2.7.3
SUMMARY OF CLINICAL EFFICACY

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LIST OF ABBREVIATIONS

Term	Definition
5-ASA	5-aminosalicylate
AE	adverse event
AESI	adverse event of special interest
AVA	anti-vedolizumab antibody; also called HAHA
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
EQ-5D	Euro Quality of Life-5D
FAS	full analysis set
FAS-CD	full analysis set-Crohn's disease
FAS-UC	full analysis set-ulcerative colitis
FDA	Food and Drug Administration
GALT	gut-associated lymphoid tissue
GI	gastrointestinal(ly)
HBI	Harvey-Bradshaw Index
HCP	health care provider
HRQOL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IgG1	immunoglobulin G1
ITT	intent-to-treat
IV	intravenous(ly)
LOCF	last observation carried forward
MAdCAM-1	mucosal addressin cell adhesion molecule-1
OLE	open-label extension
PGA	physician's global assessment
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
QW	once weekly
SAF	safety analysis set
SAF-C	safety analysis set-combined

SAP	statistical analysis plan
SC	subcutaneous(ly)
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
US	United States
VAS	visual analog scale
WPAI-UC	Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis

STUDY DEFINITIONS

Term	Study	Definition
Clinical remission by complete Mayo score (subjects with ulcerative colitis [UC])	SC-3027	A complete Mayo score of ≤2 points and no individual subscore >1 point
Clinical remission by partial Mayo score (subjects with UC)	SC-3027 SC-3030	A partial Mayo score of ≤2 points and no individual subscore >1 point
Clinical remission by Mayo score without physician's global assessment (PGA)	SC-3027	A Mayo score (without PGA) of ≤2 points and no individual subscore (without PGA) >1 point
Clinical remission by modified Mayo score	SC-3027	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. Stool frequency subscore = 0 or 1 and a prespecified specific change of 1 or more from baseline; rectal bleeding subscore = 0; and endoscopy subscore = 0 or 1 (modified so that a score of 1 does not include friability). 3. Either definition 1 or definition 2.
Clinical response (subjects with UC)	SC-3027 SC-3030 (based on partial Mayo score)	A reduction in complete Mayo score of ≥3 points and ≥30% from baseline (Week 0) (or partial Mayo score of ≥2 points and ≥25% from baseline, if the complete Mayo score was not performed at the visit), with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
Clinical remission (subjects with Crohn's disease [CD])	SC-3030	A Harvey-Bradshaw Index (HBI) score of ≤4 points
Clinical response (subjects with CD)	SC-3030	A ≥3-point decrease in HBI score from baseline
Corticosteroid-free remission	SC-3027	Defined as subjects using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52
Disease worsening	SC-3027	An increase in partial Mayo score ≥3 points from the Week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 6 value is >6) and a minimum partial Mayo score of ≥5 points
Durable clinical remission	SC-3027	Clinical remission at Weeks 6 and 52
Durable clinical response	SC-3027	Clinical response at Weeks 6 and 52
Mucosal healing	SC-3027	A Mayo endoscopic subscore of ≤1 point
Treatment failure	SC-3027	Defined as disease worsening, need for rescue medications, or need for surgical intervention for treatment of UC
Histological remission	SC-3027	Defined as Geboes score <2 or Robarts Histopathology Index (RHI) <3
Minimal histological response	SC-3027	Minimal histology activity per Geboes is defined as Geboes score <3.2. Minimal histology activity per RHI is defined as RHI <5.

1.0 BACKGROUND AND OVERVIEW

1.1 Introduction

Inflammatory bowel disease (IBD) comprises 2 major disorders: ulcerative colitis (UC) and Crohn's disease (CD). These disorders have both distinct and overlapping pathologic and clinical characteristics. Most patients are diagnosed in their teens and young adulthood. Morbidity is significant in both UC and CD and has a debilitating impact on the quality of life of this relatively young patient population.

UC is characterized by a continuous mucosal inflammation process, beginning in the rectum and progressing proximally to involve the colon but not the small bowel or upper gastrointestinal (GI) tract. It affects approximately 50 to 100 of every 100,000 people, corresponding to a prevalence of 150,000 to 300,000 people [1]. The predominant clinical symptoms of UC include chronic diarrhea, which is often bloody and mixed with mucus; in addition, patients often suffer from colicky abdominal pain, fecal urgency, tenesmus, and incontinence [2]. GI symptoms of active disease vary and are related to the extent of the colon affected by inflammation. In addition, patients may have systemic symptoms including fever, fatigue, and weight loss. Patients may also have dyspnea and palpitations due to anemia secondary to iron deficiency from blood loss, anemia of chronic disease, or autoimmune hemolytic anemia. Although UC primarily involves the bowel, it is associated with manifestations in other organ systems. Diagnosis of UC is based on the clinical symptoms and evidence of active inflammation of the rectum and colon on endoscopy and chronic changes on biopsy.

CD is a relapsing, remitting inflammatory disease that may involve any portion of the length of the GI tract from mouth to anus in a transmural fashion from mucosa to serosa. The prevalence of CD is approximately 150/100,000 of the United States (US) population, approximately 125/100,000 of the population in Western Europe [1,3,4], and 21.2/100,000 of the population in Japan [5]. The characteristic pathology involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration. Clinical manifestations of CD include diarrhea, abdominal pain, fecal urgency, and incontinence. Systemic features such as fever, weight loss, malaise, and fatigue are indicators of more extensive disease. The diagnosis of CD is usually made by histopathologic examination of endoscopic mucosal biopsy specimens obtained on ileocolonoscopy.

Vedolizumab intravenous (IV) (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; and MLN0002 IV) is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody composed of 2 light chains of the κ subclass and 2 IgG1 heavy chains that binds specifically to the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin is a pivotal mediator of gut immunity and inflammation due to its unique role in mediating the migration of lymphocytes into gut-associated lymphoid tissue (GALT) and lamina propria, via binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Thus, vedolizumab acts as a gut-selective immunomodulator.

Pharmacologic assessment of vedolizumab shows that it is a highly selective antagonist that binds to the gut-tropic $\alpha_4\beta_7$ integrin expressed on discrete populations of leukocytes involved in gut mucosal immunity [6]. Binding of MAdCAM-1 by $\alpha_4\beta_7$ mediates migration of leukocytes into GI mucosa and associated lymphoid tissue [7,8]. Vedolizumab specifically inhibits the activity of the $\alpha_4\beta_7$ integrin by selectively antagonizing binding and adhesion to MAdCAM-1 and to the extracellular matrix glycoprotein fibronectin, but does not antagonize binding to vascular cell adhesion molecule-1. By antagonizing both the $\alpha_4\beta_7$-MAdCAM-1 interaction and the associated migration of leukocytes into GI mucosa, vedolizumab reduces inflammation [9]. Of note, vedolizumab does not bind to α_4 or β_7 in association with other integrins, for example, $\alpha_4\beta_1$ or $\alpha_E\beta_7$.

The main pathogenic hallmark of both UC and CD is the increased expression of MAdCAM-1 on intestinal endothelial cells, which leads to gut inflammation secondary to leukocyte extravasation. Because of this common pathway in the pathogenesis of UC and CD, which involves the recruitment of circulating leukocytes through sequential engagement of the MAdCAM-1 on endothelial cells and $\alpha_4\beta_7$ integrin signaling molecules on leukocytes, vedolizumab, a gut-selective inhibitor of $\alpha_4\beta_7$ integrin, has the same mechanism of action in the treatment of both UC and CD. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to mucosa and GALT through adhesive interaction with MAdCAM-1, which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa in both conditions [6-9].

Vedolizumab intravenous (IV), a lyophilized formulation of vedolizumab intended for IV infusion, has been granted marketing approval in more than 65 countries worldwide, including the US and European Union, for the treatment of adult patients with moderately to severely active UC or CD for whom conventional treatments have failed, including immunomodulators, corticosteroids, or tumor necrosis factor-alpha (TNF-α) antagonists. The recommended dose regimen for vedolizumab IV is 300 mg administered by IV infusion at 0, 2, and 6 weeks and then every 8 weeks thereafter. In most regions, increasing the frequency of dosing to once every 4 weeks (Q4W) is indicated for those who have lost response to the once every 8 weeks (Q8W) regimen. Therapy for UC and CD patients should be discontinued if no evidence of therapeutic benefit is observed by Week 14.

The long-term safety and efficacy of vedolizumab IV were evaluated in a long-term, open-label extension study (C13008).

Vedolizumab subcutaneous (SC) (also known as Vedolizumab Injection, for Subcutaneous Use; Vedolizumab Solution for Injection in Pre-filled Syringe; or MLN0002 SC) is a new liquid formulation that has been developed for SC administration. The objective of vedolizumab SC is to allow the option for patients and health care providers (HCPs) to use either registered vedolizumab IV or the proposed vedolizumab SC as maintenance therapy after a response has been achieved with vedolizumab IV. To develop vedolizumab SC, vedolizumab IV was modified to ensure the long-term stability needed for a liquid product. No changes were made that would impact the primary structure of the protein, and comparable biochemical properties and in vitro functional activity have been demonstrated. Therefore, the nonclinical and clinical information from studies conducted with vedolizumab IV is considered applicable to vedolizumab SC.

Vedolizumab SC was developed and evaluated as maintenance treatment of adult patients with moderately to severely active UC or CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist and demonstrated therapeutic benefit with two or more doses of vedolizumab IV. The recommended dose regimen of vedolizumab SC is 108 mg administered by SC injection every 2 weeks and is supported by the efficacy data from the Phase 3 clinical program. This document summarizes the efficacy data of vedolizumab SC to treat patients with UC. Limited data for patients with CD from an ongoing open-label extension (OLE) study are available and discussed in this document (Section 2.2.3). Given the similarity between vedolizumab IV and vedolizumab SC, the known efficacy with vedolizumab IV provides supportive evidence for the efficacy of vedolizumab when administered SC. Supportive efficacy data from the vedolizumab IV program can be found in marketing applications for vedolizumab for IV infusion. High-level results from vedolizumab IV Study C13006 are presented in Section 3.1 of this module as a benchmark to compare efficacy between vedolizumab SC and vedolizumab IV.

1.2 Clinical Program Overview

Clinical safety and efficacy of vedolizumab were established as part of the vedolizumab IV clinical program. Cumulative worldwide postmarketing exposure since launch (through 19 November 2018) for vedolizumab IV was approximately 267,514 patient-years, which includes 153,491 patient-years in North/South America and 102,774 patient-years in Europe.

The vedolizumab SC clinical program was developed to provide the option of SC self-administration of vedolizumab to subjects with these diseases. The clinical program includes 3 phase 3 studies that support the efficacy and safety of vedolizumab SC in subjects with UC or CD and in 6 phase 1 [Module 2.7.2] clinical studies (conducted in healthy subjects) that are pertinent to the biopharmaceutics of vedolizumab SC. The phase 3 studies in the vedolizumab SC clinical program were designed to allow reference to the maintenance efficacy of approved vedolizumab IV.

The vedolizumab SC clinical program included the following phase 3 studies:

- Study MLN0002SC-3027 (hereafter Study SC-3027) is a completed phase 3, randomized, double-blind, placebo-controlled, 52-week study that evaluated the efficacy and safety of vedolizumab SC as maintenance therapy in 216 subjects with moderately to severely active UC (complete Mayo score of 6-12 with an endoscopic subscore ≥2) who achieved clinical response after 2 doses (at Weeks 0 and 2) of open-label vedolizumab IV therapy.
- Study MLN0002SC-3031 (hereafter Study SC-3031) is an ongoing phase 3, randomized, double-blind, placebo-controlled, 52-week study evaluating the efficacy and safety of vedolizumab SC as maintenance therapy in 409 subjects with moderately to severely active CD (Crohn's Disease Activity Index [CDAI] score of 220-450) who achieved clinical response after open-label vedolizumab IV therapy. Interim blinded safety data as of 31 July 2018 are summarized in Module 2.7.4. No efficacy data from this ongoing blinded study are included with this submission, but efficacy data for the nonrandomized Week 14 responder CD subjects from Study SC-3031 who entered the open-label, single-arm Study SC-3030 (ie,

a subset of the Study SC-3030 full analysis set Crohn's disease [FAS-CD]) are included in this module. Additional details are provided in Section 1.2.1.2.

- Study MLN0002SC-3030 (hereafter Study SC-3030) is an ongoing OLE study including eligible subjects from Studies SC-3027 (UC subject population) and SC-3031 (CD subject population). Study SC-3031 is still ongoing at the time of the interim data cut for Study SC-3031; therefore, treatment assignment for CD subjects randomized in Study SC-3031 remains blinded. Therefore, only a subset of the rollover subjects from Study SC-3031 (ie, those who completed a 14-week induction phase with vedolizumab IV and achieved a clinical response) were evaluated as subjects with CD (ie, nonrandomized Week 14 responder CD subjects). Study SC-3030 includes secondary and exploratory endpoints that contribute pertinent data for assessing the effects of long-term vedolizumab SC treatment. An interim clinical study report (CSR) for SC-3030, based on a 31 May 2018 data cutoff date, is provided with this submission and summarized within this module.

Vedolizumab SC was administered by subjects at home or under supervision in the clinic via prefilled syringe in the phase 3 studies (Studies SC-3027, SC-3030, and SC-3031).

An overview of the study design, study population, and efficacy endpoints for the phase 3 vedolizumab SC studies (SC-3027 and SC-3030) is presented in Table 1.a. Further details regarding study design, population, and results of primary, secondary, and key exploratory outcomes from Studies SC-3027 and SC-3030 are summarized in Section 2.1 and Section 2.2, respectively. Unless otherwise specified, all endpoints (primary, secondary, and exploratory) were prespecified. A comparison of key efficacy endpoints across individual studies is presented in Section 3.1. Baseline characteristics across SC studies are presented in Section 3.2.1. Subgroup analyses based on demographics, baseline characteristics, prior treatment failures, and concomitant medications are presented in Section 3.2.2.

A rationale for the recommended dose and dose regimen for licensure/marketing authorization is presented in Section 4.0.

Finally, analyses of data assessing the persistence of efficacy with vedolizumab SC are presented in Section 5.0. The durability of maintaining efficacy by vedolizumab SC treatment as assessed by the combined longitudinal analysis of SC-3027 and SC-3030 data is presented in Section 5.0. In addition, data relevant to the assessment of tolerance effects are also presented in this section.

Table 1.a Summary of Vedolizumab Efficacy Studies for UC

Study No.	Study Design, Population, and Dosing Regimen	Measures of Efficacy	Study Enrollment [a] and Completion Status
Controlled Study			
SC-3027	**Study Design:** Pivotal, phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled **Population:** Male or female subjects aged 18-80 years, with moderately to severely active UC (Mayo score of 6-12 points with an endoscopic subscore ≥2) and inadequate response to, loss of response to, or intolerance of 1 or more of the following therapies: immunomodulators, corticosteroids, or TNF-α antagonists **Dosing Regimen:** Induction phase (open-label): IV dosing, vedolizumab 300 mg at Weeks 0 and 2 Maintenance phase (blinded): • IV dosing, vedolizumab 300 mg Q8W from Week 6 through Week 46. • SC dosing, vedolizumab 108 mg Q2W from Week 6 through Week 50. • Placebo IV Q8W or SC Q2W from Week 6 through Week 46 or 50.	**Primary Endpoint:** • Clinical remission at 52 weeks. [b] **Secondary Endpoints:** • Mucosal healing at 52 weeks. [c] • Durable clinical response. [d,e] • Durable clinical remission. [f] • Corticosteroid-free remission. [g]	VDZ SC = 106 VDZ IV = 54 Placebo = 56 Completed

Footnotes on last table page.

Table 1.a Summary of Vedolizumab Efficacy Studies for UC (continued)

Study No.	Study Design, Population, and Dosing Regimen	Measures of Efficacy	Study Enrollment [a] and Completion Status
Other Pertinent Study With Efficacy Data			
SC-3030 (data as of 31 May 2018)	**Study Design:** Phase 3b, long-term, open-label extension, safety study with secondary and key exploratory efficacy endpoints **Population:** Male or female subjects aged 18-80 years subjects with active UC or CD, who participated in Study SC-3027 or Study SC-3031 **Dosing Regimen:** SC dosing, vedolizumab 108 mg QW or Q2W for up to 5 years	**Secondary Efficacy Endpoints:** [b] • Clinical response during long-term vedolizumab SC treatment. [i] • Clinical remission during long-term vedolizumab SC treatment. [j] **Key Exploratory Endpoints:** [k] • Changes from baseline in IBDQ, EQ-5D, and WPAI-UC scores. • Time to major UC- and CD-related events (hospitalizations, bowel surgeries, and procedures). • Proportion of subjects with reduction in corticosteroid use.	VDZ SC = 598 (287 subjects with UC; 311 subjects with CD) Ongoing

Source: SC-3027 Table 15.1.5.2 and SC-3030 Table 15.1.3.
CD: Crohn's disease; EQ-5D: Euro Quality of Life-5D; HBI: Harvey-Bradshaw Index; IBDQ: Inflammatory Bowel Disease Questionnaire; IV: intravenous; Q2W: once every 2 weeks; Q8W: once every 8 weeks; SC: subcutaneous; TNF-α: tumor necrosis factor alpha; UC: ulcerative colitis; VDZ: vedolizumab; WPAI: Work Productivity and Activity Impairment-UC Questionnaire.
[a] Enrollment at Week 6 of the respective study.
[b] For Study SC-3027, clinical remission was defined as a complete Mayo score of ≤2 points with no individual subscore >1 point.
[c] For Study SC-3027, mucosal healing was defined as Mayo endoscopic subscore of ≤1 point.
[d] For Study SC-3027, clinical response was defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline (Week 0) (or partial Mayo score of ≥2 points and ≥25% from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
[e] For Study SC-3027, durable clinical response was defined as clinical response at Weeks 6 and 52.
[f] For Study SC-3027, durable clinical remission was defined as clinical remission at Weeks 6 and 52.
[g] For Study SC-3027, corticosteroid-free remission was defined as subjects using oral corticosteroids at baseline (Week 0) who discontinued oral corticosteroids and were in clinical remission at Week 52.
[h] The primary endpoint for Study SC-3030 was safety.
[i] For Study SC-3030, clinical response was determined 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 subjects with UC, and using HBI scores (defined as a ≥3-point decreased in HBI score from baseline) in subjects with CD.
[j] For Study SC-3030, clinical remission was determined using partial Mayo scores (defined as a partial Mayo score of ≤2 and no individual subscore >1 point) in subjects with UC, and using HBI scores (defined as a HBI score of ≤4 points) in subjects with CD.
[k] These were collected and analyzed but are not being presented in the interim analysis for Study SC-3030.

1.2.1 Overview of Vedolizumab SC Maintenance Efficacy Studies

1.2.1.1 Study SC-3027

Study SC-3027 was a pivotal, phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled study designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active UC who achieved a clinical response (defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline [Week 0]) at Week 6 after open-label induction therapy with 300 mg vedolizumab IV administered at Weeks 0 and 2. The study included a vedolizumab IV reference arm to allow for within-study descriptive comparisons of efficacy, safety, and immunogenicity between vedolizumab IV and SC. Moderately to severely active UC was defined as a complete Mayo score of 6 to 12 points with an endoscopic subscore of ≥2.

Efficacy of vedolizumab SC was evaluated in a subject population who had experienced treatment failure with at least 1 previous conventional therapy with immunomodulators, corticosteroids, and/or TNF-α antagonists. Subjects who either had no prior TNF-α antagonist exposure (ie, TNF-α naive) or experienced previous treatment failure with TNF-α antagonists were enrolled.

The primary efficacy analysis was based on the proportion of subjects who achieved clinical remission at Week 52 (primary efficacy endpoint). There were 4 secondary efficacy endpoints tested in the following order only if the prior endpoint was statistically significant ($p < 0.05$): the proportion of subjects with mucosal healing at Week 52, the proportion of subjects with a durable clinical response, the proportion of subjects with durable clinical remission, and the proportion of subjects with corticosteroid-free clinical remission at Week 52. Several exploratory endpoints related to disease activity, quality of life, and various other patient-reported outcome [PRO] measures, and subgroups based on previous therapies were also assessed.

