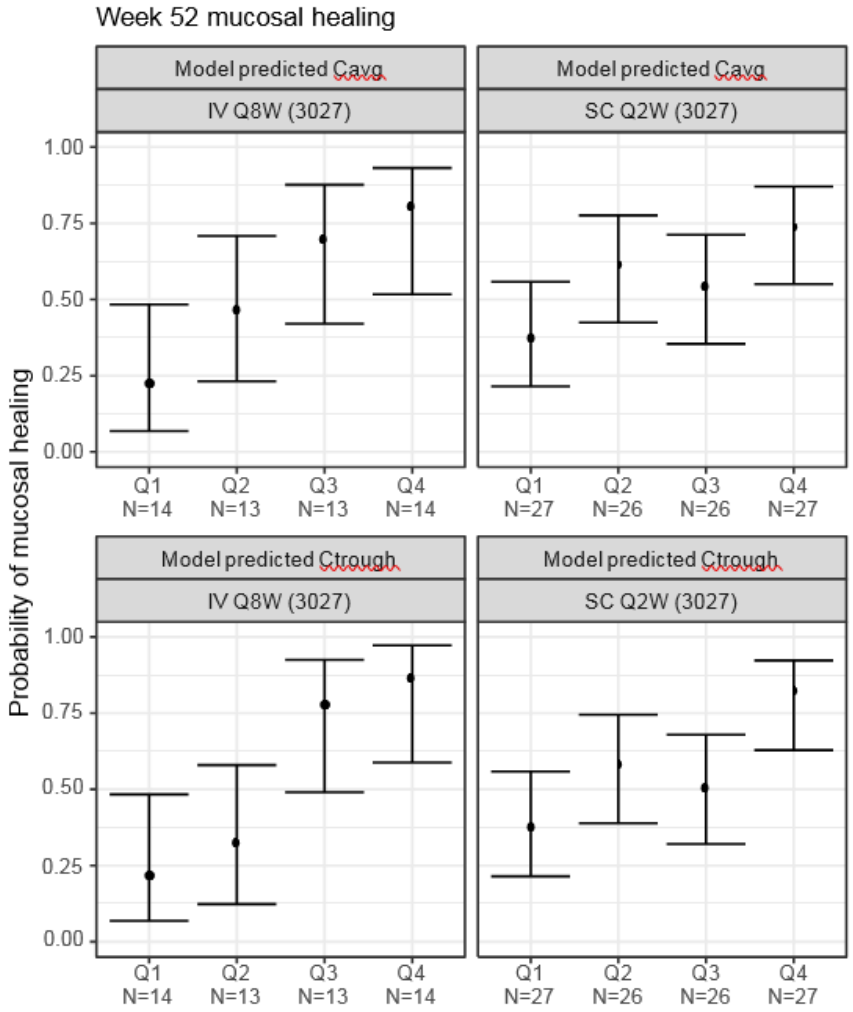
Figure 18. Probability of Week 52 Clinical Remission by Arm and Exposure (Model-Predicted $Cavg_{ss}$ and Model-Predicted $Ctrough_{ss}$)*



*Observed rates of response with 95% error bars are shown by quartile of exposure within arm.
Source: Applicant's exposure-response report, Figure 6

Week 52 mucosal healing trends were again similar between presentations with a general increase from low response for patients with low within-arm exposure to a high response rate of over 75% for patients with high within-arm exposure. Observed placebo mucosal healing was 21.4% [12.6%, 34.0%]. When using quartiles of model-predicted Cavgss calculated within the IV q8w arm, week 52 mucosal healing increased from 21.4% [6.8%, 48.3%] to 78.6% [51.7%, 93.2%] while for the SC q2w arm (when using quartiles calculated within the SC q2w arm) patient mucosal healing rates increased from 37.0% [21.5%, 55.8%] to 74.1% [55.1%, 87.1%]. When using quartiles of within-arm model-predicted Ctroughss, mucosal healing increased from 21.4% [6.84%, 48.3%] to 85.7% [58.8%, 97.2%] in the IV q8w arm and from 37.0% [21.5%, 55.8%] to 81.5% [62.8%, 92.3%] in the SC q2w arm.