1.2.1.2 Study SC-3031

Study SC-3031 is an ongoing, pivotal, phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active CD who achieved a clinical response at Week 6 with 300 mg vedolizumab IV open-label therapy at Weeks 0 and 2. The primary objective of this study is to assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active CD who achieved clinical response at Week 6 after administration of vedolizumab IV at Weeks 0 and 2. Additional details about the design of Study SC-3031 may be found in the SC-3031 protocol.

1.2.1.3 Study SC-3030

Study SC-3030 is an uncontrolled, open-label, long-term safety study in subjects with UC who participated in Study SC-3027 and in subjects with CD who had participated in Study SC-3031.

Study SC-3031 is a pivotal, phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active CD who achieved a clinical response at Week 6 with 300 mg vedolizumab IV open-label therapy at Weeks 0 and 2. Subjects who were responders at Week 6 were randomized to receive blinded injections of vedolizumab SC 108 mg or placebo SC once every 2 weeks (Q2W) from Week 6 to Week 50.

Subjects with UC or CD who completed the maintenance phase (Week 52) of the parent study or achieved a clinical response at Week 14 after having received a third vedolizumab IV infusion at Week 6 during the parent study received vedolizumab SC Q2W in Study SC-3030. Subjects with UC or CD who withdrew early from the maintenance phase of the parent study because of disease worsening or need for rescue medication in the maintenance phase of the parent study received vedolizumab SC 108 mg once weekly (QW). Subjects who experienced treatment failure (ie, disease worsening, requirement for rescue medications) while receiving vedolizumab 108 mg Q2W during Study SC-3030 received a dose escalation of vedolizumab SC 108 mg QW.

Although the primary objective of this study relates to safety, efficacy is assessed throughout the study. Secondary and key exploratory efficacy endpoints from Study SC-3030 provide pertinent data for assessing the efficacy of long-term vedolizumab SC treatment and the ability to transition from IV to SC administration in subjects receiving vedolizumab IV beyond the induction phase. Secondary and exploratory efficacy endpoints include maintenance of clinical remission, clinical response, time to major IBD related events, and changes in health-related quality of life (HRQOL).

Additional details on the design of these studies can be found in the study summaries in Section 2.0 and in the CSRs (SC-3027 CSR and SC-3030 Interim CSR [results through 31 May 2018]).

In summary, the data gathered throughout the vedolizumab SC development program, as discussed in the following sections, collectively provide substantial evidence of the effectiveness of vedolizumab SC 108 mg Q2W as maintenance therapy after clinical response to vedolizumab IV induction therapy is achieved in patients with moderately to severely active UC or CD. The main findings presented in this document are summarized below:

- The efficacy of vedolizumab SC maintenance treatment in subjects with moderately to severely active UC was demonstrated in Study SC-3027 with respect to the primary endpoint: the proportion of subjects in clinical remission at Week 52. A statistically significant treatment difference between vedolizumab SC and placebo was observed for the proportion of subjects in clinical remission at Week 52.
- The efficacy of vedolizumab SC maintenance treatment was also demonstrated with respect to the predefined secondary efficacy endpoints of mucosal healing and durable clinical response in Study SC-3027. Although not statistically significant, clinically meaningful treatment differences were observed for the secondary efficacy endpoints of durable clinical remission and corticosteroid-free remission at Week 52.

- Analysis of the primary and secondary endpoints in Study SC-3027 (clinical remission, mucosal healing, durable clinical response, durable clinical remission, and corticosteroid-free remission at Week 52) showed similar results for the vedolizumab SC and IV dosing regimens and were comparable to the results observed with vedolizumab IV maintenance treatment in the vedolizumab IV pivotal, controlled, phase 3 clinical Study C13006.
- In Study SC-3027, the efficacy results of subgroup analyses in subjects who had previously experienced treatment failure with TNF-α antagonists or in those subjects who had no prior experience with TNF-α antagonists (ie, TNF-α antagonist naive) showed that vedolizumab SC was generally superior to placebo across the primary and secondary efficacy endpoint analyses.
- A consistent treatment benefit of vedolizumab SC was observed in Study SC-3027 in subgroups based on demographic factors, disease characteristics, prior therapies, and concomitant therapies.
- Improvements in quality of life measures and a decrease in UC-related hospitalizations were also observed for those subjects receiving vedolizumab in Study SC-3027.
- Efficacy across Studies SC-3027 and SC-3030 showed that subjects who achieved therapeutic benefit from vedolizumab IV treatment, after either 2 or 3 IV doses, or chronic IV maintenance treatment, maintained response after transitioning to vedolizumab SC treatment.
- Analysis of efficacy data in Study SC-3030 shows that continued treatment with vedolizumab SC maintains clinical remission and long-term clinical response (beyond 52 weeks).
- Available data from the open-label, single-arm Study SC-3030 show that in subjects with CD who received 3 IV doses of vedolizumab before transitioning to vedolizumab SC (Q2W), treatment resulted in long-term clinical benefit as assessed by clinical remission rates and improved Harvey-Bradshaw Index (HBI) scores.
- Limited data from subjects who experienced loss of response with vedolizumab SC Q2W dosing and had their vedolizumab SC dose escalated to QW dosing suggest that efficacy may be restored with increased dosing in some subjects.

2.0 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Presented in this section are key design features and relevant maintenance efficacy results after IV induction from the individual vedolizumab SC efficacy studies. A listing of important results from these studies is presented in the appendix in Table 7.a. Exposure and safety data for these studies are described individually in the CSRs and in an integrated manner in Module 2.7.4.

2.1 Controlled Study SC-3027: Efficacy and Safety of Vedolizumab SC as Maintenance Therapy in UC

2.1.1 Design and Methodology

2.1.1.1 Study Design

Study SC-3027 was a pivotal, phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled study designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active UC who achieved a clinical response at Week 6 with open-label therapy with 300 mg vedolizumab IV at Weeks 0 and 2. The study included a vedolizumab IV reference arm to allow for within-study descriptive comparisons of efficacy, safety, and immunogenicity between vedolizumab IV and SC.

Moderately to severely active UC was defined as a complete Mayo score of 6 to 12 points with an endoscopic subscore of ≥2. Subjects who were either TNF-α antagonist naïve or with TNF-α antagonist failure were included, ensuring that approximately 50% of subjects enrolled had experienced TNF-α antagonist failure. Subjects who responded to previous use of TNF-α antagonist were NOT enrolled.

Randomization was stratified by concomitant use of oral corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure or concomitant immunomodulator (azathioprine or 6-mercaptopurine) use.

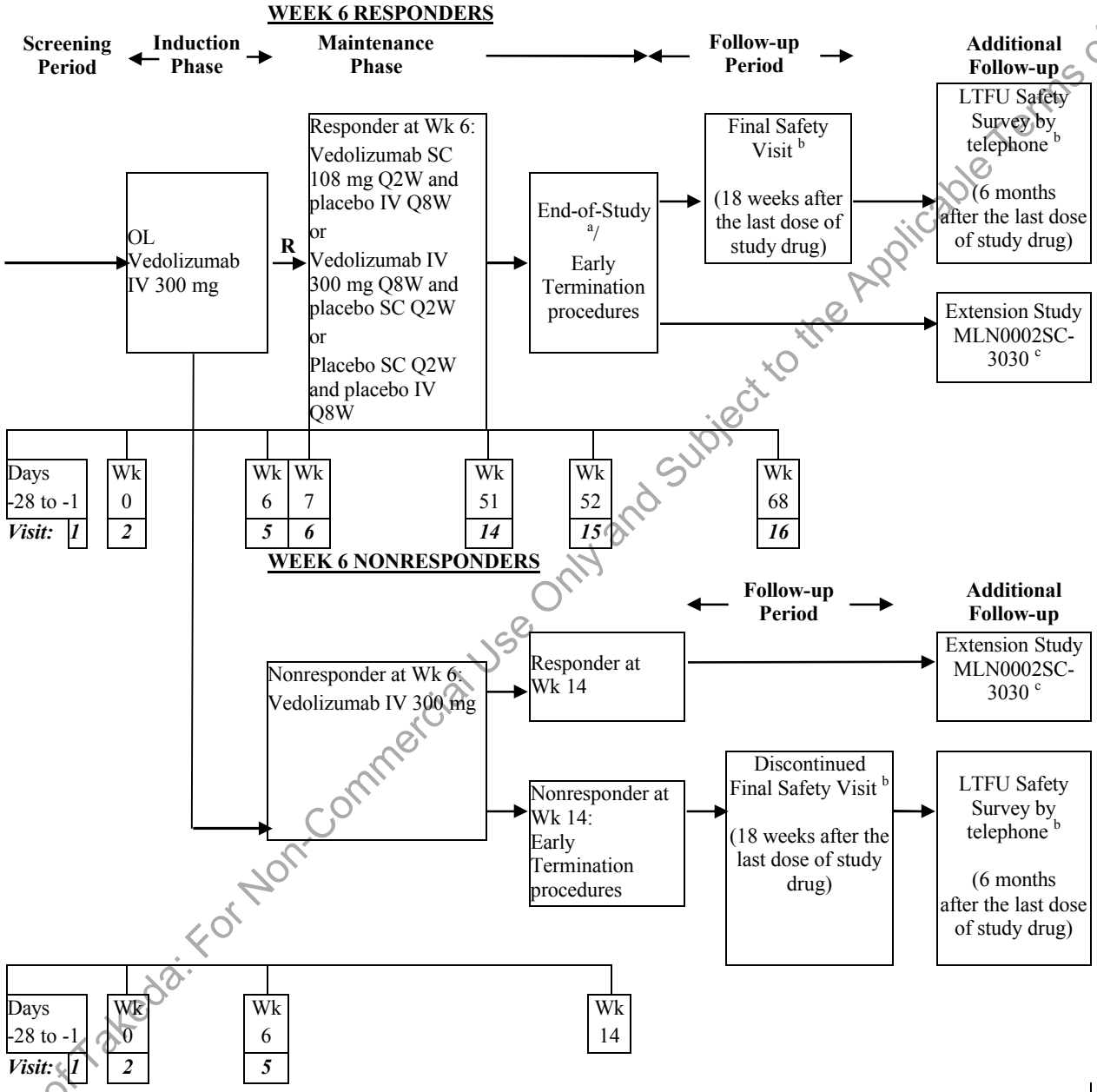
The study included a 4-week (28-day) screening period, a 6-week open-label vedolizumab IV induction phase, and a 46-week randomized, double-blind, double-dummy, placebo-controlled maintenance phase with vedolizumab SC or vedolizumab IV, with a final assessment at Week 52.

Subjects who completed Week 52 or discontinued because of disease worsening after Week 6 or because of need for rescue medications after Week 14 were eligible to participate in the OLE study (SC-3030). Subjects who did not enroll in Study SC-3030 (including those who discontinued from the maintenance phase and Week 14 nonresponder subjects) had a final safety visit 18 weeks (ie, 5 vedolizumab half-lives) after the last dose of study drug and then participated in a long-term follow-up survey 6 months after the last dose of study drug. Subjects who were Week 14 nonresponder UC subjects underwent early termination procedures at the Week 14 visit before participating in the final safety visit and long-term follow-up survey.

Subjects were trained by the HCP (investigator or designee) on the proper SC injection technique and how to manage hypersensitivity reactions potentially associated with the injection. Subjects were contacted by the HCP 24 hours before each SC injection that occurred outside of the clinic for assessments including any adverse events (AEs), progressive multifocal leukoencephalopathy (PML), and prior potential hypersensitivity or injection-site reactions associated with SC injection.

A schematic of the study design is included as Figure 2.a.

Figure 2.a Schematic of 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.

2.1.1.2 Treatment Regimen and Dose

Subjects received open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2. At Week 6, subjects were assessed for clinical response by complete Mayo score.

Subjects who did not achieve a clinical response at Week 6 were not randomized into the maintenance phase, and instead received a third open-label infusion of vedolizumab IV 300 mg at Week 6.

Subjects with a clinical response at Week 6 were randomized 2:1:1 to receive one of the following treatments beginning at Week 6 through Week 50:

- 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.

2.1.1.3 Design Considerations and Choice of Control

This phase 3 study was designed to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of vedolizumab SC as maintenance therapy in subjects with UC. The proposed vedolizumab SC maintenance dosing regimen (108 mg Q2W) was selected to provide similar steady-state exposure to that from the approved vedolizumab IV dosing regimen (300 mg Q8W), and the safety and efficacy of vedolizumab SC was expected to be similar to that of vedolizumab IV, outside of expected local administration site events, such as injection-site reactions.

To ensure the safety of subjects, and as is the standard of practice, the study design allowed subjects continued exposure to their conventional therapies (5-aminosalicylates [5-ASAs], corticosteroids, immunomodulators, antibiotics, probiotics, and antidiarrheals). In addition, the protocol mandated, and allowed for, withdrawal of subjects who were not benefiting from the study drug; thus, placebo control was considered appropriate for the study design and the subject population under study.

The study design allowed for independent assessments of vedolizumab SC efficacy as maintenance therapy by comparing the active vedolizumab SC therapy group to the placebo group during the maintenance phase. The study design also permitted double-blind, placebo-controlled comparisons of efficacy and safety parameters during the maintenance phase between the vedolizumab IV active arm and the placebo arm. However, the efficacy and safety outcomes for vedolizumab IV during the maintenance phase were exploratory endpoints for reference only.

This study enrolled subjects who had failed available therapies including corticosteroids, immunomodulators, and TNF-α antagonists. Subjects who had primary failure of TNF-α antagonists were included in the study.

2.1.1.4 Subject Population

A total of 383 subjects with moderately to severely active UC were enrolled in Study SC-3027. The key inclusion criteria included, but were not limited to, age range of 18 to 80 years; diagnosis of UC ≥6 months before screening with confirmatory histology; moderately to severely active UC (Mayo score of 6-12 with endoscopic subscore ≥2); inadequate response or intolerance to at least 1 of the following therapies: immunomodulators, corticosteroids, and/or TNF-α antagonists; and evidence of UC extending proximal to the rectum. Subjects with a long-term history of extensive colitis or pancolitis had to have documentation of surveillance colonoscopy within 12 months before the screening visit.

The exclusion criteria were divided into 3 categories: GI exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Key exclusion criteria included, but were not limited to, abdominal abscess or toxic megacolon; extensive colonic resection; ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine; prior exposure to certain nonbiologic therapies (eg, cyclosporine, thalidomide), natalizumab, efalizumab, etrolizumab, AMG 181, anti-MAdCAM-1 antibodies, or rituximab; required or anticipated surgical intervention during the study; history or evidence of adenomatous colonic polyps or colonic mucosal dysplasia; and diagnosis of Crohn's colitis or indeterminate colitis.

A complete list of the inclusion and exclusion criteria can be found in SC-3027 CSR Section 9.3.

2.1.1.5 Endpoints

The primary efficacy endpoint of Study SC-3027 was the proportion of subjects who achieved clinical remission at Week 52. Secondary endpoints were the proportion of subjects with mucosal healing at Week 52, proportion of subjects with a durable clinical response (clinical response at Weeks 6 and 52), proportion of subjects with durable clinical remission, and the proportion of subjects with baseline oral corticosteroid use who discontinued corticosteroids and achieved clinical remission at Week 52 (ie, corticosteroid-free remission).

Several PRO endpoints and exploratory endpoints were also assessed, including changes in Inflammatory Bowel Disease Questionnaire (IBDQ), Euro Quality of Life-5D (EQ-5D), and Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis (WPAI-UC) scores. Exploratory endpoints also included assessment of clinical remission by Mayo score without physician's global assessment (PGA) (defined as a Mayo score of ≤2 points and no individual subscore [without PGA] >1 point), and clinical remission by modified Mayo score defined as:

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. Stool frequency subscore = 0 or 1 and a prespecified specific change of 1 or more from baseline; rectal bleeding subscore = 0; and endoscopy subscore = 0 or 1 (modified so that a score of 1 does not include friability).
3. Either definition 1 or definition 2.

Additional prespecified exploratory endpoints included time to major UC-related events (hospitalizations, colectomies, and procedures); the proportion of subjects at Week 52 who were in clinical remission and have been corticosteroid-free for 90 or 180 days; the proportion of subjects at Week 52 who have been corticosteroid-free for 90 or 180 days, regardless of remission status; proportion of subjects with durable clinical remission, defined as clinical remission at Weeks 6 and 52 in subjects who achieved remission at Week 6; and the proportion of subjects with clinical response or clinical remission (by partial Mayo score) at ≥80% or ≥60% study visits, including the final visit (ie, Week 52 visit). In addition, other exploratory endpoints included PK, immunogenicity (eg, the proportion of subjects with positive anti-vedolizumab antibody [AVA]), changes in fecal calprotectin levels, and histological changes. All exploratory endpoints were predefined in the SC-3027 Statistical Analysis Plan (SAP). Post hoc analyses that were not predefined in the SC-3027 SAP were also performed.

2.1.1.6 Analysis Plan

The full analysis set (FAS), which included all randomized subjects who received at least 1 dose of study drug, was used for the summary of the efficacy endpoints, except for corticosteroid-free remission– or response-related endpoints, which were analyzed using a subset of the FAS subjects with baseline concomitant oral corticosteroid use. All statistical testing was performed at a 2-sided 0.05 level of significance. A fixed-sequence testing approach was used to control the type 1 error rate at 5% for the comparison of vedolizumab SC versus placebo for primary and secondary endpoints. The implementation of this fixed-sequence testing approach is that statistical testing for each secondary endpoint would be performed only if the preceding endpoint had statistically significant results ($p < 0.05$). For all other endpoints in the study, comparisons between vedolizumab IV versus placebo, no multiplicity adjustments were made for p-values or CIs. All subjects with missing data for determination of endpoint status were considered as nonresponders in the analysis.

The primary and secondary endpoints were analyzed using the Cochran-Mantel-Haenszel (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 CMH method adjusted treatment difference and corresponding 95% CIs for the vedolizumab SC and placebo groups are presented. Similarly, the CMH method adjusted treatment difference including the 95% CIs for the vedolizumab IV arm versus placebo are presented for the primary and each of the secondary endpoints. In accordance with the US Food and Drug Administration (FDA) Ulcerative Colitis Clinical Trial Endpoints guidance [10], a sensitivity analysis was performed in which the complete Mayo score and partial Mayo score for each subject were calculated for postscreening visits.

A sensitivity analysis was conducted to assess the impact of dropouts for different missing mechanisms using a hybrid approach, where nonresponder imputation was used for subjects who discontinued because of an AE or lack of efficacy (under missing not at random assumption), and other discontinuation/missing was imputed using multiple imputation (under missing at random assumption). Missing subscores for each component of the complete Mayo score were imputed by treatment group via a multivariate stepwise approach using fully conditional

specification (FCS ordinal logistic) methods [11], respectively. Missing baseline visit subscores, if any, would be imputed using relevant demographic and baseline disease characteristic data (namely, age, duration of UC, baseline disease severity), and subsequent visits were imputed using all the previous visits in a stepwise fashion. Partial Mayo score and complete Mayo score were derived accordingly. Fifty imputation datasets were computed for each component of Mayo score. This sensitivity analysis was performed for the primary efficacy endpoint and all secondary endpoints.

Changes from baseline to Week 52 in IBDQ, EQ-5D scores, and WPAI-UC components were analyzed in an analysis of covariance model with treatment as a factor and baseline score as covariate. Changes from Week 6 to Week 52 were analyzed in a similar fashion. No formal hypothesis testing was performed for PRO endpoints. Missing data were imputed using the last available observation carried forward (LOCF) method.

Time to colectomies, other UC-related procedures, and UC-related hospitalizations were analyzed using the Wei-Lin-Weissfeld Cox regression model with treatment group, baseline complete Mayo score, randomization stratum, and geographic region as independent variables. For each of the components, the treatment groups were compared by log-rank tests, with Kaplan-Meier estimates of event rates 24 and 48 weeks after randomization.

A Cox proportional hazards regression model was used for time to disease worsening and time to treatment failure adjusting for covariates of baseline complete Mayo score, randomization strata, and geographical region.

All additional binary efficacy endpoints were analyzed using the same statistical methods as the primary and secondary efficacy endpoints.