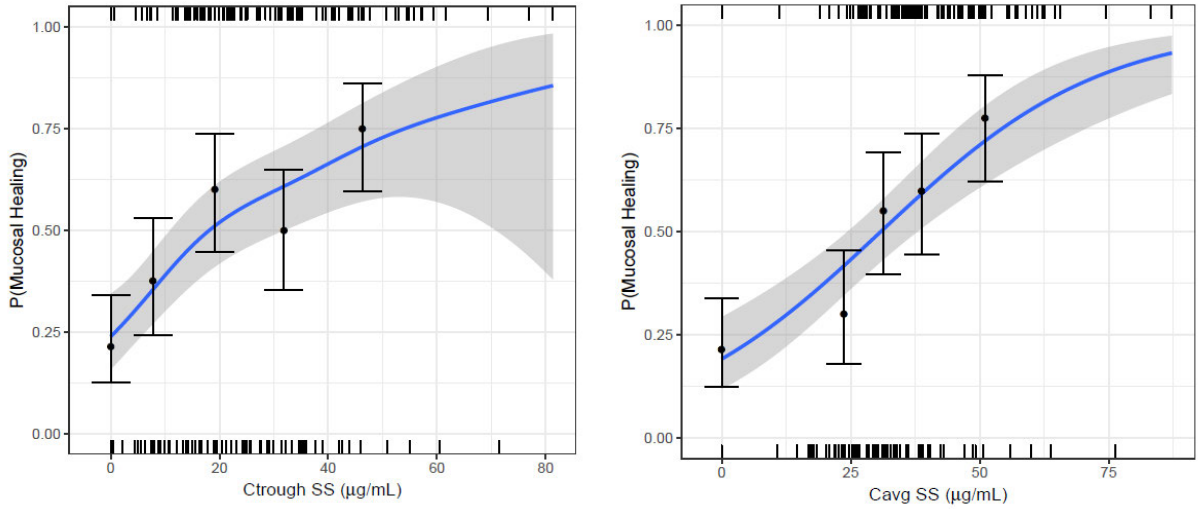
Figure 19. Probability of Week 52 Mucosal Healing by Arm and Exposure (Model-Predicted $Cavg_{ss}$, Model-Predicted $Ctrough_{ss}$, and Observed $Ctrough_{ss}$)*



*Observed probability of response with 95% error bars are shown by quartile of exposure
Source: Applicant's exposure-response report, Figure 7

To describe the ER over the continuous range of studied exposure in Study 3027, model-predicted Cavgss and model-predicted Troughss from the SC and IV arm in the maintenance phase were each combined, the combined quartiles of exposure were calculated per exposure metric, and patients were categorized according to the combined exposure quartiles. Figure 1 and Figure 20 show the ER trend for both week 52 clinical remission and week 52 mucosal healing. When using combined model-predicted Cavgss, a monotonically increasing rate of response is seen in increasing exposure. Use of model-predicted Troughss, on the other hand, shows increasing response from quartile 1 to 2 of the combined model-predicted Troughss, a decrease from quartile 2 to 3, and then again increasing response from quartile 3 to 4.

Figure 20.Probability of Week 52 Mucosal Healing for All Patients Randomized to the Maintenance Phase (i.e., Combined Placebo, IV Q8w, and SC Q2w Arms) by Model-Predicted $Ctrough_{ss}$ and Model-Predicted $Cavg_{ss}$*



* Observed rates of response with 95% error bars are shown by quartile of combined exposure; a gam smooth and its 95% ci shown with the blue line and grey shaded area
Source: Applicant's exposure-response report, Figure 9

Logistic Regression

To assess ER of the week 52 endpoints while adjusting for other clinically relevant covariates, logistic regression was used to relate the two week 52 endpoints to the model-predicted steady-state exposure metrics. A base model adjusting only for exposure was evaluated to assess functional form for inclusion of exposure. Residual diagnostics and goodness-of-fit criteria such as examination of the residuals against exposure and Akaike information criterion (AIC) were used to select the best functional form relating exposure to the endpoint. A full model was then fit by including parameters to capture the effect of baseline endoscopic scores, baseline rectal bleeding scores, baseline albumin levels, and prior TNF- experience. Finally, an interaction model was fit that included parameters to capture the interaction among treatment, exposure, and the prognostic covariates.

Week 52 clinical remission

ER was significantly increasing across all models, and the slope of ER on the log-odds of clinical remission changed little from the base model (2.19 [1.14, 3.24], mean and 95% CI) to the covariate adjusted models (2.02 [0.90, 3.14]). Parameter estimates for the covariates included: a positive effect of albumin (lower baseline albumin is associated with reduced probability of clinical remission), a negative effect of having prior TNF- failure (as opposed to naive) with patients with prior failure having odds of clinical remission 0.43 (0.21, 0.87) times those of patients who are TNF- naive, and no significant effect of baseline endoscopic scores or baseline rectal bleeding scores.

Predictions from the model-predicted Cavgss full model at covariate settings of interest (i.e., significant covariates) are shown in Table 60. Significant ER is estimated in all groupings (i.e., within groups of prior TNF- use, and across albumin levels), as seen by non-overlap of Q4 and Q1 exposure. Higher response is predicted for patients who are TNF- naive, but the confidence intervals generally overlap with TNF- failures. Despite significance of the model parameter, no clinical difference exists between the first, second, and third quartiles of albumin.

Table 60. Predicted Mean Rate of Clinical Remission (Mean, 95% CI) From the Full Model Using Log-Linear Exposure (Model-Predicted $Cavg_{ss}$ µg/mL)

Prior TNF	Albumin	Q1 (13.7 µg/mL)	Q2 (31.5 µg/mL)	Q3 (40.0 µg/mL)	Q4 (65.8 µg/mL)
Naive	Albumin (Q1)	11.3 (3.07, 33.8)	40.6 (23.1, 60.9)	52.6 (33.1, 71.3)	75.2 (51.9, 89.5)
Naive	Albumin (med)	15.5 (4.60, 41.2)	49.7 (32.1, 67.4)	61.6 (43.9, 76.7)	81.4 (62.5, 92.0)
Naive	Albumin (Q3)	19.0 (5.81, 47.3)	55.8 (37.7, 72.5)	67.2 (50.0, 80.8)	84.9 (68.1, 93.7)
Failure	Albumin (Q1)	5.19 (1.24, 19.3)	22.7 (10.3, 42.9)	32.3 (16.0, 54.4)	56.6 (30.1, 79.8)
Failure	Albumin (med)	7.34 (1.86, 24.8)	29.9 (15.2, 50.3)	40.8 (22.9, 61.6)	65.4 (39.8, 84.4)
Failure	Albumin (Q3)	9.19 (2.36, 29.7)	35.2 (18.6, 56.5)	46.9 (27.5, 67.3)	70.7 (45.7, 87.4)

Note: Predictions are made for prior TNF-α naive and failures, the 25th, 50th, and 75th percentiles of albumin (corresponding to 40, 43, and 45 g/L), and the median of the four bins of exposure by quartile (model-predicted $Cavg_{SS}$ of 13.7, 31.5, 40.0, and 65.8 µg/mL). Baseline rectal score and baseline endoscopy were not significant in the model and are fixed to a score of 0 or 1 for baseline rectal score, and moderate disease for baseline endoscopy.
S**ource:** Applicant's exposure-response report, Table 11.