2.1.2 Demographics

Of the 614 subjects screened for enrollment, 383 subjects were enrolled into the open-label induction phase. Subjects who completed the induction phase (ie, received open-label IV vedolizumab at Weeks 0 and 2) and achieved a clinical response at Week 6, as assessed by complete Mayo score, were randomized into the maintenance phase.

Of the 383 subjects who received 2 open-label IV induction doses of vedolizumab, 216 subjects were randomized into the maintenance phase (placebo: 56 subjects; vedolizumab SC: 106 subjects; and vedolizumab IV: 54 subjects).

Baseline (ie, Week 0) demographic characteristics were summarized for the safety analysis set-combined (SAF-C; ie, all subjects who received at least 1 dose of vedolizumab IV). Because the actual treatment any subject received was the same as the randomized treatment, the SAF is the same population as the FAS. The FAS included all 216 randomized subjects. Overall, baseline demographics were similar for vedolizumab and placebo subjects in the SAF-C and FAS populations. In the overall population, there was a higher proportion of male subjects than female subjects (60.2% and 39.8%, respectively). Most (83.8%) subjects were white. The median age was 38.0 years; most subjects were ≥35 years of age (58.8%) and few subjects were ≥65 years (6.0%). The median body weight was 71.65 kg and the median body mass index (BMI) was

24.02 kg/m^2. A total of 13.0% were enrolled at sites in North America and 87% were enrolled at sites outside of North America (SC-3027 Table 15.1.8.1).

In the FAS treatment groups, durations of UC were similar in all treatment groups (median 5.32 years in placebo; median 5.93 years in vedolizumab SC and 6.79 for vedolizumab IV). Nearly 62% of subjects had severe UC (ie, Mayo score of 9-12); 42.1% of subjects had left-sided colitis and 35.6% had pancolitis. Baseline disease activity, as assessed by the complete Mayo score, was similar in the 3 groups, as was the category of baseline fecal calprotectin (SC-3027 Table 15.1.8.2).

Overall, more subjects had no prior TNF-α antagonist use (61.1%; 132 of 216 subjects) than previous TNF-α antagonist failure (38.9%; 84 of 216 subjects). Prior corticosteroid and immunomodulator use was reported by 62.5% (135 of 216 subjects), and prior use of only corticosteroids was reported by 32.9% (71 of 216 subjects). At baseline, 41.7% (90 of 216 subjects) reported corticosteroid use (SC-3027 Table 15.1.8.2) and 32.4% (70 of 216 subjects) were receiving concomitant immunomodulators at baseline (SC-3027 Table 2.1 post hoc). Extraintestinal manifestations of UC occurred in 25 of 216 subjects (11.6%). The most common extraintestinal manifestation was arthritis/arthralgia (17 of 216 subjects [7.9%]) (SC-3027 Table 15.1.8.2).

2.1.3 Efficacy Results

2.1.3.1 Primary Efficacy Endpoint

The results from the analysis of the primary efficacy endpoint for this study, the proportion of subjects with clinical remission at Week 52, are summarized in Table 2.a.

The primary endpoint for this maintenance study was met. A higher remission rate was observed for vedolizumab SC subjects (46.2%) than for placebo subjects (14.3%), and this treatment difference was statistically significant ($p < 0.001$) and clinically meaningful. The adjusted difference by the CMH method between the vedolizumab SC group and placebo was 32.3% (95% CI, [19.7 to 45.0], $p < 0.001$).

Table 2.a Study SC-3027 Primary Efficacy Endpoint (FAS)

Clinical Remission [a]	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)
95% CI [b]	(6.4, 26.2)	(36.5, 56.2)	(29.2, 56.8)
Adjusted difference, 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: SC-3027 Table 15.2.1.1.1.
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.
[b] The 95% CIs of the clinical remission rate at Week 52 were based on the Clopper-Pearson method. The 95% CI of the 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 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 remissions in either treatment group was ≤5.

2.1.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are summarized in Table 2.b.

Similarly, clinically meaningful treatment effects with vedolizumab SC over placebo were observed for the secondary endpoints. Statistically significant treatment differences favoring vedolizumab SC treatment over placebo were observed for rates of mucosal healing at Week 52 (vedolizumab SC: 56.6%; placebo: 21.4%, p <0.001) and durable clinical response (vedolizumab SC: 64.2%; placebo: 28.6%, p <0.001).

Clinically meaningful differences favoring vedolizumab SC over placebo were observed for durable clinical remission and corticosteroid-free remission, although these differences were not statistically significant. The rate of durable clinical remission was 15.1% (16 of 106 subjects) in the vedolizumab SC group and 5.4% (3 of 56 subjects) in the placebo group. 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.

Table 2.b Study SC-3027 Secondary Efficacy Endpoints (FAS)

	PBO N = 56	VDZ SC 108 mg N = 106	VDZ IV 300 mg N = 54
Number (%) of subjects achieving mucosal healing at Week 52 [a]	12 (21.4)	60 (56.6)	29 (53.7)
95% CI [b]	(11.6, 34.4)	(46.6, 66.2)	(39.6, 67.4)
Adjusted difference, vedolizumab vs placebo		35.7	32.2
95% CI [b]		(22.1, 49.3)	(15.7, 48.7)
P-value, vedolizumab vs placebo [c]		<0.001	<0.001
Number (%) of subjects achieving durable clinical response [d]	16 (28.6)	68 (64.2)	39 (72.2)
95% CI [b]	(17.3, 42.2)	(54.3, 73.2)	(58.4, 83.5)
Adjusted difference, vedolizumab vs placebo		36.1	44.5
95% CI [b]		(21.2, 50.9)	(28.3, 60.6)
P-value, vedolizumab vs placebo [c]		<0.001	<0.001
Number (%) of subjects achieving durable clinical remission [e]	3 (5.4)	16 (15.1)	9 (16.7)
95% CI [f]	(1.1, 14.9)	(8.9, 23.4)	(7.9, 29.3)
Difference, vedolizumab vs placebo		9.7	11.3
95% CI [f]		(-6.6, 25.7)	(-7.1, 29.9)
P-value, vedolizumab vs placebo [g]		0.076	0.071
Number (%) of subjects achieving corticosteroid-free clinical remission [h,i]	2 (8.3)	13 (28.9)	6 (28.6)
95% CI [f]	(1.0, 27.0)	(16.4, 44.3)	(11.3, 52.2)
Difference, vedolizumab vs placebo		20.6	20.2
95% CI [f]		(-4.5, 43.7)	(-9.8, 47.8)
P-value, vedolizumab vs placebo [g]		0.067	0.121

Source: SC-3027 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).
FAS: full analysis set; IV: intravenous; IWRS: interactive web response system; 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.
All subjects received open-label vedolizumab IV induction treatment at Weeks 0 and 2 and achieved clinical response at Week 6.
[a] Mucosal healing, defined as a Mayo endoscopic subscore of ≤1 point, at Week 52 was the first secondary efficacy endpoint.
[b] The 95% CIs of the proportion were based on the Clopper-Pearson method. 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.
[c] The p-values were obtained using a Cochran-Mantel-Haenszel test stratified 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.
[d] Durable clinical response (response at both Weeks 6 and 52) was the second secondary efficacy endpoint.
[e] Durable clinical remission, defined as remission at both Week 6 and Week 52, was the third secondary efficacy endpoint.
[f] The 95% CIs of the durable clinical remission rate were based on the Clopper-Pearson method. The 95% CI of the difference was based on the exact method.
[g] 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.
[h] Corticosteroid-free remission, defined as subjects using oral corticosteroids at baseline (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, was the fourth secondary efficacy endpoint.
[i] PBO: N = 24; VDZ SC: N = 45; VDZ IV: N = 21.

2.1.3.3 Exploratory Analyses

2.1.3.3.1 Exploratory Subgroup Analyses

The beneficial effects of vedolizumab on the primary (clinical remission at Week 52) and secondary endpoints (mucosal healing, durable clinical response, durable clinical remission, and corticosteroid-free remission at Week 52) were also consistently observed in exploratory subgroup analyses. These subgroup analyses include subjects without prior exposure to TNF-α antagonist therapy (referred to as *TNF-α antagonist–naïve subjects*) and subjects who had experienced prior treatment failure with TNF-α antagonists (SC-3027 Table 15.2.3.1.10, 15.2.3.2.10, 15.2.3.3.10, 15.2.3.4.10, and 15.2.3.5.10). These subgroup analyses are further discussed in Section 3.2.

2.1.3.3.2 Sustained Maintenance of Efficacy in Study SC-3027

Maintenance of Clinical Remission and Clinical Response (Based on Partial Mayo Scores) Throughout the Maintenance Phase

In Study SC-3027, durable clinical remission (defined as clinical remission at both Weeks 6 and 52) was evaluated as a secondary endpoint. Prespecified analyses were conducted to further evaluate the durability of clinical remission throughout the maintenance phase in subjects reaching clinical remission at Week 6 (N = 96) (SC-3027 Table 15.2.3.4.9).

At the request of the Committee for Medicinal Products for Human Use (CHMP), an additional assessment for durable clinical remission was undertaken to evaluate the proportion of subjects who were in clinical remission in at least 80% of clinic visits including the final visit during the maintenance phase of the study. Because subjects enrolling in the study had severe, acute flares and may have responded without achieving clinical remission by the end of the induction phase at Week 6, this exploratory analysis that required subjects to be in remission at multiple study visits is a rigorous assessment of sustained clinical remission throughout the maintenance phase.

These analyses of clinical remission were based on the partial Mayo score, defined as a partial Mayo score ≤2 and no individual subscore (excluding endoscopy) >1.

Clinical remission, based on the partial Mayo score, is summarized in Table 2.c. In the FAS population, a higher proportion of subjects treated with vedolizumab SC (55.7%) had clinical remission in at least 80% of the study visits in the maintenance phase compared with subjects treated with placebo (17.9%) (p <0.001). Similarly, a higher proportion of subjects in the vedolizumab SC group (59.4%) had clinical remission in at least 60% of the study visits during the maintenance phase compared with subjects treated with placebo (19.6%) (p <0.001).

Table 2.c Proportion of Subjects at Week 52 With Clinical Remission by Partial Mayo Score at ≥80% or ≥60% of Study Visits Including the Final Visit (FAS)

Clinical Remission [a]	PBO N = 56	VDZ SC 108 mg N = 106	VDZ IV 300 mg N = 54
Clinical remission at ≥80% of study visits			
Number (%) of subject achieving clinical remission	10 (17.9)	59 (55.7)	25 (46.3)
95% CI [b]	(8.9, 30.4)	(45.7, 65.3)	(32.6, 60.4)
Difference from placebo		37.8	28.2
95% CI for difference from placebo [b]		(24.9, 50.8)	(12.1, 44.3)
P-value for difference from placebo [c]		<0.001	0.001
Clinical remission at ≥60% of study visits			
Number (%) of subjects achieving clinical remission	11 (19.6)	63 (59.4)	31 (57.4)
95% CI [b]	(10.2, 32.4)	(49.5, 68.9)	(43.2, 70.8)
Difference from placebo		39.9	37.8
95% CI for difference from placebo [b]		(26.5, 53.3)	(21.5, 54.1)
P-value for difference from placebo [c]		<0.001	<0.001

Source: SC-3027 Table 15.2.5.1.10 (≥80% of study visits) and 15.2.5.1.11 (≥60% of study visits).
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 partial Mayo Score ≤2 and no individual subscore (excluding endoscopy) >1.
[b] The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method. The 95% CI of the treatment difference was based on the normal approximation method, or the exact method if the number of remissions in each treatment group is ≤5.
[c] The p-values were obtained using a Cochran-Mantel-Haenszel test stratified 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 remissions in either treatment group was ≤5.

Clinical response, based on partial Mayo score, was defined as a reduction in partial Mayo score of ≥2 points and ≥25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

Analyses of the proportion of subjects who had clinical response defined by partial Mayo score showed that while on vedolizumab SC treatment, 66.0% of subjects had a clinical response in at least 80% of the study visits during the maintenance phase compared with 25.0% of placebo-treated subjects (p <0.001) (SC-3027 Table 15.2.5.1.8). Similarly, 66.0% of subjects treated with vedolizumab SC had a clinical response in at least of 60% of the study visits during the maintenance phase compared with 26.8% of subjects treated with placebo (p <0.001) (SC-3027 Table 15.2.5.1.9).

Analyses of Partial Mayo Scores

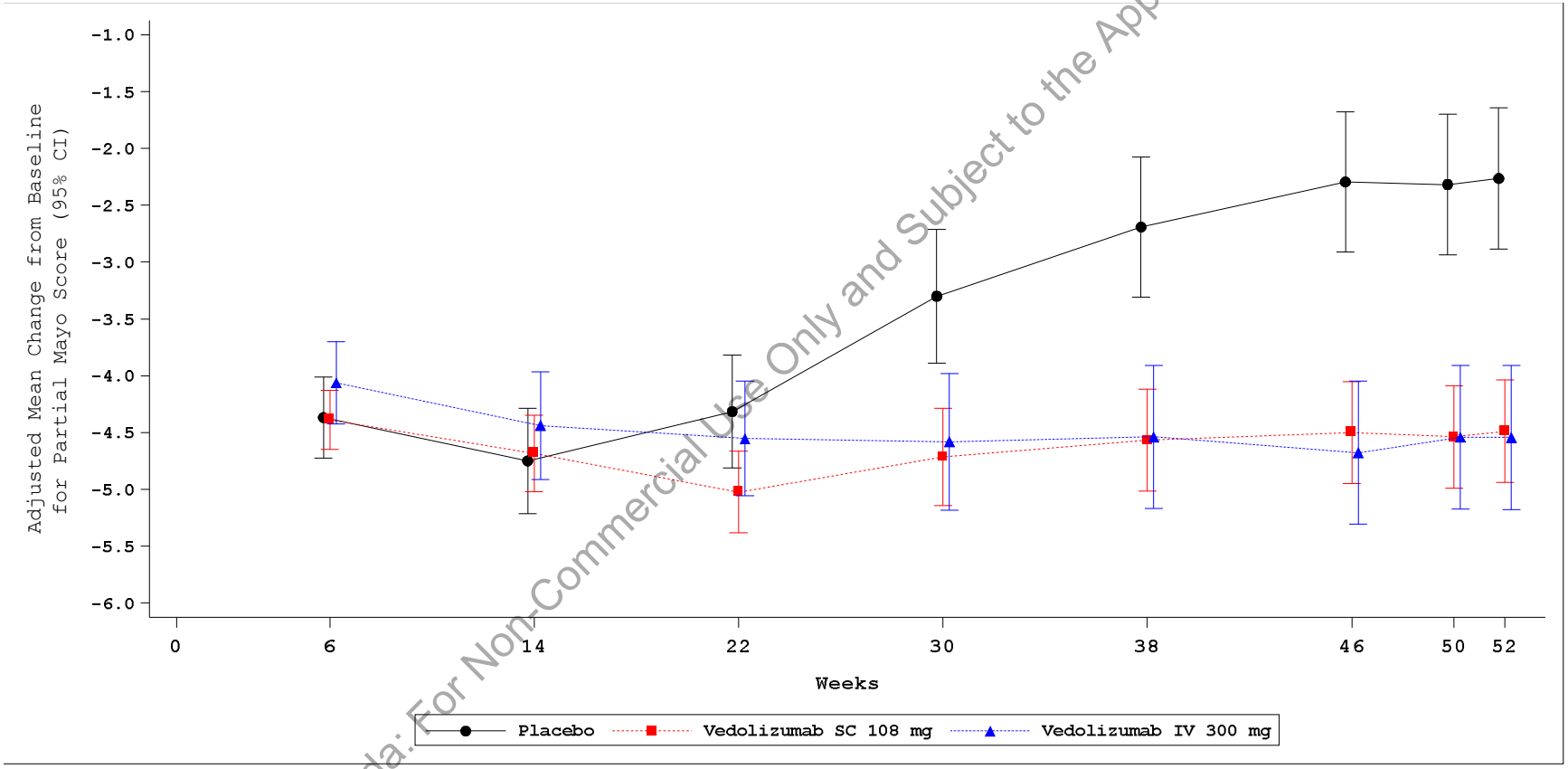
The results of the primary endpoint (Table 2.a) and secondary endpoints (Table 2.b) demonstrated the sustainability of vedolizumab efficacy from Week 6 through Week 52.

Partial Mayo scores can also provide valuable data about the sustainability of vedolizumab efficacy during the maintenance phase. Partial Mayo scores, which exclude the endoscopic component of the complete Mayo score, enabled disease activity to be continually evaluated throughout Study SC-3027, without requiring subjects to repeat sigmoidoscopies at every study visit.

The sustained therapeutic benefit of vedolizumab maintenance therapy was also demonstrated by sustained decreases in partial Mayo scores (Figure 2.b) and sustained clinical remission (SC-3030 Figure 15.2.14.4.2.2). For subjects who achieved clinical response at Week 6, the change from Week 6 in the mean partial Mayo score was calculated.

Partial Mayo score by study visit is presented for the FAS population (LOCF) in SC-3027 Table 15.2.10.1.2.2. Partial Mayo scores across all 3 groups improved up to Week 14 because of the initial 2 doses of vedolizumab IV treatment at Weeks 0 and 2. After vedolizumab SC treatment, improved partial Mayo scores were maintained up to Week 52, while worsening scores were observed in the placebo group (mean [SD] change from baseline to Week 52: -2.3 [2.78], placebo; -4.4 [2.63], vedolizumab SC). Adjusted mean partial Mayo scores (change from Week 0, LOCF) are presented for the FAS in Figure 2.b. Vedolizumab SC treatment had a similar effect on partial Mayo scores as with vedolizumab IV maintenance treatment.

Figure 2.b Study SC-3027 Adjusted Mean Partial Mayo Score LOCF (95% CI) Change From Baseline (Week 0) by Study Visit (FAS)



Source: SC-3027 Figure 4 (post hoc).
FAS: full analysis set; IV: intravenous; LOCF: last observation carried forward; SC: subcutaneous.
Least squares means and 95% CIs are from an analysis of covariance model with factor of treatment and baseline (Week 0) as covariates at each visit.

2.1.3.3.3 Reduction in Oral Corticosteroid Use

As previously described, subjects who achieved a response at Week 6 began a corticosteroid tapering regimen as outlined in the SC-3027 protocol. For subjects who could not tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids could have been increased to the subject's original dose at the start of induction therapy. In such cases, the tapering regimen was reinitiated within 2 weeks. Changes from baseline in corticosteroid use at Week 52 were part of the exploratory analyses.

Long-term use of corticosteroids is associated with significant side effects and tolerance effects; thus, an important measure of clinical benefit for new UC therapies is the extent to which subjects can discontinue use of corticosteroids and the extent to which they can stay corticosteroid-free. Approximately 41.7% of the FAS subjects were on corticosteroids at baseline (Week 0) (SC-3027 Table 15.1.8.2) and were to taper these medications after Week 6 according to a predefined protocol-specified regimen.

In the SAP-prespecified exploratory analyses, corticosteroid-free clinical remission was evaluated in subjects who had not been treated with corticosteroids for 90 days and 180 days before Week 52. Among these subjects, 26.7% of subjects in the vedolizumab SC 108 mg group were in clinical remission at Week 52 and corticosteroid-free for 90 days, compared with 8.3% of placebo subjects. Similar differences were observed for subjects who were in clinical remission at Week 52 and corticosteroid-free for 180 days (SC-3027 Table 15.2.5.1.4 and 15.2.5.1.5).

These data represent an important indicator of clinically meaningful benefit of vedolizumab SC treatment because of the known detrimental effects of chronic corticosteroid therapy.