Week 52 mucosal healing

Predictions from the interaction model of model-predicted Cavgss at covariate settings of inter est are shown in Table 61. Significant ER is seen only for patients who are prior TNF-failures, as seen by non-overlap of Q4 and Q1 exposure for those patients. Patients who were prior TNF-α naive had consistent mucosal healing rates across increasing exposure and were higher than those of the TNF-α failures up to model-predicted Cavgss of about 40 µg/mL. At exposures higher than about 40 µg/mL, efficacy was similar between prior TNF-α experiences. For patients at median albumin levels and who were TNF-α naive, the probability of week 52 mucosal healing increased from 43.3% [15.3%, 77.8%] at 13.7 µg/mL (the median model-predicted Cavgss in quartile 1) to 81.1% [58.7%, 92.8%] for patients at 65.8 µg/mL, representative of quartile 4 model-predicted Cavgss exposure Likewise, for patients at median albumin levels who had moderate baseline endoscopic scores and who had experienced prior TNF-α failure, the probability of week 52 mucosal healing increased from 9.21% [1.65%, 37.9%] to 90.6% [68.2%, 97.7%] (Table 61).

Table 61. Predicted Mean Rate of Week 52 Mucosal Healing (Mean, 95% CI) From the Interaction Model Using Loglinear Exposure (Model-Predicted $Cavg_{ss}$ µg/mL)

Prior TNF	Albumin	Q1 (13.7 µg/mL)	Q2 (31.5 µg/mL)	Q3 (40.0 µg/mL)	Q4 (65.8 µg/mL)
Naive	Albumin (Q1)	39.4 (12.6, 74.7)	61.4 (41.5, 78.1)	67.3 (47.7, 82.3)	77.8 (52.3, 91.8)
Naive	Albumin (med)	44.3 (15.3, 77.8)	66.1 (48.3, 80.2)	71.6 (54.7, 84.0)	81.1 (58.7, 92.8)
Naive	Albumin (Q3)	47.7 (17.1, 80.1)	69.0 (51.6, 82.3)	74.2 (58.0, 85.7)	83.1 (62.1, 93.6)
Failure	Albumin (Q1)	7.66 (1.35, 33.4)	48.1 (27.0, 69.9)	65.0 (40.9, 83.3)	88.7 (62.5, 97.4)
Failure	Albumin (med)	9.21 (1.65, 37.9)	53.2 (32.2, 73.0)	69.4 (47.3, 85.2)	90.6 (68.2, 97.7)
Failure	Albumin (Q3)	10.4 (1.85, 41.6)	56.5 (35.0, 75.8)	72.2 (50.5, 86.8)	91.7 (71.2, 98.0)

Note: Predictions are made for prior TNF-α naive and failures, albumin levels of 40, 43, and 45 g/L, and the median of the four bins of exposure by quartile (model-predicted $Cavg_{SS}$ of 13.7, 31.5, 40.0, and 65.8 µg/mL). Baseline rectal score and baseline albumin were not significant in the model and are fixed to a score of 0 or 1 for baseline rectal score, and median albumin levels (43 g/L).
Source: Applicant's exposure-response report, Table 15

Exploratory analyses of confounding and drug effect in low exposure

Patients with prior TNF-α failures and patients with more severe disease at baseline were identified as having a higher propensity to fall in the lowest exposure quartile. Notwithstanding the potential confounding in the estimation of the ER relationships, this analysis suggests that the efficacy profile of the SC presentation in patients with a propensity toward low exposure similar the IV presentation.