2.1.3.4 PROs

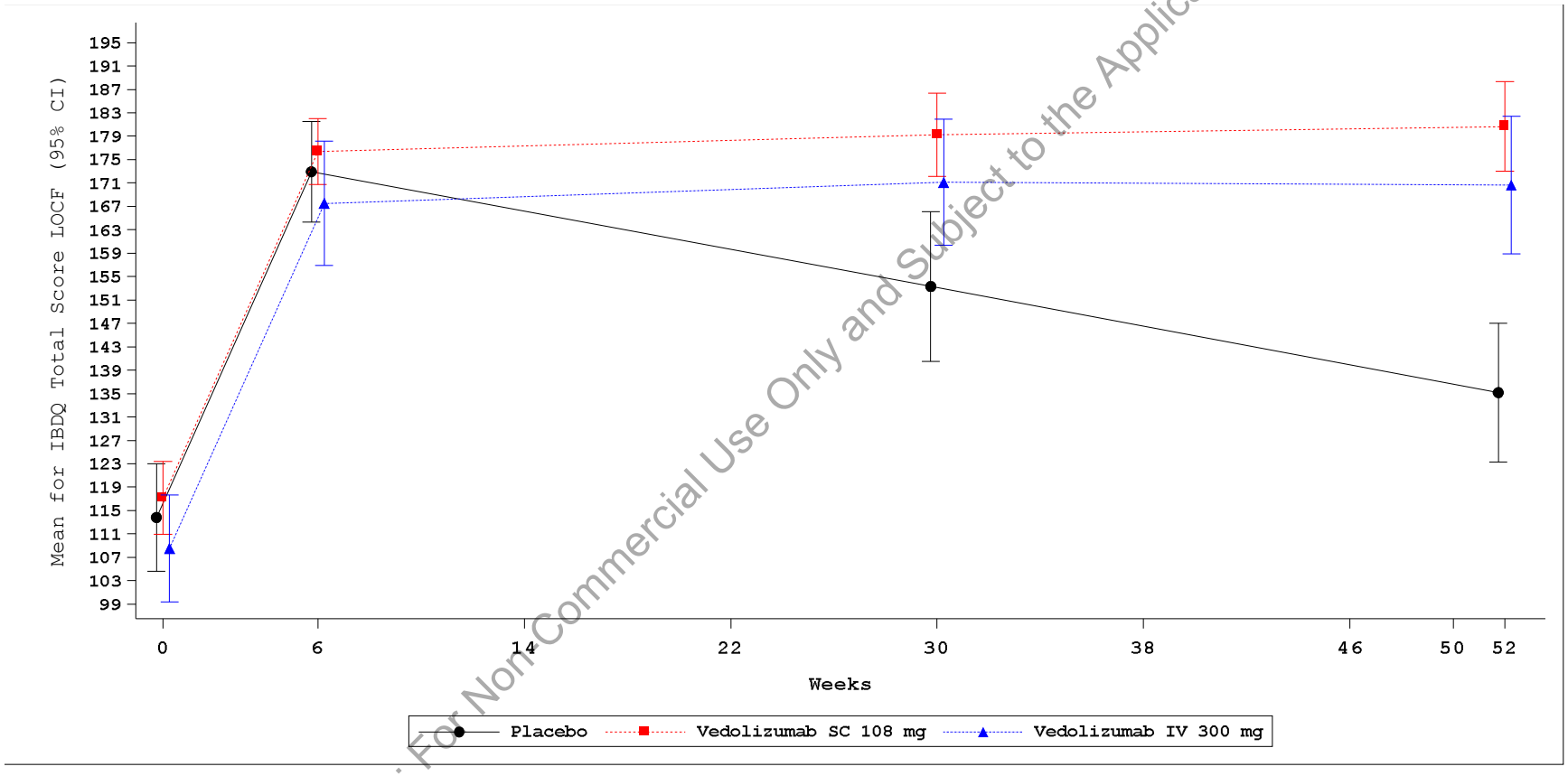
IBDQ Total Score

In addition to assessments based on clinical observations, improvements with vedolizumab in quality of life measures were assessed in prespecified exploratory analyses. The total IBDQ scores improved after the open-label induction phase and were similar at Week 6 in all 3 treatment groups (placebo mean ± SD: 172.93 ± 32.214; vedolizumab SC mean ± SD: 176.41 ± 29.248; vedolizumab IV mean ± SD: 167.50 ± 38.891) (SC-3027 Table 15.2.4.1.1 and Figure 2.c).

The mean IBDQ scores gradually decreased (worsened) in the placebo group during the maintenance phase (placebo mean ± SD: 135.16 ± 44.357 at Week 52) and remained consistent in the vedolizumab SC group during the maintenance phase (vedolizumab SC mean ± SD: 180.65 ± 39.719 at Week 52) (SC-3027 Table 15.2.4.1.1 and Figure 2.c).

These data support the clinical benefit of vedolizumab treatment compared with placebo.

Figure 2.c Study SC-3027 IBDQ Total Score LOCF by Study Visit (FAS)



Source: SC-3027 Figure 5.2 (post hoc)
FAS: full analysis set; IBDQ: Inflammatory Bowel Disease Questionnaire; IV: intravenous; LOCF: last observation carried forward; SC: subcutaneous.

EQ-5D and WPAI-UC

Similar improvements in HRQOL measures were observed in vedolizumab-treated subjects with EQ-5D scores (SC-3027 Table 15.2.10.4.6 [visual analogue scale, VAS] and 15.2.10.4.7 [EQ-5D Index]). During the maintenance phase, the scores gradually decreased (worsened) in the placebo group while subjects in both vedolizumab treatment groups maintained the EQ-5D up to Week 52. A similar trend was observed in the EQ-5D VAS score analysis. The results were also consistent in the EQ-5D subscore analyses (SC-3027 Table 15.2.10.4.1-15.2.10.4.5), with the greatest improvement observed in the vedolizumab SC group relative to placebo indicated in usual activities (Table 15.2.10.4.3) followed by pain/discomfort (SC-3027 Table 15.2.10.4.4) and anxiety/depression (SC-3027 Table 15.2.10.4.5) subscores at Week 52.

Vedolizumab SC maintenance treatment was associated with decreased impairment and greater productivity as assessed by WPAI-UC impairment scores; in contrast, subjects in the placebo group showed increasing activity impairment scores during the maintenance phase (SC-3027 Table 15.2.10.2.4). Subjects treated with vedolizumab SC had greater improvement in all subscores of the WPAI-UC (absenteeism score, presenteeism score, overall work productivity loss score, and activity impairment scores) compared with placebo (SC-3027 Table 15.2.4.3.1).

2.1.3.4.1 Time From Randomization to Treatment Failure

Treatment failure was defined as disease worsening or the need for rescue medications or surgical intervention for treatment of UC. Subjects who did not experience any of these events were censored at the date of last assessment/visit/contact, whichever occurred last.

At Week 48, the Kaplan-Meier estimate of the probability of subjects not having experienced treatment failure is 0.799 for the vedolizumab SC group, which is higher than the placebo group (0.686). Interpretation of the results is limited because of the small number of subjects with events in all treatment groups. However, the hazard ratio for vedolizumab SC versus placebo showed a benefit for the vedolizumab SC treatment (0.44, 95% CI, [0.2, 0.9]) (SC-3027 Table 15.2.9.2.2).

2.1.3.4.2 Time From Randomization to Disease Worsening

Time to disease worsening was measured as a predefined exploratory endpoint in Study SC-3027. Disease worsening was defined as an increase in partial Mayo score of ≥3 points from the Week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 6 value was >6 points) and a minimum partial Mayo score ≥5 points.

The hazard ratio for vedolizumab SC versus placebo was 0.21 (95% CI, 0.0, 1.2) (SC-3027 Table 15.2.9.2.1). The small number of events observed limits interpretation of the data.

2.1.3.4.3 Major UC-Related Events

UC-related events were defined as UC-related hospitalizations, colectomies, and UC-related procedures (ie, abscess drainage, bowel resection, fistulotomy, or other with reason code of

treatment for condition under study or rescue procedure). Overall, few subjects experienced UC-related hospitalizations and UC-related procedures. No subjects had colectomies during the study (SC-3027 Table 15.2.9.1.4). There was a numeric difference favoring vedolizumab SC between vedolizumab SC and placebo for the time from randomization to UC-related hospitalizations analysis (0.967; 95% CI, [0.930 to 1.000], p = 0.011) (SC-3027 Table 15.2.9.1.1). However, because of the small number of subjects who experienced UC-related events during the study, interpretation of these results is limited.

2.1.3.5 Other Exploratory Endpoints

2.1.3.5.1 Reduction in Fecal Calprotectin

Open-label vedolizumab IV induction therapy reduced the number of subjects with the most severe category of fecal calprotectin (>500 µg/g) by Week 6 in all treatment groups. After Week 6, the vedolizumab SC group showed continued improvement in this biomarker of disease activity through the Week 52 measurements as demonstrated by the shift from the most severe toward less severe categories and decrease in the mean fecal calprotectin levels (ie, ≤250 µg/g, which is indicative of mucosal healing). In contrast, fewer placebo-treated subjects shifted from the most severe category to the least severe category. Vedolizumab SC treatment appeared to have similar effect to vedolizumab IV therapy.

Table 2.d Study SC-3027 Summary of Fecal Calprotectin by Visit As Observed (FAS)

Study Visit	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)
Baseline [a]			
n	56	102	52
≤250 µg/g	5 (8.9)	9 (8.8)	2 (3.8)
>250 to ≤500 µg/g	7 (12.5)	6 (5.9)	4 (7.7)
>500 µg/g	44 (78.6)	87 (85.3)	46 (88.5)
Week 6			
n	50	97	49
≤250 µg/g	15 (30.0)	39 (40.2)	16 (32.7)
>250 to ≤500 µg/g	4 (8.0)	13 (13.4)	8 (16.3)
>500 µg/g	31 (62.0)	45 (46.4)	25 (51.0)
Week 30			
n	46	90	38
≤250 µg/g	18 (39.1)	50 (55.6)	23 (60.5)
>250 to ≤500 µg/g	6 (13.0)	6 (6.7)	6 (15.8)
>500 µg/g	22 (47.8)	34 (37.8)	9 (23.7)
Week 52			
n	18	72	39
≤250 µg/g	8 (44.4)	50 (69.4)	27 (69.2)
>250 to ≤500 µg/g	0	7 (9.7)	3 (7.7)
>500 µg/g	10 (55.6)	15 (20.8)	9 (23.1)

Source: SC-3027 Table 15.2.12.2.
FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; VDZ: vedolizumab.
[a] Baseline is defined as the last nonmissing measurement before or on the date of the first dose of study drug (study Day 1).

2.1.3.5.2 Supplemental Analyses Requested by the US FDA

Clinical Remission Based on Alternate Definition Proposed by the FDA

The maintenance-related analyses summarized in this section were conducted in response to a request received from the US FDA. The primary endpoint of clinical remission at Week 52, and secondary endpoints of durable clinical remission (clinical remission at both Weeks 6 and 52) and corticosteroid-free clinical remission, were evaluated using an alternate definition of clinical remission based on modified Mayo score (clinical remission in the FDA Ulcerative Colitis Clinical Trial Endpoints guidance [10]), defined as follows:

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. Stool frequency subscore = 0 or 1 and a prespecified specific change of 1 or more from baseline; rectal bleeding subscore = 0; and endoscopy subscore = 0 or 1 (modified so that a score of 1 does not include friability).
3. Either of these 2 definitions.

Based on these FDA definitions and their combination, the following results were observed:

Analysis of clinical remission based on the FDA definitions of clinical remission showed similar results to the primary efficacy endpoint analysis, and vedolizumab SC was superior to placebo (Table 2.e). Additionally, all secondary endpoint analyses using the FDA-proposed definition of clinical remission were consistent with the main analyses (FAS) (SC-3027 Table 15.2.1.1.2 and 15.2.2.3.2).

Table 2.e Study SC-3027 Proportion of Subjects With Clinical Remission Based on a Modified Mayo Score at Week 6 and Week 52 (FAS)

Treatment Group	Statistic	Alternate Clinical Remission Definition		
		Definition 1 [a]	Definition 2 [b]	Definition 3 [c]
Placebo	N	56	56	56
	Number (%) achieving clinical remission	6 (10.7)	8 (14.3)	8 (14.3)
	95% CI	(4.0, 21.9)	(6.4, 26.2)	(6.4, 26.2)
Vedolizumab SC [d]	N	106	106	106
	Number (%) achieving clinical remission	42 (39.6)	47 (44.3)	49 (46.2)
	95% CI	(30.3, 49.6)	(34.7, 54.3)	(36.5, 56.2)
	Difference from placebo	29.2	30.5	32.3
	95% CI	(17.0, 41.4)	(17.9, 43.2)	(19.7, 45.0)
	P-value	<0.001	<0.001	<0.001
Vedolizumab IV [e]	N	54	54	54
	Number (%) achieving clinical remission	19 (35.2)	22 (40.7)	22 (40.7)
	95% CI	(22.7, 49.4)	(27.6, 55.0)	(27.6, 55.0)
	Difference from placebo	24.0	26.1	26.1
	95% CI	(8.9, 39.0)	(10.3, 41.8)	(10.3, 41.8)
	P-value	0.003	0.002	0.002

Source: SC-3027 Table 15.2.5.1.1 (Definition 1), 15.2.5.1.2 (Definition 2), and 15.2.5.1.3 (Definition 3).
FAS: full analysis set; IV: intravenous; SC: subcutaneous.
All subjects with missing data for the determination of endpoint status were categorized as nonresponders.
The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method. The 95% CI of the treatment difference was based on the normal approximation method, or the exact method if the number of remissions in each treatment group was ≤5.
The p-values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization strata (concomitant use of corticosteroids, clinical remission at Week 6, and previous tumor necrosis factor-alpha antagonist failure or concomitant immunomodulator use) or Fisher's Exact test if the number of remissions in either treatment group was ≤5.
[a] Clinical remission (alternate definition 1) was defined as 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).
[b] Clinical remission (alternate definition 2) was defined as stool frequency subscore = 0 or 1 and a prespecified change of 1 or more from baseline, rectal bleeding subscore = 0, and endoscopy subscore = 0 or 1 (modified so that a score of 1 does not include friability).
[c] Either definition 1 or 2.
[d] Subjects received vedolizumab SC 108 mg once every 2 weeks.
[e] Subjects received vedolizumab IV 300 mg once every 8 weeks.

2.1.4 Conclusions

In Study SC-3027, vedolizumab SC was efficacious as demonstrated by statistically significant results in the primary efficacy endpoint of clinical remission at Week 52 with a clinical

remission rate of 46.2% for vedolizumab SC compared with 14.3% for placebo (adjusted difference from placebo 32.3% (95% CI, [19.7 to 45.0]; p <0.001). Results for assessment of clinical remission using an alternate definition requested by FDA were similar.

Similarly, statistically significant treatment effects favoring vedolizumab SC over placebo were also observed for predefined secondary endpoints of mucosal healing and durable clinical response (p <0.001 for both endpoints). A clinically meaningful effect of vedolizumab SC over placebo was observed for the predefined secondary endpoints of durable clinical remission at Weeks 6 and 52 and corticosteroid-free remission at Week 52. Although the results were not statistically significant, a greater proportion of subjects treated with vedolizumab SC achieved durable clinical remission (vedolizumab SC: 15.1%; placebo: 5.4%) and corticosteroid-free remission (vedolizumab SC: 28.9%; placebo: 8.3%) than in placebo subjects, with a treatment difference consistent with that seen previously with vedolizumab IV.

The results of the CHMP-requested analysis of durable clinical remission that evaluated the proportion of subjects in clinical remission for at least 80% of study visits during the maintenance phase, including the final visit, showed a treatment difference favoring vedolizumab SC over placebo (p <0.001). This analysis is a better assessment of sustained clinical remission during the maintenance phase because the subject population of Study SC-3027 had severe, acute flares at the time of enrollment and may not have achieved clinical remission by the end of the induction phase at Week 6.

Across all endpoints, there were no apparent differences in the magnitude of treatment benefit between vedolizumab SC and vedolizumab IV treatments, although not formally evaluated. These treatment differences observed with vedolizumab SC and IV treatment in Study SC-3027 were comparable to those from the prior pivotal vedolizumab IV Study C13006 (see Section 3.1).

Vedolizumab SC was efficacious in TNF-α antagonist–naive subjects and in those who had experienced prior treatment failure with these agents (see Section 3.2.2). In addition to the TNF-α antagonist status, strong internal consistency of the results was also supported by exploratory subgroups analyzed based on demographic factors and baseline disease characteristics (SC-3027 Figure 15.1.1.1).

Methods and results are presented in full in the SC-3027 CSR.

2.2 Other Efficacy Data: Vedolizumab SC Long-term Open-label Extension Study (Study SC-3030)

2.2.1 Design and Methodology

2.2.1.1 Study Design

Study SC-3030 is an ongoing phase 3b OLE study evaluating the long-term safety and efficacy of vedolizumab SC in subjects with UC or CD who participated in Study SC-3027 or Study SC-3031. From this OLE study of vedolizumab SC therapy, data regarding the occurrence of important clinical events resulting from chronic vedolizumab SC administration will be obtained.

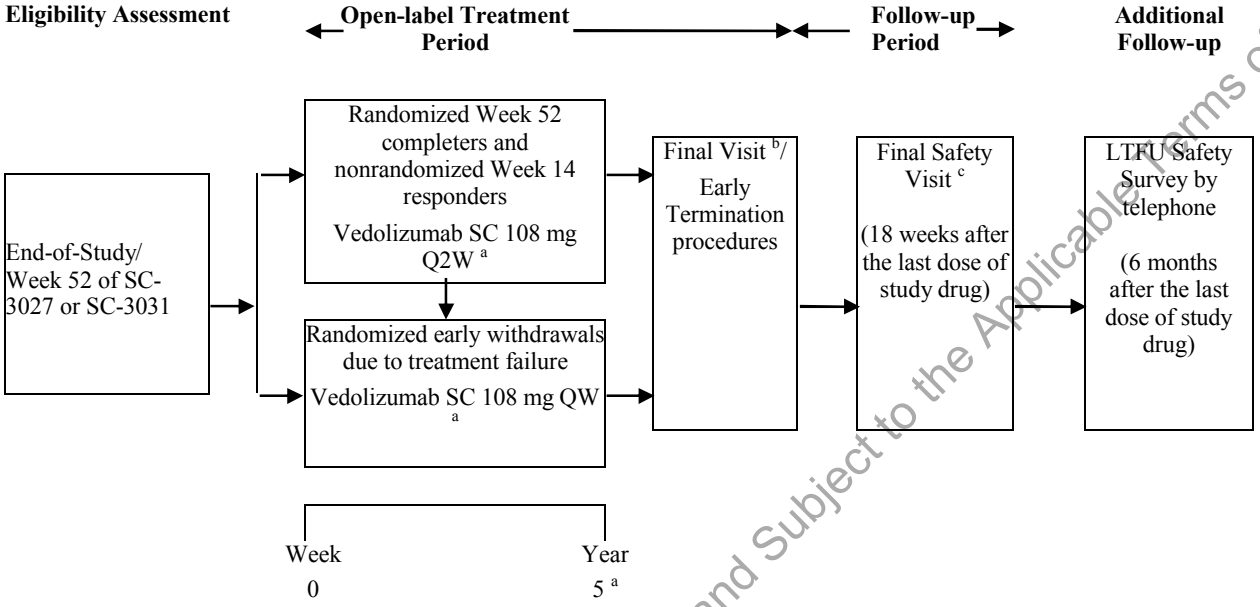
Important clinical events including those related to safety and adverse events of special interest (AESIs) as well as efficacy data (eg, maintenance of clinical remission/clinical response, quality of life, and various other PRO measures) are being collected. These long-term safety data for vedolizumab SC dosing are meant to complement the safety data gathered from Studies SC-3027 and Study SC-3031.

It is anticipated that the duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be for up to a maximum of 5 years. After the final dose of vedolizumab SC on the study, subjects will complete a final safety visit 18-weeks after the last dose received. Additionally, upon completion (or withdrawal) of this study, subjects will participate in a 6-month (from their last study drug dose) follow-up survey.

Subjects received training regarding the proper SC injection technique and how to manage hypersensitivity reactions potentially associated with the injection as described in Section 2.1.1.1. For all SC dosing occurring outside of the clinic, subjects will receive a phone call from study staff within 24 hours before every injection for these scheduled doses to administer the PML subjective checklist and inquire about general health status and experience with the prior injection.

A schematic of the study design is included as Figure 2.d.

Figure 2.d Schematic of SC-3030 Study Design



AI: autoinjector; LTFU: long-term follow-up; NSD: needle safety device; PFS: prefilled syringe; Q2W: once every 2 weeks; QW: once weekly; SC: subcutaneous.
[a] Subjects will switch to self-injection of vedolizumab SC in PFS + AI. Once the subject has switched to administer vedolizumab SC via PFS + AI, they will continue with all study-related procedures using the chosen presentation until the completion of the study or requested otherwise by the sponsor. Subjects may be switched back to PFS or to PFS + NSD only at the sponsor's request if any concern or issue is identified with PFS + AI.
Japan only: Subjects will have the option to switch to self-injection of vedolizumab SC in PFS + NSD or PFS + AI at any scheduled or unscheduled visit beginning at the Week 16 visit.
[b] Duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be for up to a maximum of 5 years from the initiation of the open-label extension study, or if the subject withdraws from the study, or the sponsor decides to close the study.
[c] Subjects who withdraw early will return 18 weeks after the last dose of vedolizumab SC for final safety assessments at the early termination visit.

2.2.1.2 Treatment Regimen and Dose

Subjects in this OLE study have participated in either the SC-3027 or SC-3031 study:

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

- Subjects who experienced treatment failure (ie, disease worsening, requirement for rescue medications) while receiving vedolizumab 108 mg Q2W during Study SC-3030 received a dose escalation of SC 108 mg QW.

The first dose of vedolizumab in this OLE study (ie, Week 0) should occur no more than 4 weeks after the last dose of study drug in the parent study. Subjects who discontinued the maintenance phase of the parent study (randomized early terminator subjects) received their first OLE dose of vedolizumab SC within 4 weeks after the last SC dose. For the Week 6 nonresponders who achieved clinical response at Week 14 after the third vedolizumab IV infusion, subjects were to receive their first OLE vedolizumab SC dose within 7 days (preferably 3) of Week 14 of the parent study.

2.2.1.3 Subject Population

As of the data cutoff date of 31 May 2018, a total of 598 rollover subjects were enrolled in Study SC-3030 (SC-3030 Table 15.1.3), and 595 subjects had received at least 1 dose of open-label treatment with vedolizumab SC (SC-3030 Table 15.1.7.1). One of the key inclusion criteria for a subject rolling over into Study SC-3030 (ie, from Study SC-3027 or Study SC-3031) includes confirmation, in the opinion of the investigator, that treatment in the respective previous study was well tolerated. Subjects who withdrew early from Study SC-3027 or Study SC-3031 must have withdrawn because of treatment failure (ie, as determined by disease worsening or need for rescue medications from Week 14). Another key inclusion criterion required subjects with a family history of colorectal cancer, personal history of colorectal cancer risk, aged >50 years, or other known risk factor must have been up-to-date on colorectal cancer surveillance.

Subjects experiencing treatment failure in Study SC-3027 or SC-3031 only because of receiving rescue medications (and without meeting the definition for disease worsening) before Week 14 are not eligible to participate in Study SC-3030. Other key exclusion criteria for rollover subjects included having required major surgical intervention for IBD during or after participation in a prior vedolizumab study, currently requiring major surgical intervention for IBD, or anticipated to require major surgical intervention for IBD during the conduct of Study SC-3030. Subjects were also excluded from Study SC-3030 if they had received live vaccinations within 30 days before vedolizumab administration, or developed a significant comorbid unstable or uncontrolled medical disorder that would, in the opinion of the investigator, compromise subject safety or confound study results. Additionally, subjects could not have withdrawn from a previous vedolizumab study because of a study drug-related AE or have psychiatric disease or substance abuse problems at the time of study entry.

A complete list of the inclusion and exclusion criteria can be found in SC-3030 Interim CSR (results through 31 May 2018) Section 9.3.

2.2.1.4 Endpoints

The primary endpoints in Study SC-3030 are related to safety. The secondary endpoints are:

- The 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 subjects with UC, and HBI scores (defined as a ≥3-point decreased in HBI score from baseline) in subjects with CD.
- The 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 subjects with UC, and HBI scores (defined as a HBI score of ≤4 points) in subjects with CD.

Several PRO endpoints and exploratory endpoint analyses, including IBDQ, EQ-5D, and WPAI-UC scores; PK; immunogenicity (eg, proportion of subjects with positive AVA); and resource utilization endpoints are planned for this long-term study. However, because limited data were available at the time of the 31 May 2018 data cut, these analyses are not included in this overall efficacy assessment.

2.2.1.5 Analysis Populations

The efficacy population was defined as the FAS, including all enrolled UC subjects (FAS-UC) and all enrolled CD subjects (FAS-CD) of SC-3030. Analysis of efficacy variables was conducted using the FAS. Because parent study SC-3031 was ongoing at the time of the interim data cut for Study SC-3030, the treatment assignment for CD subjects in Study SC-3031 remains blinded. Thus, only a subset of the FAS-CD is included in this interim assessment for efficacy.

The safety analysis set (SAF) included all subjects who received at least 1 dose of study medication in Study SC-3030.

2.2.1.6 Analysis Plan

The statistical objective of the efficacy analysis in Study SC-3030 is to descriptively summarize the efficacy endpoints rather than formal hypothesis testing for statistical inference. Descriptive statistics, including 95% CIs where appropriate, are provided for all clinical efficacy variables of interest. Analysis of efficacy variables was conducted in the FAS-UC by previous treatment group in Study SC-3027 (including nonrandomized Week 14 responder UC subjects, placebo, vedolizumab SC, and vedolizumab IV) and in the FAS-CD by previous treatment group in SC-3031 (including nonrandomized Week 14 responders, placebo, and vedolizumab SC).

Descriptive statistics, including 95% CIs, were reported to summarize the partial Mayo score (subjects with UC) and HBI score (subjects with CD). The change from baseline in partial Mayo and HBI scores are summarized by time point, and the means are plotted over time. The proportion of subjects who are in clinical remission and clinical response are summarized by time point.

2.2.1.7 Data Sets Analyzed

Secondary and exploratory efficacy assessments were made on the FAS population, which consists of all subjects who participated in Study SC-3027 or Study SC-3031 and received any amount of vedolizumab in Study SC-3030, and had at least 1 postbaseline efficacy assessment in the previous study (FAS-UC and FAS-CD, respectively).

For subjects with UC, results are provided for 3 groups of subjects depending on their disposition and treatment group in Study SC-3027: randomized completers of the maintenance phase, nonrandomized Week 14 responders, and randomized early terminators.

- *Randomized completer subjects* received vedolizumab IV during the induction phase of Study SC-3027, achieved clinical response at Week 6, were subsequently randomized to the Study SC-3027 maintenance phase to receive vedolizumab SC 108 mg Q2W, vedolizumab IV 300 mg Q8W, or placebo, and completed 52 weeks of therapy in Study SC-3027. These subjects then rolled over to Study SC-3030, during which they received open-label vedolizumab SC 108 mg Q2W. If these subjects experienced disease worsening during Study SC-3030, they were dose escalated to vedolizumab SC 108 mg QW.
- *Randomized early terminator subjects* received vedolizumab IV during the induction phase of Study SC-3027, achieved clinical response at Week 6, and were subsequently randomized to the maintenance phase of Study SC-3027 to receive vedolizumab SC 108 mg Q2W, vedolizumab IV 300 mg Q8W, or placebo, but withdrew between Weeks 6 and 52 because of disease worsening or the need for rescue medications. These subjects then rolled over to Study SC-3030, during which they received open-label vedolizumab SC 108 mg QW.
- *Nonrandomized Week 14 responder UC subjects* received vedolizumab IV during the induction phase of Study SC-3027, were nonresponders at Week 6, but did achieve a clinical response at Week 14 after receiving a third vedolizumab IV infusion at Week 6. These subjects then rolled over to Study SC-3030, during which they received open-label vedolizumab SC 108 mg Q2W. If these subjects experienced disease worsening during Study SC-3030, they were dose escalated to vedolizumab SC QW.

Presentation of results in these groups is based on the subject treatment group during Study SC-3027.

For subjects with CD, results are provided only for the nonrandomized Week 14 responder CD subjects (N = 97) in Study SC-3031, that is, subjects who received 2 doses of open-label vedolizumab IV induction (Weeks 0 and 2) and did not achieve a clinical response at Week 6 but did achieve a clinical response at Week 14 after receiving a third vedolizumab IV infusion at Week 6 in Study SC-3031. At the time of the 31 July 2018 interim analysis, Study SC-3031 is ongoing, and treatment assignments of the subjects randomized in the maintenance phase are blinded.

2.2.2 Subjects With UC

Data presented in this section are from subjects who participated in Study SC-3027 before enrolling in Study SC-3030.

2.2.2.1 Demographics

Of the 598 subjects who entered Study SC-3030, 287 were from Study SC-3027 (subjects with UC) (SC-3030 Table 15.1.3). Of these subjects with UC, 57 were randomized early terminator subjects, and 123 were randomized completer subjects (SC-3030 Table 15.1.5.2). Fifty-two subjects were previously treated with placebo, 89 subjects with vedolizumab SC, and 39 subjects with vedolizumab IV during the maintenance phase of Study SC-3027. A total of 107 nonrandomized Week 14 responder UC subjects enrolled into Study SC-3030 (SC-3030 Table 15.1.5.1).

Overall, demographic characteristics were balanced across the UC safety population (SC-3030 Table 15.1.8.1.1). In the overall UC population, there was a higher proportion of male subjects than female subjects (58.2% and 41.8%, respectively). Most subjects (78.2%) were white. The median age was 39.0 years; most subjects were aged ≥35 years (60.0%), and few subjects were aged ≥65 years (8.1%). With respect to geographic distribution, 15.8% were enrolled at sites in North America, and 84.2% were enrolled at sites outside of North America, mostly across Europe (61.8%).

In the overall population of UC subjects, the mean duration of UC was 8.32 years and 45.3% of subjects had a duration ≥7 years. Overall, 15.3% of subjects had an extraintestinal manifestation (Study SC-3030 Table 15.1.8.2.1.1).

2.2.2.2 Efficacy Results

Study SC-3030 is an ongoing, open-label, uncontrolled study. Efficacy analyses in Study SC-3030 were considered secondary or exploratory in nature.

Two baselines were used for analysis of long-term efficacy in Study SC-3030:

- SC-3030 Week 0: When values were compared with those from Week 0 of Study SC-3030, the SC-3030 Week 0 data were defined as the last nonmissing measurement before or on the date of the first dose of study drug in Study SC-3030.
- SC-3027 baseline: When values were compared with baseline of Study SC-3027 (hereafter referred to as *baseline* for this study), those baseline data were defined as the last nonmissing measurement before or on the date of the first dose of study drug in Study SC-3027.

Long-term efficacy analyses were performed in Study SC-3030 by longitudinally integrating data collected during the study and that from prior studies. For subjects with UC, data from Study SC-3027 and Study SC-3030 were integrated. Efficacy analyses for subjects with UC include presentations of mean partial Mayo scores and the proportions of subjects who achieved clinical remission and clinical response at selected time points. Each of these analyses is discussed for 3 groups of subjects, depending on their disposition and treatment group during

Study SC-3027, as discussed above: randomized completer subjects, randomized early terminator subjects, and nonrandomized Week 14 responder UC subjects.

Clinical remission for the UC subject population from Study SC-3027 was based on partial Mayo score, defined as a Mayo score of ≤2 points and no individual subscore >1 point. Clinical response was 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.

Because Study SC-3030 was ongoing at the time of the 31 May 2018 data cut, not all subjects had reached visits at later time points in the study. Therefore, the results as presented are based on the evaluable subjects per visit (see SC-3030 Interim CSR [results through 31 May 2018] Section 9.7.1.4 for more details).

2.2.2.3 Efficacy Population of Randomized Completer Subjects

2.2.2.3.1 Durability of Clinical Remission and Response

To evaluate whether the efficacy of vedolizumab SC is maintained over time, analyses of clinical remission and clinical response rates are presented for the randomized completer subjects (ie, subjects who completed 52 weeks of therapy in Study SC-3027; FAS-UC) by treatment group in Study SC-3027. Of the 287 subjects in the FAS-UC population, 123 subjects were randomized completer subjects (SC-3030 Table 15.1.3 and 15.1.5.2). Subjects whose vedolizumab SC dose was escalated to QW were considered nonresponders/nonremitters in the analyses presented in this section.

Because of the 31 May 2018 data cutoff date, few subjects have completed study visits beyond Week 24 of Study SC-3030.

Rates of clinical remission and clinical response at selected time points in Studies SC-3027 and SC-3030 are presented for the FAS-UC population of randomized completer subjects in Table 2.f.

Randomized Vedolizumab SC Completer Subjects: Randomized completer subjects who were treated with vedolizumab SC Q2W during the Study SC-3027 maintenance phase and continued vedolizumab SC Q2W treatment during Study SC-3030 maintained clinical remission beyond Week 52. In this population, 92.5% (62 of 67 evaluable subjects) were in clinical remission at Week 0 of Study SC-3030, and 66.7% (16 of 24 evaluable subjects) maintained clinical remission at Week 24. Similarly, in the population of randomized completer subjects who were treated with vedolizumab SC in Study SC-3027, 97.0% (65 of 67 evaluable subjects) entered Study SC-3030 in clinical response, and 70.8% (17 of 24 evaluable subjects) maintained clinical response at Week 24 of Study SC-3030.

Randomized Vedolizumab IV Completer Subjects: Randomized completer subjects who were treated with vedolizumab IV in Study SC-3027 and transitioned to vedolizumab SC administration at Week 0 of Study SC-3030 maintained clinical remission and clinical response rates during Study SC-3030. At Week 24 of Study SC-3030, 76.9% (10 of 13 evaluable subjects)

of this subject population was in clinical remission, and 76.9% (10 of 13 evaluable subjects) of these subjects achieved clinical response. The analysis of this population also provides evidence that transitioning from vedolizumab IV treatment to vedolizumab SC at Week 52 is effective in maintaining clinical remission and clinical response long term.

Further details of the analyses, including additional time points, are presented in the SC-3030 Interim CSR [results through 31 May 2018].

Table 2.f Proportion of UC Subjects With Clinical Remission and Clinical Response, Randomized Completer Subjects Who Received Vedolizumab SC Q2W During Study SC-3030 (FAS-UC), Interim Analysis Through 31 May 2018

		Vedolizumab SC 108 mg During Study SC-3030 [a]		
Visit		**PBO N = 20**	**VDZ SC 108 mg N = 68**	**VDZ IV 300 mg N = 35**
Clinical remission [b]				
SC-3030 Week 0	N	19	67	35
	n (%)	10 (52.6)	62 (92.5)	27 (77.1)
Week 24	N	7	24	13
	n (%)	6 (85.7)	16 (66.7)	10 (76.9)
Clinical response [c]				
SC-3030 Week 0	N	19	67	35
	n (%)	15 (78.9)	65 (97.0)	35 (100.0)
Week 24	N	7	24	13
	n (%)	6 (85.7)	17 (70.8)	10 (76.9)

Source: SC-3030 Table 15.2.2.2 (clinical remission) and 15.2.1.2 (clinical response).
FAS-UC: full analysis set-ulcerative colitis; IV: intravenous; PBO: placebo; Q2W: once every 2 weeks; QW: once weekly; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.
Subjects who have withdrawn from Study SC-3030 with missing data for determination of endpoint status were categorized as nonresponders. Subjects who were ongoing in Study SC-3030 with missing data for determination of endpoint status were categorized as nonresponders only up to the visit reached by the time of interim data cut.
Included randomized subjects who completed the maintenance phase (Week 52 drug/placebo) of Study SC-3027 (Week 0 of Study SC-3027 as baseline) and randomized subjects who completed Week 52 drug/placebo (Week 0 of Study SC-3027 as baseline).
Subjects who had their dose escalated from vedolizumab SC Q2W to QW dosing were considered nonresponders.
[a] Subjects (randomized completer subjects or nonrandomized Week 14 responder UC subjects from Study SC-3027) could have received either Q2W or QW dosing in Study SC-3030.
[b] Clinical remission was defined as a partial Mayo score of ≤2 points and no individual subscore >1 point.
[c] Clinical response was defined as a reduction in partial Mayo score of ≥2 points and ≥25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

In addition, analysis of efficacy in the randomized placebo subjects in Study SC-3027 who were then treated with vedolizumab SC Q2W in Study SC-3030 after 46-week interruption after IV treatment was conducted. Clinical remission rates at selected time points in Studies SC-3027 and

SC-3030 are presented in Table 2.f and in SC-3030 Table 15.2.2.2). In this group, clinical remission rates rose from 52.6% (10 of 19 evaluable subjects) at Week 0 of Study SC-3030 to 75.0% (6 of 8 evaluable subjects) at Week 16 and 85.7% (6 of 7 evaluable subjects) at Week 24 of Study SC-3030. These results indicate that treatment with vedolizumab SC after an extended interruption of vedolizumab treatment maintains therapeutic benefits.

2.2.2.3.2 Nonrandomized Week 14 Responder UC Subjects

The nonrandomized Week 14 responder UC subjects achieved clinical response after receiving a third infusion of vedolizumab IV at Week 14 in Study SC-3027 before beginning vedolizumab SC treatment in Study SC-3030. Of the 287 subjects in the FAS-UC population, 107 subjects were nonrandomized Week 14 UC responder subjects (SC-3030 Table 15.1.3 and 15.1.5.2).

Clinical remission and clinical response rates at selected time points in Study SC-3030 are presented for the nonrandomized Week 14 UC responder subjects in Table 2.g. In these analyses, dose escalation was considered treatment failure (ie, nonresponders/nonremitters).

At Week 0 of Study SC-3030, 57.0% of the nonrandomized Week 14 responder UC subjects were in clinical remission after IV treatment; clinical remission was maintained after receiving vedolizumab SC treatment in Study SC-3030. At Week 40 of Study SC-3030, the time point at which subjects had received vedolizumab treatment for 54 weeks (14 weeks of induction treatment in Study SC-3027 and 40 weeks of vedolizumab SC treatment in Study SC-3030), the clinical remission rate was 39.2% (40 of 102 evaluable subjects) for subjects receiving vedolizumab SC Q2W.

These data also support that transitioning to vedolizumab SC after 3 vedolizumab IV induction doses maintains therapeutic benefits long-term.

Further details of the analyses, including additional time points, are presented in the SC-3030 Interim CSR [results through 31 May 2018].

Table 2.g Proportion of UC Subjects With Clinical Remission and Clinical Response, Nonrandomized Week 14 UC Responder Subjects Who Received Vedolizumab SC Q2W During Study SC-3030 (FAS-UC) - Interim Analysis Through 31 May 2018

		VDZ SC 108 mg During Study SC-3030
		Nonrandomized Week 14 Responders
Visit		N = 107
Clinical remission		
SC-3030 Week 0	N	107
	n (%)	61 (57.0)
Week 40	N	102
	n (%)	40 (39.2)
Clinical response		
SC-3030 Week 0	N	107
	n (%)	100 (93.5)
Week 40	N	102
	n (%)	49 (48.0)

Source: SC-3030 Table 15.2.2.2 (clinical remission) and Table 15.2.1.2 (clinical response).
FAS-UC: full analysis set-ulcerative colitis; IV: intravenous; Q2W: once every 2 weeks; QW: once weekly; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.
All subjects with missing data for determination of endpoint status are categorized as nonresponders.
Subjects who withdrew from Study SC-3030 with missing data for determination of endpoint status were categorized as nonresponders. Subjects who were ongoing in Study SC-3030 with missing data for the determination of endpoint status were categorized as nonresponders only up to the visit reached by the time of interim data cut.
Clinical remission was defined as a partial Mayo score of ≤2 and no individual subscore >1 point in UC subjects.
Clinical remission was assigned as *nonresponder* for subjects who dose escalated from vedolizumab SC Q2W to QW dosing.
Clinical response was 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.

2.2.2.3.3 Recapturing Clinical Response in Randomized Subjects With UC Who Lost Clinical Response in Study SC-3027 (Randomized Early Terminator Subjects)

To evaluate whether lost efficacy is regained with vedolizumab SC treatment, analyses of clinical remission rates and clinical response rates based on partial Mayo scores are presented for the randomized early terminator subjects (ie, subjects withdrawn from the maintenance phase of Study SC-3027 because of disease worsening or the need for rescue medications) by treatment group from Study SC-3027 and who transitioned to weekly dosing. Fifty-seven of the 287 subjects in the FAS-UC population of Study SC-3030 had withdrawn prematurely from Study SC-3027 (SC-3030 Table 15.1.5.2).