Reviewer's Comments: *The Applicant's E-R analyses for SC presentation were based on the exposure and efficacy data of Study SC3027 at one dose level. Lower albumin level appeared to be associated with lower efficacy. The impact of body weight on efficacy was not discussed despite significant effect identified on PK. In addition, as the Applicant also noted, interpretation of the exposure-efficacy relationships should take caution due to potential confounding factors that have not been identified.*

15.3.5. Reviewer's Analysis

Background:

- Body weight was identified as one of potential clinically significant baseline covariates for vedolizumab clearance, however, the effect of body weight on clinical remission was not clear.
- Following the Applicant's proposed IV-to-SC switching time (at the next scheduled IV dosing date), it would take >10 weeks to re-achieve vedolizumab steady-state, if the switch happened following an IV maintenance dose (Figure 3). This is not consistent with what was evaluated in Study SC3027, where the first SC dose was given 4 weeks after the 2nd IV induction dose and vedolizumab concentrations reached steady-state immediately after.

Objectives:

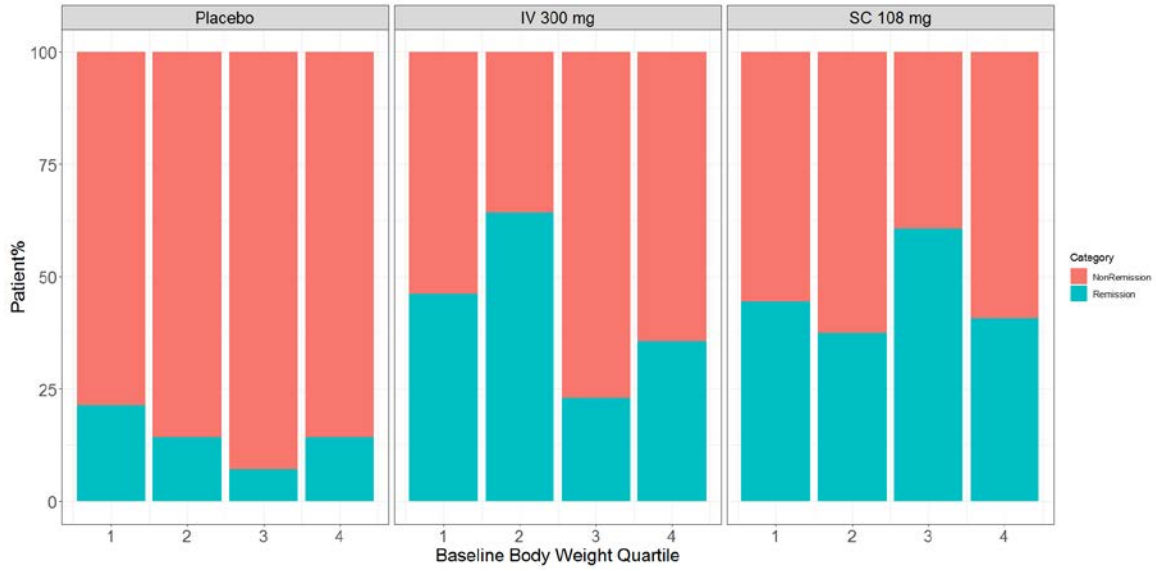
- To explore the effect of body weight on clinical remission in Study SC3027;
- To identify an IV-to-SC switching time that vedolizumab concentrations can be maintained at the steady-state following the switch.

Methods: Remission data at Week 52 and covariate data of Study SC3027 were used to generate graphics to visualize the effect of the body weight on the primary efficacy endpoint. The Applicant's final population PK model was used to simulate the PK profiles for different IV-to-SC switching scenarios. NONMEM v7.3 and R was used for simulation and graphic generation.

Results and Discussion

Quartile analysis showed no apparent relationship between clinical remission rate and baseline body weight in the vedolizumab SC arm (Figure 21). As such, adjusting vedolizumab SC dose based on body weight may not be needed.