Clinical remission and clinical response rates at selected time points in Studies SC-3027 and SC-3030 are presented for the Study SC-3027 population of randomized early terminator subjects who continued into Study SC-3030 and received vedolizumab SC (QW dosing) in Table 2.h.

At entry into Study SC-3030, 9.4% of the randomized early terminator subjects treated with placebo in Study SC-3027 were in clinical remission. No subjects in either vedolizumab group were in clinical remission at Week 0 of Study SC-3030. Increases in the proportions of evaluable subjects who achieved clinical remission were observed for all randomized early terminator subject groups during treatment with vedolizumab SC QW in Study SC-3030 as early as 4 weeks after starting vedolizumab SC QW treatment (Table 2.h).

Table 2.h Proportion of UC Subjects With Clinical Remission and Clinical Response, Randomized Early Terminator Subjects (FAS-UC), Interim Analysis Through 31 May 2018

Visit		PBO N = 32	VDZ SC 108 mg N = 21	VDZ IV 300 mg N = 4
Clinical remission [a]				
SC-3027 Week 6	N	32	21	4
	n (%)	22 (68.8)	12 (57.1)	1 (25.0)
Week 30	N	32	21	4
	n (%)	10 (31.3)	4 (19.0)	0
SC-3030 Week 0	N	32	21	4
	n (%)	3 (9.4)	0	0
Week 4	N	32	21	4
	n (%)	13 (40.6)	7 (33.3)	2 (50.0)
Week 8	N	31	21	4
	n (%)	16 (51.6)	7 (33.3)	0
Week 16	N	28	21	4
	n (%)	19 (67.9)	7 (33.3)	1 (25.0)
Week 24	N	24	18	4
	n (%)	13 (54.2)	5 (27.8)	0
Clinical response [b]				
SC-3027 Week 6	N	32	21	4
	n (%)	32 (100.0)	20 (95.2)	3 (75.0)
Week 30	N	32	21	4
	n (%)	14 (43.8)	7 (33.3)	2 (50.0)
SC-3030 Week 0	N	32	21	4
	n (%)	0	0	0
Week 4	N	32	21	4
	n (%)	20 (62.5)	9 (42.9)	3 (75.0)
Week 8	N	31	21	4
	n (%)	22 (71.0)	10 (47.6)	0
Week 16	N	28	21	4
	n (%)	21 (75.0)	10 (47.6)	2 (50.0)
Week 24	N	24	18	4
	n (%)	16 (66.7)	7 (38.9)	0

Source: SC-3030 Table 15.2.2.1 (clinical remission), Table 15.2.1.1 (clinical response), Table 15.2.14.1.1 (combined analysis).
FAS-UC: full analysis set-ulcerative colitis; IV: intravenous; PBO: placebo; QW: once weekly; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.
The analyses were performed in Studies SC-3027 and SC-3030 separately. For SC-3030 visits, SC-3030 Week 0 was used as baseline.
Data for all visits presented in this table were based on partial Mayo score.
Includes subjects who withdrew early from the Study SC-3027 maintenance phase between Weeks 6 and 52.
Subjects who have completed or withdrawn from Study SC-3030 with missing data for determination of endpoint status were categorized as nonresponders. Subjects ongoing in the Study SC-3030, with missing data for determination of endpoint status were categorized as nonresponders only up to the visit reached by the time of the interim data cut.
Subjects received vedolizumab SC 108 mg QW during Study SC-3030.
[a] Clinical remission was defined as a partial Mayo score of ≤2 and no individual subscore >1 point.
[b] Clinical response was 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 subjects with UC.

2.2.2.3.4 Increased Dosing Frequency (Q2W to QW)

For subjects who experienced disease worsening while receiving vedolizumab SC Q2W treatment during Study SC-3030, the frequency of vedolizumab SC administration was increased to QW. There were 33 UC subjects who required dose escalation during Study SC-3030. Of these subjects, 29 were nonrandomized Week 14 responder UC subjects and 4 were randomized completer subjects (2 subjects previously randomized to vedolizumab SC and 2 subjects previously randomized to vedolizumab IV treatment during Study SC-3027). Dose escalation of vedolizumab SC resulted in recapturing clinical remission in 38.5% (10 of 26 evaluable subjects) at Week 24 of Study SC-3030 (SC-3030 Table 30.6.2.2, post hoc).

These data showed that in the few subjects who experienced treatment failure while on vedolizumab SC Q2W in Study SC-3030, increasing the dosing frequency of 108 mg vedolizumab injections from a Q2W to QW regimen recaptured the lost efficacy in some subjects.

2.2.3 Subjects With CD

Data presented in this section are from subjects who participated in the parent Study SC-3031 before enrolling in Study SC-3030. Subjects who completed the maintenance phase (Week 52 assessment) of Study SC-3031 or were randomized to the maintenance phase but discontinued early because of treatment failure were eligible to enroll in Study SC-3030. Subjects who were nonresponders at Week 6 received a third vedolizumab IV infusion and subsequently showed a response at Week 14 (ie, nonrandomized Week 14 responder CD subjects) were eligible to participate in Study SC-3030.

Because Study SC-3031 is ongoing and data are blinded, only efficacy data from the nonrandomized Week 14 responder CD subjects (N = 97) as of the 31 May 2018 data cutoff date are summarized in this section.

2.2.3.1 Demographics

Overall, demographic characteristics were similar across the Study SC-3030 CD safety population (ie, nonrandomized Week 14 responder CD subjects and the combined randomized subjects rolling over to Study SC-3030 regardless of their Study SC-3031 disposition and treatment). In the overall population, there was a similar proportion of male subjects and female subjects (53.2% and 46.8%, respectively). Most (90.0%) subjects were white. The median age was 35.5 years; more than half of subjects were aged ≥35 years (53.5%), few subjects were aged ≥65 years (3.5%), and 55.8% of subjects had never smoked (SC-3030 Table 15.1.8.1.1).

More than half of subjects had a duration of CD of 7 or more years (50.5% for nonrandomized Week 14 responder CD subjects and 58.4% for combined randomized subjects). Baseline disease activity, as assessed by category of CDAI score and category of baseline fecal calprotectin, was similar in both groups. In more than half of the subjects, the disease involved the colon (20.9% colon only, 44.4% ileocolonic). Of the 311 subjects, 25.4% had fistulizing disease, and 62.1% had prior or ongoing extraintestinal manifestations (SC-3030 Table 15.1.8.2.2.1).

2.2.3.2 Efficacy Results for the Subject Population of Week 14 Responder CD Subjects

Because Study SC-3030 is a long-term safety study, efficacy analyses in Study SC-3030 were secondary or exploratory in nature. Efficacy analyses for subjects with CD included the proportion of subjects who achieved clinical remission and changes in the HBI scores at selected time points (ie, at every clinic visit).

Because Study SC-3030 was ongoing at the time of 31 May 2018 data cutoff date, few subjects had reached visits beyond Week 64 of Study SC-3030 (combined vedolizumab treatment of 78 weeks, including the 14-week vedolizumab IV treatment in Study SC-3031).

To evaluate whether the efficacy of vedolizumab SC is maintained among nonrandomized Week 14 responder CD subjects, analyses of clinical remission rates are presented for the FAS-CD population of nonrandomized Week 14 responder CD subjects. At the time of the 31 May 2018 interim data cut for Study SC-3030, 97 of 311 subjects in the total FAS-CD population were nonrandomized Week 14 responder CD subjects who had rolled over from Study SC-3031 (SC-3030 Table 15.1.5.1).

At Week 0 of Study SC-3030, 45.4% (44 of 97 evaluable subjects) of nonrandomized Week 14 responder CD subjects were in clinical remission, which was maintained with vedolizumab SC treatment during Study SC-3030. At Week 40 of Study SC-3030, at which time point these subjects had received vedolizumab treatment for 54 weeks (14 weeks of vedolizumab IV induction treatment in Study SC-3031 and 40 weeks of vedolizumab SC treatment in Study SC-3030), the clinical remission rate was 30.9% (17 of 55 evaluable subjects) (SC-3030 Table 15.2.2.2).

2.2.4 Conclusions

The interim exploratory efficacy results from ongoing, OLE Study SC-3030 supported that vedolizumab SC treatment maintains long-term clinical remission and clinical response rates (beyond 52 weeks) in subjects treated with 108 mg vedolizumab SC Q2W. In addition, data from Study SC-3030 support that transitioning from initial vedolizumab IV treatment to SC maintenance treatment will maintain therapeutic benefit, regardless of the duration of the initial IV treatment. Furthermore, results from Study SC-3030 suggest that subjects who responded to initial vedolizumab IV induction therapy, then reinitiated vedolizumab treatment with SC after an extended treatment interruption, retained clinical benefits long-term. Also, per available data, CD subjects who needed 3 infusions of vedolizumab IV induction therapy to achieve therapeutic benefit maintained long-term benefits with vedolizumab SC maintenance treatment.

Methods and results are presented in full in the SC-3030 Interim CSR [results through 31 May 2018].

3.0 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

In this section, efficacy data from individual studies are presented by similar endpoints to better understand the effects of vedolizumab treatment. This section is divided into 2 main subsections:

- Section 3.1 presents a side-by-side comparison of key maintenance efficacy endpoints of the vedolizumab SC and IV treatments in controlled Study SC-3027 with the prior vedolizumab IV maintenance treatments in controlled Study C13006 that supported the registration of IV administration.
- Section 3.2 presents data supporting the efficacy of vedolizumab SC maintenance treatment based on data from Study SC-3027 subgroup analyses according to prior TNF-α antagonist treatment (TNF-α antagonist–naive subjects or subjects who experienced previous treatment failure with TNF-α antagonists).

3.1 Comparison Across SC and IV Vedolizumab Maintenance Therapies

To characterize the efficacy of SC administration relative to the approved IV route, this section describes results from Study SC-3027 for both SC and IV administration with reference to maintenance data from Study C13006. While acknowledging cross-study limitations, this analysis provides supportive evidence that efficacy with SC is expected to be similar to that seen with IV in the clinic.

Study C13006 was conducted as part of the vedolizumab IV clinical development program, and the CSR was submitted in the marketing applications for vedolizumab (ENTYVIO) for IV injection. Study C13006 was a phase 3, randomized, placebo-controlled, double-blind, multicenter study designed to evaluate the efficacy and safety of vedolizumab IV in subjects with moderately to severely active UC. The study included separate induction and maintenance phases that evaluated vedolizumab IV when administered as 300 mg IV doses at Weeks 0 and 2 followed by 300 mg IV doses either Q4W or Q8W starting at Week 6 through Week 52. The design, study population, and endpoints were like those in Study SC-3027. Please refer to the C13006 CSR for full study details and results.

3.1.1 Study Populations for Studies SC-3027 and C13006

Comparisons of datasets, select demographics, and baseline characteristics for subjects in Studies SC-3027 and C13006 (maintenance phase) are presented below

A complete summary of all available demographics and baseline characteristics for these studies can be found in the respective CSRs (SC-3027 and C13006).

3.1.1.1 Datasets Analyzed

In Study SC-3027, a total of 383 subjects received 2 open-label IV induction doses of vedolizumab, and 216 of these subjects were randomized into the maintenance phase of Study SC-3027 (placebo: 56 subjects; vedolizumab SC: 106 subjects; and vedolizumab IV: 54 subjects). All 216 subjects were included in the SAF (Integrated Summary of Efficacy SC-3027 and C13006 Table 30.7.6.1).

In Study C13006, the maintenance study intent-to-treat (ITT) population included 373 vedolizumab subjects who had a clinical response during the induction phase and were randomized to 1 of 2 vedolizumab IV dosing regimens (300 mg Q4W: 125 subjects; or 300 mg Q8W: 122 subjects) or placebo (126 subjects) during the maintenance phase (Integrated Summary of Efficacy SC-3027 and C13006 Table 30.7.6.1).

3.1.1.2 Baseline Demographics

Study C13006 was designed to evaluate the efficacy of vedolizumab IV in subjects with moderate to severe UC. Study SC-3027 was designed to evaluate the efficacy of vedolizumab in a population with similar characteristics and likely to respond to vedolizumab IV induction.

Baseline demographic characteristics for Studies SC-3027 and C13006 are shown in Table 3.a. Baseline demographic characteristics were similar in both studies and across the treatment groups in each study.

Table 3.a Baseline Demographics (Studies SC-3027 and C13006)

	SC-3027 FAS			C13006 Maintenance ITT		
Parameter	**PBO N = 56**	**VDZ SC 108 mg Q2W N = 106**	**VDZ IV 300 mg Q8W N = 54**	**PBO N = 126**	**VDZ IV 300 mg Q4W N = 125**	**VDZ IV 300 mg Q8W N = 122**
Gender, n (%)						
Male	34 (60.7)	65 (61.3)	31 (57.4)	69 (54.8)	68 (54.4)	70 (57.4)
Female	22 (39.3)	41 (38.7)	23 (42.6)	57 (45.2)	57 (45.6)	52 (42.6)
Race, n (%)						
White	42 (75.0)	92 (86.8)	47 (87.0)	101 (80.2)	101 (80.8)	104 (85.2)
Black	0	0	2 (3.7)	2 (1.6)	1 (0.8)	4 (3.3)
Native Hawaiian or other islander	0	0	0	0	1 (0.8)	0
Asian	13 (23.2)	14 (13.2)	5 (9.3)	20 (15.9)	21 (16.8)	13 (10.7)
American Indian or Alaskan	1 (1.8)	0	0	1 (0.8)	0	1 (0.8)
Other	0	0	0	2 (1.6)	1 (0.8)	0
Age (years) [a]						
Mean (SD)	39.4 (11.70)	38.1 (13.12)	41.6 (14.11)	40.3 (13.92)	38.6 (14.21)	41.0 (12.85)
Median	37.0	36.0	40.5	39.9	35.7	39.7
Minimum, maximum	21, 66	18, 69	18, 68	18, 74	19, 76	19, 78
Age (years), n (%)						
<35	21 (37.5)	49 (46.2)	19 (35.2)	54 (42.9)	57 (45.6)	44 (36.1)
≥35	35 (62.5)	57 (53.8)	35 (64.8)	72 (57.1)	68 (54.4)	78 (63.9)

Footnotes on last table page.

Table 3.a Baseline Demographics (Studies SC-3027 and C13006) (continued)

	SC-3027 FAS			C13006 Maintenance ITT		
Parameter	**PBO N = 56**	**VDZ SC 108 mg Q2W N = 106**	**VDZ IV 300 mg Q8W N = 54**	**PBO N = 126**	**VDZ IV 300 mg Q4W N = 125**	**VDZ IV 300 mg Q8W N = 122**
Body weight (kg)						
Mean (SD)	73.96 (20.915)	71.58 (17.171)	76.95 (16.933)	74.73 (20.423)	71.77 (16.710)	78.17 (18.758)
Median	71.15	70.00	75.20	74.75	69.60	77.55
Minimum, maximum	40.6, 160.0	44.0, 131.0	50.6, 124.8	35.7, 160.0	37.9, 119.0	42.6, 132.7
BMI (kg/m^2)						
Mean (SD)	24.66 (5.819)	24.07 (4.718)	26.21 (4.887)	25.85 (6.063)	24.49 (4.697)	26.80 (6.263)
Median	23.94	23.60	26.50	25.07	23.64	26.05
Minimum, maximum	14.1, 51.1	17.0, 41.0	16.3, 35.3	15.3, 52.2	15.6, 39.7	16.1, 48.2
Geographic region, n (%)						
North America	9 (16.1)	9 (8.5)	10 (18.5)	36 (28.6)	37 (29.6)	49 (40.2)
South America	1 (1.8)	3 (2.8)	1 (1.9)	0	0	0
Western/Northern Europe	6 (10.7)	10 (9.4)	6 (11.1)	20 (15.9)	25 (20.0)	23 (18.9)
Central Europe	19 (33.9)	51 (48.1)	24 (44.4)	26 (20.6)	25 (20.0)	20 (16.4)
Eastern Europe	8 (14.3)	17 (16.0)	7 (13.0)	10 (7.9)	11 (8.8)	12 (9.8)
Asia/Australia/Africa	13 (23.2)	16 (15.1)	6 (11.1)	34 (27.0)	27 (21.6)	18 (14.8)

Source: Integrated Summary of Efficacy SC-3027 and C13006 Table 30.7.6.2.
BMI: body mass index; FAS: full analysis set; ITT: intent to treat; IV: intravenous; PBO: placebo; Q2W: once every 2 weeks; Q8W: once every 8 weeks; SC: subcutaneous; VDZ: vedolizumab.
[a] For SC-3027, age at date of informed consent. For C13006, age is defined as (1 + first dose date - birth date) / 365.25.

3.1.1.3 Baseline UC Disease Characteristics

The baseline UC disease characteristics from the maintenance phase of Studies SC-3027 and C13006 are shown in Table 3.b.

The baseline UC disease characteristics were similar between Studies SC-3027 and C13006, including the duration of the disease and disease localization. The percentage of subjects with severe UC disease, as assessed by the complete Mayo score, was higher in the Study SC-3027 study population than in the Study C13006 population.

All baseline disease characteristic parameters were well balanced across the treatment groups within both studies.

Table 3.b Baseline UC Disease Characteristics (Studies SC-3027 and C13006)

Parameter	Study SC-3027 FAS			Study C13006 Maintenance ITT		
	PBO N = 56	VDZ SC 108 mg Q2W N = 106	300 mg VDZ IV Q8W N=54	PBO N = 126	VDZ IV 300 mg Q4W N = 125	VDZ IV 300 mg Q8W N = 122
Duration of UC (years)						
Mean (SD)	7.36 (7.147)	7.96 (6.217)	8.18 (5.929)	7.77 (6.876)	7.65 (7.019)	6.24 (4.758)
Median	5.32	5.93	6.79	5.35	5.00	5.40
Minimum, maximum	0.6, 30.3	0.6, 29.8	0.5, 30.9	0.5, 29.7	0.5, 37.5	0.7, 26.3
Baseline disease activity						
Mild (Mayo score <6)	0	0	0	6 (4.8)	1 (0.8)	5 (4.1)
Moderate (Mayo score = 6-8)	20 (35.7)	46 (43.4)	17 (31.5)	63 (50.0)	72 (57.6)	62 (50.8)
Severe (Mayo score = 9-12)	36 (64.3)	60 (56.6)	37 (68.5)	57 (45.2)	52 (41.6)	55 (45.1)
Categorical baseline fecal calprotectin						
≤250 µg/g	5 (8.9)	9 (8.5)	2 (3.7)	25 (19.8)	21 (16.8)	26 (21.3)
>250 to ≤500 µg/g	7 (12.5)	6 (5.7)	4 (7.4)	13 (10.3)	19 (15.2)	18 (14.8)
>500 µg/g	44 (78.6)	87 (82.1)	46 (85.2)	84 (66.7)	77 (61.6)	73 (59.8)
Missing	0	4 (3.8)	2 (3.7)	44 (3.2)	8 (6.4)	5 (4.1)
Disease localization, n (%)						
Proctosigmoiditis	7 (12.5)	15 (14.2)	7 (13.0)	9 (7.1)	14 (11.2)	18 (14.8)
Left sided colitis	24 (42.9)	46 (43.4)	21 (38.9)	53 (42.1)	45 (36.0)	51 (41.8)
Extensive colitis	4 (7.1)	7 (6.6)	7 (13.0)	17 (13.5)	14 (11.2)	14 (11.5)
Pancolitis	21 (37.5)	37 (34.9)	19 (35.2)	47 (37.3)	52 (41.6)	39 (32.0)
Missing	0	1 (0.9)	0	0	0	0

Source: Integrated Summary of Efficacy SC-3027 and C13006 Table 30.7.6.3.
FAS: full analysis set; ITT: intent to treat; IV: intravenous; PBO: placebo; Q2W: once every 2 weeks; Q8W: once every 8 weeks; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.