Figure 21. Clinical Remission at Week 52 by Baseline Body Weight in Study SC-3027

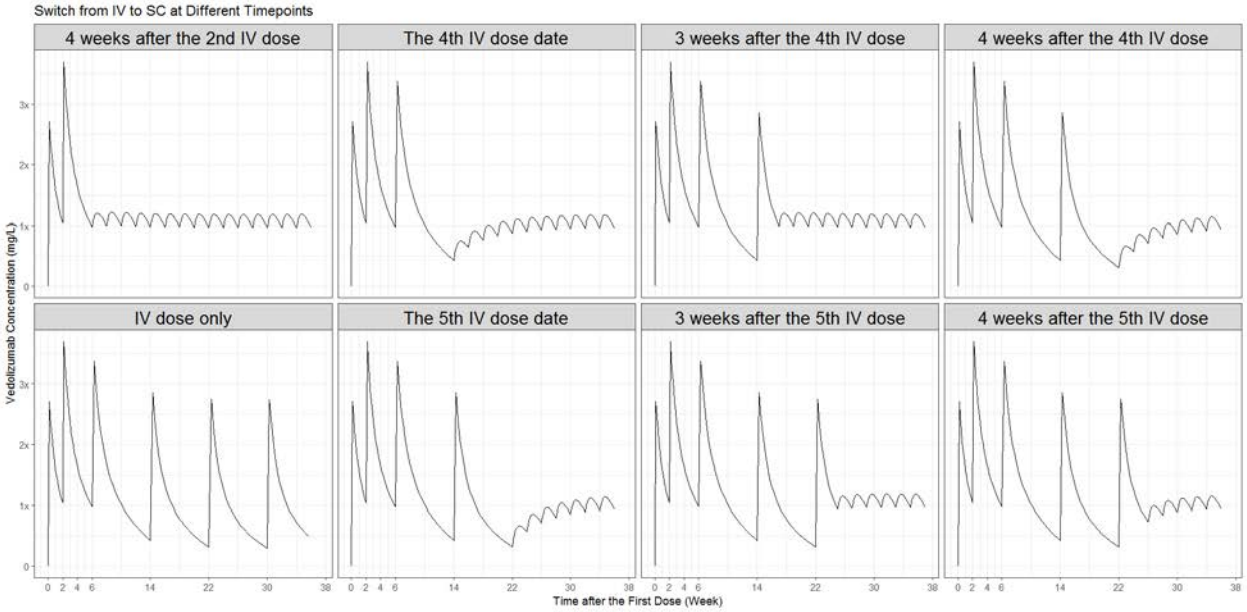


Source: Reviewer's analysis using remission data from the statistics reviewer

The simulated vedolizumab PK profile under different example IV-to-SC switching scenarios are shown in Figure 22. The Applicant's proposed switching time (Panel 2 and Panel 6) is not consistent with what was implemented in Study SC3027 (Panel 1) and would delay the re-achievement of steady-state for more than 10 weeks, which may lead to temporatry loss of efficacy. Based on the simulation results, initiating SC regimen 3 weeks following an IV maintenance dose (Panels 3 and 7) would allow vedolizumab concentrations to reaches steady-state immediately after.

Therefore, initiating the SC regimen 3-4 weeks after the last IV dose, following at least two IV infusions could be a better dosing option for patients with UC.

Figure 22. Simulated Vedolizumab PK Profiles Under Different IV-to-SC Switching Scenarios



Source: Reviewer's simulation based on Applicant's final population PK model

NDA/BLA Multidisciplinary Review and Evaluation BLA761133
Entyvio SC (vedolizumab SC)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Jie Cheng, Ph.D.	OTS/OCP/DIIP	Section 6 Appendix 15.4	**Select one:** _X_ Authored ___ Approved
	Signature: Jie Cheng -S (Affiliate) Digitally signed by Jie Cheng -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013573366, cn=Jie Cheng -S (Affiliate) Date: 2019.12.13 16:07:06 -05'00'			
Clinical Pharmacology Secondary Reviewer	Anand Balakrishnan, Ph.D.	OTS/OCP/DIIP	Section 6 Appendix 15.4	**Select one:** _X_ Authored _X_ Approved
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Clinical Pharmacology Team Leader	Jie (Jack) Wang, Ph.D.	OTS/OCP/DTPM	Section 6 Appendix 15.4	**Select one:** ___ Authored _X_ Approved
	Signature Jie Wang -S Digitally signed by Jie Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jie Wang -S, 0.9.2342.19200300.100.1.1=2000739081 Date: 2019.12.13 16:17:07 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Hongshan Li, Ph.D.	OTS/OCP/DPM	Section 6 Appendix 15.4	**Select one:** _X_ Authored ___ Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hongshan Li -S, 0.9.2342.19200300.100.1.1=2001098258 Date: 2019.12.16 14:48:52 -05'00'			