3.1.1.4 Prior and Concomitant UC Therapies

As specified in the protocols for Studies SC-3027 and C13006, subjects who were either TNF-α antagonist naïve or experienced previous treatment failure with TNF-α antagonists were included to ensure that approximately 50% of subjects enrolled had experienced TNF-α antagonist failure. Subjects who responded to previous treatment with TNF-α antagonists were not eligible to participate in either study.

In the FAS of Study SC-3027, the proportions of subjects who reported previous treatment failure with TNF-α antagonists were 35.7%, 37.7%, and 44.4% for placebo, vedolizumab SC, and vedolizumab IV, respectively. The proportions of subjects with no prior TNF-α antagonist

use were 64.3%, 62.3%, and 55.6% for placebo, vedolizumab SC, and vedolizumab IV, respectively (SC-3027 Table 15.1.8.2).

In the ITT population of Study C13006, the proportions of subjects who reported previous treatment failure with TNF-α antagonists were 30%, 32%, and 35% for placebo, vedolizumab IV Q4W, and vedolizumab IV Q8W, respectively. The proportions of subjects with no prior TNF-α antagonist use were 63%, 58%, and 59% for placebo, vedolizumab IV Q4W, and vedolizumab IV Q8W, respectively (C13006 Table 14.1.1.6AM).

In Study SC-3027, baseline UC therapy included immunomodulator and corticosteroid medications that subjects received at Week 0 and Week 6, respectively. Concomitant UC medications included 5-ASAs, corticosteroids, or immunomodulators that started after the Week 6 randomization.

In Study C13006, baseline UC therapy included immunomodulator or corticosteroid medications that subjects received at Week 0. Concomitant UC medications included 5-ASA, corticosteroid, and immunomodulator therapy that began any time after Week 0.

Use of baseline UC therapies and use of concomitant UC therapies are summarized for Studies SC-3027 and C13006 in Table 3.c. More subjects in Study C13006 reported corticosteroid use at baseline than subjects in Study SC-3027. However, concomitant UC therapies were similar across both studies and across the treatment groups within each study. In both studies, 5-ASAs were the most common concomitant IBD medication, followed by concomitant corticosteroids and concomitant immunomodulators.

Table 3.c Use of UC Therapy at Baseline and Use of Concomitant UC Therapy (Studies SC-3027 and C13006)

	Study SC-3027 FAS			Study C13006 Maintenance ITT		
	PBO N = 56	VDZ SC 108 mg Q2W N = 106	VDZ IV 300 mg Q8W N = 54	PBO N = 126	VDZ IV 300 mg Q4W N = 125	VDZ IV 300 mg Q8W N = 122
Use of UC therapies at baseline of current study [a]	33 (58.9)	65 (61.3)	29 (53.7)	99 (78.6)	93 (74.4)	91 (74.6)
Use of corticosteroids at baseline	24 (42.9)	45 (42.5)	21 (38.9)	72 (57.1)	73 (58.4)	70 (57.4)
Use of immunomodulators at baseline	17 (30.4)	38 (35.8)	15 (27.8)	51 (40.5)	45 (36.0)	43 (35.2)
Subjects with at least 1 concomitant medication [b]	52 (92.9)	98 (92.5)	47 (87.0)	119 (94.4)	115 (92.0)	109 (89.3)
5-Aminosalicylic acids	44 (78.6)	85 (80.2)	44 (81.5)	97 (77.0)	97 (77.6)	85 (69.7)
Corticosteroids	28 (50.0)	54 (50.9)	27 (50.0)	79 (62.7)	75 (60.0)	73 (59.8)
Immunomodulators	18 (32.1)	36 (34.0)	17 (31.5)	42 (33.3)	40 (32.0)	39 (32.0)

Source: Integrated Summary of Efficacy Table SC-3027 and C13006 30.7.6.4.
FAS: full analysis set; ITT: intent to treat; IV: intravenous; PBO: placebo; Q2W: once every 2 weeks; Q4W: once every 4 weeks; Q8W: once every 8 weeks; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.
[a] For Study C13006, baseline is defined as Week 0 for both corticosteroids and immunomodulators; for Study SC-3027, baseline was defined as Week 0 for immunomodulators and Week 6 for corticosteroids.
[b] For Study C13006, concomitant medications reflect those taken at any time after Week 0; for Study SC-3027, concomitant medications reflect those taken at any time after the Week 6 randomization.

3.1.2 Descriptive Comparison of Efficacy Results Across Individual Studies (Studies SC-3027 and C13006)

Study SC-3027 investigated the effects of vedolizumab SC maintenance treatment in subjects with moderate to severe UC and was designed similarly to Study C13006, which investigated the effect of vedolizumab IV in the same target population. Comparisons of efficacy assessments in these subjects from Studies SC-3027 and C13006 (maintenance phases) are discussed in this section.

Side-by-side presentation of key efficacy results (primary endpoint of clinical remission and key secondary endpoints of mucosal healing at Week 52, durable clinical response, durable clinical remission, and corticosteroid-free remission at Week 52) for subjects in Studies SC-3027 and C13006 (maintenance phase) are presented below.

3.1.2.1 Primary and Key Secondary Efficacy Endpoints for Studies SC-3027 and C13006

The primary endpoint in both Studies SC-3027 and C13006 was clinical remission at Week 52, and the results are summarized in Table 3.d.

Study SC-3027 included an IV reference arm in the maintenance phase of the study for a within-study comparison with the vedolizumab SC maintenance treatment. Although no formal

statistical analysis between the vedolizumab SC and IV groups was performed in Study SC-3027, the results for these vedolizumab groups appeared generally similar. In the primary endpoint analysis of clinical remission, 46.2% of subjects treated with vedolizumab SC and 42.6% of subjects treated with vedolizumab IV (Q8W, maintenance phase) achieved clinical remission at Week 52 (Table 3.d).

In Study C13006, 2 vedolizumab IV dosing regimens (Q8W and Q4W) were studied as maintenance treatment in the same target population of subjects with moderate to severe UC. The proportion of subjects in clinical remission at Week 52 while on vedolizumab IV Q8W treatment was 41.8%, which was comparable to the results for both vedolizumab treatments in Study SC-3027 (Table 3.d).

Both Studies SC-3027 and C13006 used similar secondary endpoints to further assess the efficacy of vedolizumab maintenance therapy. Analyses for mucosal healing, durable clinical response, durable clinical remission, and corticosteroid-free remission from Studies SC-3027 and C13006 are presented in Table 3.d

In Study SC-3027, subjects treated with vedolizumab SC showed a similar rate of improvement for all secondary endpoint evaluations as subjects treated with vedolizumab IV within Study SC-3027. No formal statistical analysis comparing vedolizumab SC and IV was conducted for Study SC-3027. Furthermore, results obtained for all secondary endpoints with vedolizumab SC treatment in Study SC-3027 were comparable to the results of IV vedolizumab treatment in the controlled Study C13006.

These data show that the efficacy of vedolizumab SC is comparable to the known efficacy of vedolizumab IV.

Table 3.d Primary and Key Secondary Efficacy Endpoint (Studies C13006 and SC-3027)

	Study SC-3027 (FAS)			Study C13006 Maintenance ITT		
	PBO N = 56	VDZ SC 108 mg Q2W N = 106	VDZ IV 300 mg Q8W N = 54	PBO N = 126	VDZ IV 300 mg Q4W N = 125	VDZ IV 300 mg Q8W N = 122
Clinical remission at Week 52						
Number (%) achieving clinical remission	8 (14.3)	49 (46.2)	23 (42.6)	20 (15.9)	56 (44.8)	51 (41.8)
95% CI	(6.4, 26.2)	(36.5, 56.2)	(29.2, 56.8)	(10.0, 23.4)	(35.9, 54.0)	(32.9, 51.1)
Adjusted treatment difference		32.3	27.9		29.1	26.1
95% CI		(19.7, 45.0)	(12.3, 43.5)		(17.9, 40.4)	(14.9, 37.2)
P-value, vedolizumab vs placebo [a,b]		<0.001	<0.001		<0.001	<0.001
Key secondary efficacy endpoints						
Number (%) achieving mucosal healing at Week 52	12 (21.4)	60 (56.6)	29 (53.7)	25 (19.8)	70 (56.0)	63 (51.6)
95% CI	(11.6, 34.4)	(46.6, 66.2)	(39.6, 67.4)	(13.3, 27.9)	(46.8, 64.9)	(42.4, 60.8)
Adjusted treatment difference		35.7	32.2		36.3	32.0
95% CI		(22.1, 49.3)	(15.7, 48.7)		(24.4, 48.3)	(20.3, 43.8)
P-value, vedolizumab vs placebo [a,b]		<0.001	<0.001		<0.001	<0.001
Number (%) achieving durable clinical response	16 (28.6)	68 (64.2)	39 (72.2)	30 (23.8)	65 (52.0)	69 (56.6)
95% CI	(17.3, 42.2)	(54.3, 73.2)	(58.4, 83.5)	(16.7, 32.2)	(42.9, 61.0)	(47.3, 65.5)
Adjusted treatment difference		36.1	44.5		28.5	32.8
95% CI		(21.2, 50.9)	(28.3, 60.6)		(16.7, 40.3)	(20.8, 44.7)
P-value, vedolizumab vs placebo [a,b]		<0.001	<0.001		<0.001	<0.001
Number (%) achieving durable clinical remission	3 (5.4)	16 (15.1)	9 (16.7)	11 (8.7)	30 (24.0)	25 (20.5)
95% CI	(1.1, 14.9)	(8.9, 23.4)	(7.9, 29.3)	(4.4, 15.1)	(16.8, 32.5)	(13.7, 28.7)
Adjusted treatment difference		9.7	11.3		15.3	11.8
95% CI		(-6.6, 25.7)	(-7.1, 29.9)		(6.2, 24.4)	(3.1, 20.5)
P-value, vedolizumab vs placebo [a,b]		0.076	0.071		<0.001	0.008
Number (%) achieving corticosteroid-free remission at Week 52 [c]	2 (8.3)	13 (28.9)	6 (28.6)	10 (13.9)	33 (45.2)	22 (31.4)
95% CI	(1.0, 27.0)	(16.4, 44.3)	(11.3, 52.2)	(6.9, 24.1)	(33.5, 57.3)	(20.9, 43.6)

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Table 3.d Primary and Key Secondary Efficacy Endpoint (Studies C13006 and SC-3027) (continued)

	Study SC-3027 (FAS)			Study C13006 Maintenance ITT		
	PBO N = 56	VDZ SC 108 mg Q2W N = 106	VDZ IV 300 mg Q8W N = 54	PBO N = 126	VDZ IV 300 mg Q4W N = 125	VDZ IV 300 mg Q8W N = 122
Adjusted treatment difference		20.6	20.2		31.4	17.6
95% CI		(-4.5, 43.7)	(-9.8, 47.8)		(16.6, 46.2)	(3.9, 31.3)
P-value, vedolizumab vs placebo [d,e]		0.067	0.121		<0.001	0.012

Source Integrated Summary of Efficacy SC-3027 and C13006 Table 30.2.6.1 and 30.2.6.2.
FAS: full analysis set; ITT: intent to treat; IV: intravenous; PBO: placebo; Q2W: once every 2 weeks; Q4W: once every 4 weeks; Q8W: once every 8 weeks; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha; VDZ: vedolizumab
Subjects with missing data for determination of endpoint status were categorized as nonresponders.
The 95% CIs of the proportion were based on the Clopper-Pearson method. The 95% CI of the adjusted treatment difference is based on the normal approximation method, or the exact method if the number of remissions in either treatment group is ≤5.
[a] For Study SC-3027, the p-values were obtained using a Cochran-Mantel-Haenszel test (comparing vedolizumab SC versus placebo or vedolizumab IV versus placebo) stratified by randomization strata including concomitant use of corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure or concomitant immunomodulator use, or using Fisher's Exact test if the number of responses in either treatment group is ≤5.
[b] For Study C13006, the p-values were obtained using a Cochran-Mantel-Haenszel test (comparing vedolizumab IV versus placebo) stratified by randomization strata including concomitant use of oral corticosteroids, previous exposure to TNF-α antagonists or concomitant immunomodulator use, and enrollment in Cohort 1 or Cohort 2 in the induction phase.
[c] Corticosteroid-free remission at Week 52 was analyzed in a subset of the FAS or maintenance ITT subjects with baseline concomitant oral corticosteroid use (by interactive voice response system at time of randomization). Study SC-3027: PBO: N = 24; VDZ SC: N = 45; VDZ IV: N = 21. Study C13006: PBO: N = 72; VDZ IV Q8W: N = 70; VDZ IV Q4W: N = 73.
[d] For Study SC-3027, the p-values were obtained using a Cochran-Mantel-Haenszel test (comparing vedolizumab SC versus placebo or vedolizumab IV versus placebo) stratified by randomization strata including clinical remission status at Week 6, previous TNF-α antagonists failure or concomitant immunomodulator use (ignoring strata component of concomitant use of corticosteroids), or Fisher's Exact test if the number of responses in either treatment group is ≤5.
[e] For Study C13006, the p-values were obtained using a Cochran-Mantel-Haenszel test (comparing vedolizumab IV versus placebo) stratified by randomization strata including previous exposure to TNF-α antagonist or concomitant immunomodulator use and enrollment in Cohort 1 or Cohort 2 in the induction phase (ignoring strata component of concomitant use of oral corticosteroids).

3.2 Comparison Across SC Studies

3.2.1 Study Populations

Several analyses were performed to evaluate how consistent the effect of vedolizumab SC treatment was across subgroups in Studies SC-3027 and SC-3030. Complete summaries of all available demographics and baseline characteristics for these studies can be found in the respective CSRs (SC-3027 CSR and SC-3030 Interim CSR).

3.2.2 Efficacy Results in Subpopulations

In this section, subgroup analyses of data from the maintenance phase of Study SC-3027 and from Study SC-3030 are presented. Collectively, these results indicate a consistent benefit of vedolizumab SC maintenance across subgroups of subjects including those who had no prior exposure to TNF-α antagonists (ie, TNF-α naïve) and those subjects who previously experienced treatment failure with TNF-α antagonists.

Additionally, the beneficial effect of vedolizumab SC treatment was consistent across subgroups based on demographics, baseline disease characteristics, prior treatment failures (other than TNF-α treatment), and concomitant medications. The findings are consistent with what is already known from studies with vedolizumab IV.

The complete details of the subgroup analyses, including evaluation for secondary endpoints, are presented in SC-3027 CSR Section 11.4.1.3.1.

3.2.2.1 Subgroups Based on Prior Treatment Failure

Subgroup analyses were performed on the primary and secondary efficacy endpoints from Study SC-3027 based on prior TNF-α antagonist treatment status. By design, all subjects who were eligible for Study SC-3027 were either TNF-α antagonist naïve or experienced previous treatment failure with TNF-α antagonists (ie, subjects who responded to previous treatment with TNF-α antagonists were not eligible). Approximately 50% of the subjects enrolled in Study SC-3027 were to be TNF-α naïve. By design, all subjects who were TNF-α antagonist naïve had experienced previous treatment failure with immunomodulators and/or corticosteroids. Results are summarized in Table 3.e for Study SC-3027.

For both TNF-α antagonist naïve or subjects who had previously experienced treatment failure with TNF-α antagonist therapy in Study SC-3027, significantly higher proportions of subjects with vedolizumab SC treatment achieved clinical remission at Week 52 than subjects who received placebo ($p < 0.001$ and $p = 0.023$ for vedolizumab SC versus placebo in TNF-α antagonist–naïve subjects and subjects who had previously experienced treatment failure with TNF-α antagonist therapy, respectively) (Table 3.e). In both subgroups, the frequency of remission was similar in the vedolizumab SC and vedolizumab IV groups.

Similar trends were observed in both subgroups for all secondary endpoint analyses, indicating that vedolizumab SC treatment is consistently beneficial in both TNF-α antagonist–naïve subjects and those who experienced prior TNF-α antagonist treatment failure.

Table 3.e Key Efficacy Endpoints in Subjects by Prior TNF-α Antagonist Use or Failure (Study SC-3027 Maintenance Phase)

Endpoint	Subjects Without Prior TNF-α Antagonist Use			Subjects With Prior TNF-α Antagonist Failure		
	PBO (N = 56)	VDZ SC 108 mg (N = 106)	VDZ IV 300 mg (N = 54)	PBO (N = 56)	VDZ SC 108 mg (N = 106)	VDZ IV 300 mg (N = 54)
Clinical remission at Week 52 [a]						
N	37	67	32	19	39	22
Number (%) of subjects achieving clinical remission at Week 52	7 (18.9)	36 (53.7)	17 (53.1)	1 (5.3)	13 (33.3)	6 (27.3)
95% CI [b]	(8.0, 35.2)	(41.1, 66.0)	(34.7, 70.9)	(0.1, 26.0)	(19.1, 50.2)	(10.7, 50.2)
Difference, vedolizumab vs placebo and 95% CI [c]		32.1 (15.2, 49.0) [d]			28.1 (1.3, 52.9) [d]	
Mucosal healing at Week 52 [e]						
N	37	67	32	19	39	22
Number (%) of subjects achieving mucosal healing at Week 52	11 (29.7)	42 (62.7)	19 (59.4)	1 (5.3)	18 (46.2)	10 (45.5)
95% CI [b]	(15.9, 47.0)	(50.0, 74.2)	(40.6, 76.3)	(0.1, 26.0)	(30.1, 62.8)	(24.4, 67.8)
Difference, vedolizumab vs placebo and 95% CI [c]		31.2 (12.7, 49.7)			40.9 (14.7, 64.1)	
Durable clinical response [f]						
N	37	67	32	19	39	22
Number (%) of subjects achieving durable clinical response	13 (35.1)	42 (62.7)	25 (78.1)	3 (15.8)	26 (66.7)	14 (63.6)
95% CI [b]	(20.2, 52.5)	(50.0, 74.2)	(60.0, 90.7)	(3.4, 39.6)	(49.8, 80.9)	(40.7, 82.8)
Difference, vedolizumab vs placebo and 95% CI [c]		25.8 (6.5, 45.0)			50.9 (24.9, 72.7)	
Durable clinical remission [g]						
N	37	67	32	19	39	22
Number (%) of subjects achieving durable clinical remission	3 (8.1)	15 (22.4)	8 (25.0)	0	1 (2.6)	1 (4.5)
95% CI [b]	(1.7, 21.9)	(13.1, 34.2)	(11.5, 43.4)		(0.1, 13.5)	(0.1, 22.8)
Difference, vedolizumab vs placebo and 95% CI [c]		14.3 (-5.9, 33.5)			2.6 (-24.3, 29.2)	

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Table 3.e Key Efficacy Endpoints in Subjects by Prior TNF-α Antagonist Use or Failure (Study SC-3027 Maintenance Phase) (continued)

Endpoint	Subjects Without Prior TNF-α Antagonist Use			Subjects With Prior TNF-α Antagonist Failure		
	PBO (N = 56)	VDZ SC 108 mg (N = 106)	VDZ IV 300 mg (N = 54)	PBO (N = 56)	VDZ SC 108 mg (N = 106)	VDZ IV 300 mg (N = 54)
Corticosteroid-free clinical remission [h,i]						
N	12	23	10	12	22	11
Number (%) of subjects achieving corticosteroid-free remission at Week 52	1 (8.3)	7 (30.4)	4 (40.0)	1 (8.3)	6 (27.3)	2 (18.2)
95% CI [b]	(0.2, 38.5)	(13.2, 52.9)	(12.2, 73.8)	(0.2, 38.5)	(10.7, 50.2)	(2.3, 51.8)
Difference, vedolizumab vs placebo and 95% CI [c]		22.1 (-13.8, 53.3)			18.9 (-16.2, 52.1)	

Source: Study SC-3027 Table 15.2.3.1.10 (clinical remission), 15.2.3.2.10 (mucosal healing), 15.2.3.3.10 (durable clinical response), 15.2.3.4.10 (durable clinical remission), and 15.2.3.5.10 (corticosteroid-free remission).
IV: intravenous; PBO: placebo; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha; VDZ: vedolizumab.
TNF-α antagonist use was obtained from the interactive voice response system and refers to subjects with prior use, regardless of prior response.
[a] Clinical remission is defined as a complete Mayo score of ≤2 points and no individual subscore >1 point.
[b] The 95% CIs of the proportion were based on the Clopper-Pearson method.
[c] The 95% CIs of the difference were based on the normal approximation method, or the exact method if the number of remissions in either treatment group was ≤5.
[d] P-value for vedolizumab SC vs placebo (primary endpoint): <0.001 (TNF-α–naïve subgroup); p = 0.023 (prior TNF-α antagonist failure subgroup).
[e] Mucosal healing is defined as a Mayo endoscopic subscore of ≤1 point.
[f] Durable clinical response is defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline (Week 0) (or partial Mayo score of ≥2 points and ≥25% from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point at both Weeks 6 and 52.
[g] Durable clinical remission is defined as complete Mayo score of ≤2 points and no individual subscore >1 point at both Weeks 6 and 52.
[h] Corticosteroid-free remission is defined as subjects using oral corticosteroids at baseline (determined by interactive voice response system at time of randomization) who had discontinued oral corticosteroids and were in clinical remission based on the complete Mayo score at Week 52.
[i] N (PBO) = 24; N (VDZ SC) = 45; N (VDZ IV) = 21.