Pharmacometrics Team Leader	Lian Ma, Ph.D.	OTS/OCP/DPM	Section 6 Appendix 15.4	**Select one:** __X__ Authored __X__ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2019.12.13 16:39:54 -05'00'			

DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Pharmacologist	Tamal Chakraborti Ph.D.	ODE III/DGIEP	Section 5	**Select one:** __X_ Authored __ Approved
	Signature: Tamal K. Chakraborti -S Digitally signed by Tamal K. Chakraborti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300143215, cn=Tamal K. Chakraborti -S Date: 2019.12.13 12:37:34 -05'00'			
Supervisory Pharmacologist	Sushanta Chakder, Ph.D.	ODE III/DGIEP	Section 5	**Select one:** ___ Authored _X_ Approved
	Signature: Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144003, cn=Sushanta K. Chakder -S Date: 2019.12.13 12:52:04 -05'00'			
DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Statistical Team Reviewer	Ling Lan, Ph.D.	OB/DBIII	Sections 7 and 8.1 Appendix 15.1.4 and 15.1.5	**Select one:** __X_ Authored __ Approved
	Signature: Ling Lan -S Digitally signed by Ling Lan -S Date: 2019.12.13 11:33:22 -05'00'			
Statistical Team Leader	George Kordzakhia, Ph.D.	OB/DBIII	Section 8.1 (authored & approved) Appendix 15.1.4 and 15.1.5 (approved)	**Select one:** _X_Authored _X_ Approved

	Signature: George Kordzakhia -S Digitally signed by George Kordzakhia -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300390764, cn=George Kordzakhia -S Date: 2019.12.13 11:42:26 -05'00'			
Deputy Director	Gregory Levin, Ph.D.	OB/DBIII	Sections 1, 7, 8	**Select one:** ___ Authored _X_ Approved
	Signature: Gregory P. Levin -S Digitally signed by Gregory P. Levin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001127703, cn=Gregory P. Levin -S Date: 2019.12.13 11:48:25 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Marjorie Dannis, M.D.	ODEIII/DGIEP	1.1, 2.1, 2.2,3.1, 3.2, 8.2, 9, 10,11, 12, 13, 15.3	**Select one:** _X_ Authored Approved
	Signature: Marjorie F. Dannis -S Digitally signed by Marjorie F. Dannis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300398148, cn=Marjorie F. Dannis -S Date: 2019.12.13 18:01:49 -05'00'			
Clinical Team Leader/CDTL	Tara Altepeter, M.D.	ODEIII/DGIEP	Authored: Section 1.2 Approved: all sections	**Select one:** _X_ Authored _X_ Approved (all sections)
	Signature: Tara Altepeter -S Digitally signed by Tara Altepeter -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tara Altepeter -S, 0.9.2342.19200300.100.1.1=2001813963 Date: 2019.12.13 23:07:23 -05'00'			
Deputy Director for Safety	Joyce Korvick, M.D., MPH	ODEIII/DGIEP	Sections: All sections	**Select one:** ___ Authored _X_ Approved
	Signature: Joyce A. Korvick -S Digitally signed by Joyce A. Korvick -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300087128, cn=Joyce A. Korvick -S Date: 2019.12.15 14:43:50 -05'00'			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOYCE A KORVICK
12/17/2019 10:07:40 AM