4.0 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Vedolizumab is recommended for the treatment of adult patients with moderately to severely active UC or CD who have had an inadequate response with, lost response to, or were intolerant of either conventional therapy or a TNF-α antagonist. Analysis of safety and efficacy from phase 3 studies (SC-3027 and SC-3030) supports the dosing recommendation of 108 mg administered by SC injection Q2W to patients demonstrating a therapeutic benefit after 2 or more doses of vedolizumab IV.

The dose regimen is based on the following considerations: mechanism of action (Module 2.4), formulation (Module 2.3), PK (Module 2.7.2 Section 3), efficacy profile of vedolizumab SC (Sections 2.0, 3.0, and 5.0), the exposure-response relationship (Module 2.7.2 Section 3.4), the safety profile (Module 2.7.4), and safety experience.

A first key consideration is that all patients share the $\alpha_4\beta_7$ target on peripheral circulating lymphocytes and the companion binding site of MAdCAM-1. The original phase 3 program for UC and CD defined a range of blood drug levels that are associated with inhibition of this $\alpha_4\beta_7$ target on peripheral circulating lymphocytes. These blood levels are associated with safety and efficacy of using vedolizumab IV either Q4W or Q8W; however, these blood drug levels may be achieved using either the IV or SC route of administration.

No changes during development of vedolizumab SC were made that would impact the primary structure of the protein, and comparable biochemical properties and in vitro functional activity to vedolizumab IV have been demonstrated. Therefore, biological activity and the behavior in peripheral circulating blood should be similar to identical drug levels resulting from different administration routes (Module 3).

An important observation is that the PK of SC administration achieves blood levels in the range of blood levels associated with IV administration. The observed trough concentrations of vedolizumab 108 mg SC Q2W are within variability of vedolizumab 300 mg IV Q4W (Module 2.7.2 Table 3.b). The median observed trough concentration of vedolizumab in patients with UC at Week 46 in Study SC-3027 was 36.4 µg/mL (min 6.4; max 76.4 µg/mL) for the SC Q2W regimen as compared with 39.0 µg/mL (min 4.0; max 179 µg/mL) for the IV Q4W regimen in Study C13006. The simulated average concentration at steady state ($C_{av,ss}$) for 108 mg SC Q2W is within variability of vedolizumab 300 mg IV Q8W (Module 2.7.2 Table 3.c). The population PK analysis showed that vedolizumab PK had similar characteristics in UC and CD patients (Module 2.7.2 Table 3.i). Population PK analyses from phase 3 studies have identified factors that have a clinically meaningful impact on clearance, but no dose adjustments are warranted on the basis of covariates tested (Module 2.7.2 Section 3.3.2). Race (Asian, non-Asian) had no impact on the clearance of vedolizumab (Module 2.7.2 Table 3.i).

The SC phase 3 program is used to validate the conclusion of similarity of the IV and SC routes of administration that comes from these structure, function, and PK conclusions.

Results from the primary efficacy analyses of Study SC-3027 were statistically significant for SC 108 mg Q2W. The primary endpoint for this maintenance study, the proportion of subjects with clinical remission at Week 52, was met. A higher remission rate was observed for subjects receiving vedolizumab SC (46.2%) than placebo (14.3%), and this treatment difference was statistically significant ($p < 0.001$) and clinically meaningful (Table 2.a). Similarly, the efficacy of vedolizumab SC consistently favored vedolizumab SC over placebo across the secondary endpoints of clinical response, mucosal healing, durable clinical remission, and corticosteroid-free remission. Analysis of these secondary endpoints showed that the results were similar between the vedolizumab SC and vedolizumab IV groups in Study SC-3027 (Table 2.b).

In addition, when referenced to the vedolizumab registration study, the efficacy seen with 108 mg vedolizumab SC Q2W in Study SC-3027 was similar to vedolizumab IV administered Q8W and Q4W in Study C13006.

The exposure-response analysis for subjects with UC (SC-3027) suggests that higher clinical remission rates and mucosal healing rates were achieved with higher PK exposure (Module 2.7.2 Section 3.4).

The safety data provide important validation of the similarity of the IV and SC routes of administration. The phase 3 studies did not show any difference in the safety and tolerability profile between 300 mg IV Q4W and 108 mg SC Q2W. Comprehensive safety analyses of the 2 vedolizumab maintenance dosing regimens of 300 mg IV Q8W and 108 mg SC Q2W are included in the CSR for SC-3027 and in the Summary of Clinical Safety (Module 2.7.4).

The prior long-term safety studies with vedolizumab enhance these safety observations. Takeda has generated long-term data supporting the safety and efficacy of vedolizumab IV administered Q4W for up to 9.5 years as treatment of subjects with moderately to severely UC or CD in phase 3 studies from the IV program. All subjects in Study C13008 were treated with 300 mg vedolizumab IV, administered Q4W. A total of 2243 subjects entered the study and their exposure, including their exposure in their previous study, is summarized as follows. Of the 2243 subjects, 60% had 2 years of exposure, 52% had 3 years of exposure, 25% had 6 years of exposure, and 5 subjects (<1%) with UC had ≥9.5 years of exposure. Overall, the results of safety analysis in both study populations (UC and CD) were consistent with the known safety profile of vedolizumab as reflected in current product labeling. This application includes data from Study C13008; safety results are summarized in Module 2.7.4. Takeda concludes that the PK, safety, and efficacy data generated with vedolizumab 108 mg SC Q2W, together with the analyses presented here, support vedolizumab SC with a dose recommendation of 108 mg Q2W SC.

The data collected in the vedolizumab SC program support the proposed dosing schedule. In the clinical Studies SC-3027 and SC-3030, subjects started vedolizumab SC treatment at approximately the same time as the next scheduled vedolizumab IV infusion. The first SC dose should be administered in place of the next scheduled IV dose and Q2W thereafter.

5.0 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

Clinical data from Study SC-3027 supporting the persistence of efficacy with vedolizumab through 52 weeks of treatment are summarized in Section 5.1 and presented in detail in Section 2.1.3.3.2 of this module.

Section 5.2 discusses the exploratory analyses of persistent efficacy beyond 52 weeks of longitudinal treatment within Studies SC-3027 and SC-3030.

5.1 Persistence of Efficacy: 52 Weeks of Treatment

5.1.1 Primary and Secondary Endpoints of Clinical Remission at 52 Weeks

In the pivotal Study SC-3027, the sustained therapeutic benefit of vedolizumab SC was demonstrated in the predefined primary endpoint analyses at Week 52. The primary efficacy endpoint of clinical remission was met with vedolizumab SC, with a statistically significant treatment difference from placebo ($p < 0.001$) (Section 2.1.3.1 Table 2.a).

Similar benefits of vedolizumab treatment were observed in the 4 predefined secondary endpoints at Week 52, which included mucosal healing at Week 52 ($p < 0.001$), durable clinical response (clinical response at Weeks 6 and 52; $p < 0.001$), durable clinical remission (clinical remission at Weeks 6 and 52), and corticosteroid-free remission at Week 52 (Section 2.1.3.2 Table 2.b).

A significantly higher percentage of subjects in the vedolizumab SC treatment group met the predefined secondary endpoints of mucosal healing and durable clinical response as compared with subjects receiving placebo. Although not statistically significant, treatment with vedolizumab SC was associated with clinically meaningful differences favoring vedolizumab SC over placebo for durable clinical remission and corticosteroid-free remission (Section 2.1.3.2 Table 2.b).

In summary, the results obtained in the primary and secondary endpoint analyses of Study SC-3027 confirmed that the beneficial therapeutic activity achieved with vedolizumab SC was consistently sustained through 52 weeks. Vedolizumab SC showed similar efficacy to vedolizumab IV for all analyzed endpoints in Study SC-3027.

5.1.2 Sustainability of Maintenance

Additional analyses that demonstrate the sustainability of vedolizumab SC therapy are described below.

5.1.2.1 Analyses of Partial Mayo Scores, Clinical Remission, and Clinical Response Rates From Week 6 to Week 52

The therapeutic benefit of vedolizumab SC maintenance therapy was also demonstrated by sustained decreases in partial Mayo scores during the Study SC-3027 maintenance phase (Figure 2.b).

Furthermore, in addition to achieving the primary endpoint of clinical remission at Week 52, analyses were performed for the proportion of subjects who achieved clinical remission in at least 60% and 80% of the visits in the maintenance phase of the study. Because subjects enrolling in the study had severe, acute flares and may have achieved clinical response but not remission by the end of the induction phase at Week 6 of Study SC-3027, this exploratory analysis better assesses sustained clinical remission during the maintenance phase. A significantly higher proportion of vedolizumab SC–treated subjects had clinical remission, defined by a partial Mayo score in at least 80% of the study visits in the maintenance phase, than placebo-treated subjects ($p < 0.001$) (Section 2.1.3.3.2).

Similarly, a significantly higher proportion of vedolizumab SC–treated subjects were in clinical response, defined by a partial Mayo score, in at least 80% of the study visits in the maintenance phase than placebo-treated subjects ($p < 0.001$). The results were similar for subjects who achieved clinical remission and clinical response for at least 60% of study visits, indicating that clinical remission and clinical response rates were sustained during Study SC-3027 (Section 2.1.3.3.2).

5.1.2.2 Changes in Other PRO Assessments From 6 to 52 Weeks

Vedolizumab SC treatment maintained symptomatic improvements in HRQOL assessments achieved with the initial vedolizumab IV induction treatment. The IBDQ, EQ-5D, and WPAI-UC scores consistently showed a beneficial effect of long-term vedolizumab SC treatment (Section 2.1.3.4).

In addition, exploratory endpoint analyses of the time to disease worsening and time to treatment failure over 52 weeks provide further support for sustained treatment benefit with vedolizumab SC treatment (Section 2.1.3.4).

5.1.3 Summary

The results from Study SC-3027 demonstrate that treatment benefits were consistently sustained throughout the 52-week duration of the study, with comparable magnitudes of treatment effect observed with vedolizumab IV treatment.

5.2 Persistence of Efficacy Beyond 52 Weeks

The persistence of efficacy with long-term vedolizumab treatment beyond 52 weeks was assessed using integrated longitudinal data from Study SC-3027 and the ongoing, long-term, OLE Study SC-3030.

Assessments of the persistence of efficacy were based on the partial Mayo score, including changes from baseline, clinical remission rates, and clinical response rates. For these long-term assessments, the partial Mayo score was selected over the complete Mayo score because it does not include an endoscopy assessment, hence facilitating subject participation during long-term follow-up. Because Study SC-3030 is an ongoing, long-term study and few subjects have reached later time points, the combined results for Studies SC-3027 and SC-3030 are presented up to Week 78.

5.2.1 Statistical Analysis Methods

The statistical analyses of long-term integrated persistence of efficacy are descriptive in nature, and no formal statistical hypothesis testing was performed for these analyses. Point estimations along with 95% CIs are presented for selected exploratory efficacy parameters. For UC-related assessments, descriptive statistics, including 95% CIs, for observed values and change in partial Mayo score from baseline of the previous studies are summarized, and the means of partial Mayo scores are plotted over time. For additional details, refer to the SC-3030 ISAP.

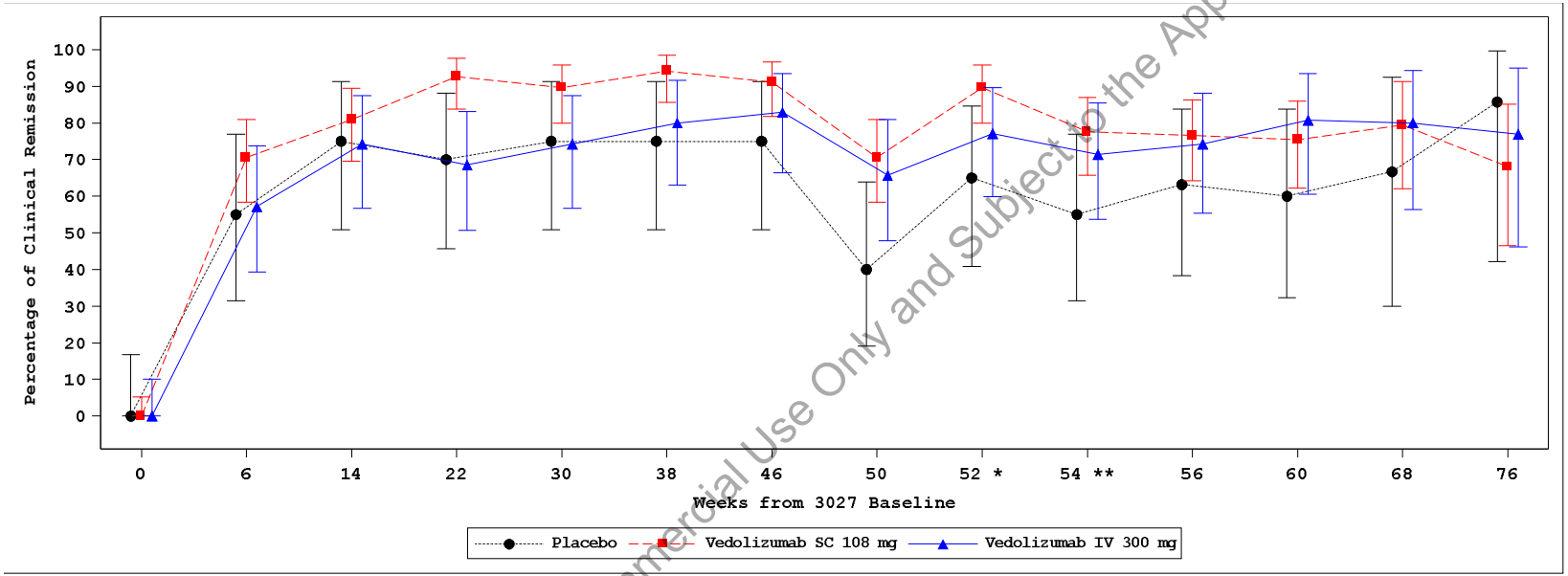
5.2.2 Clinical Remission Among Randomized Completer Subjects After Long-term Vedolizumab Treatment

Long-term clinical remission rates were calculated for the population of Study SC-3027 randomized completer subjects (ie, those subjects who completed the Week 52 assessment in Study SC-3027) who had a baseline (Week 0) in Study SC-3030 and an assessment at the study visit under considerations or who terminated prematurely from Study SC-3030 before the study visit. Clinical remission rates over time among all Study SC-3027 UC randomized completer subjects for long-term efficacy are presented in SC-3030 Table 15.2.14.2.2.1 and summarized in Figure 5.a for the set. The figure presents the frequency of remission in subjects who received the randomized treatment in the maintenance phase of Study SC-3027 (ie, placebo, vedolizumab SC, or vedolizumab IV in the first 52 weeks in the figure); all subjects (including the placebo arm in Figure 5.a) received open-label vedolizumab SC treatment after Week 52 of Study SC-3027.

In general, randomized completer subjects who continued with vedolizumab SC treatment in Study SC-3030 maintained high clinical remission rates over time (or up to 78 weeks) regardless of the treatment they received in Study SC-3027.

Of note, there was a decrease in the clinical remission rate at Week 50 across all Study SC-3027 treatment groups. The Week 50 and Week 52 visits were both clinic visits, and the Week 50 clinic visit window was narrow; therefore, all subject data collected outside of the narrow visit window at Week 50 were considered missing and therefore, as nonresponders in this analysis.

Figure 5.a 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) - Data as of 31 May 2018



Source: SC-3030 Figure 15.2.14.2.2.2 (combined analysis)
FAS-UC: full analysis set-ulcerative colitis; IV, intravenous; Q2W: once every 2 weeks; QW: once weekly; SC, subcutaneous; UC: ulcerative colitis.
All subjects with missing data for determination of endpoint status were categorized as nonremitters. Subjects ongoing in Study SC-3030 with missing data for determination of endpoint status were categorized as nonremitters only up to the visit reached by the 31 May 2018 interim data cutoff date.
The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method.
Clinical remission was defined as a partial Mayo score of ≤2 points and no individual subscore >1 point.
Data presented are for the UC efficacy population, which included subjects who rolled over from Study SC-3027 to Study SC-3030.
After Week 52, subjects could be receiving vedolizumab SC either QW or Q2W.
* Week 52 ends on the day of the first open-label extension SC dose of SC-3030. The first dose of SC-3030 was assigned to Week 52 in this analysis visit window. Week 52 in this analysis combined Week 52 of SC-3027 and Week 0 of SC-3030.
** Week 54 for SC-3030 patients with Q2W dose.

5.2.3 Clinical Response Among Randomized Completer Subjects After Long-term Vedolizumab Treatment

Long-term clinical response rates were calculated as described in Section 5.2.1. Clinical response rates over time among all Study SC-3027 UC randomized completer subjects for long-term efficacy are summarized in Table 5.a. Randomized completer subjects who continued with vedolizumab SC treatment in Study SC-3030 maintained high clinical response rates over time regardless of the treatment they received in Study SC-3027.

Table 5.a Proportion of Study SC-3030 UC Subjects With Clinical Response Among Study SC-3027 Randomized Completer Subjects (FAS-UC)

Visit		PBO N = 20	VDZ SC 108 mg N = 68	VDZ IV 300 mg N = 35
SC-3027 Week 6	N	20	68	35
	n (%)	20 (100.0)	66 (97.1)	34 (97.1)
Week 52	N	20	68	35
	n (%)	15 (75.0)	61 (89.7)	33 (94.3)
SC-3030 Week 0	N	19	67	35
	n (%)	15 (78.9)	65 (97.0)	35 (100.0)
Week 24	N	7	24	13
	n (%)	6 (85.7)	18 (75.0)	10 (76.9)

Source: SC-3030 Table 15.2.14.2.1.
FAS-UC: full analysis set-ulcerative colitis; IV: intravenous; PBO: placebo; SC, subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.
Randomized subjects who complete Week 52 of SC-3027 study drug (SC-3027 Week 0 as baseline) have been included.
Clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline (or partial Mayo score of ≥2 points and ≥25% from baseline) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
Clinical response at SC-3027 Week 6 and Week 52 is assessed based on complete Mayo score. For all other visits, it is based on partial Mayo score.
The analyses were performed on SC-3027 and SC-3030 separately.

5.2.4 Summary

Results from the long-term longitudinal analyses of Studies SC-3027 and SC-3030 support the efficacy of vedolizumab beyond 52 weeks.

Tolerance Effects

Tolerance effects have not been observed in the vedolizumab development program. Tolerance effects were assessed in the maintenance phase of Study SC-3027 by monitoring time to disease worsening and time to treatment failure in the FAS population. During the first year of vedolizumab therapy, no evidence of disease worsening or treatment failure was observed

(additional details are in SC-3027 CSR Section 11.4.1.4.4 and 11.4.1.4.5); the clinical responses achieved by subjects were sustained over time (see Section 2.2.2.3.1). These findings were supported by the Study SC-3030 interim analyses of subjects beyond 52 weeks and up to 76 weeks in Study SC-3030. These findings were consistent with those observed with vedolizumab IV.

5.3 Effect of Human Antihuman Antibodies on Efficacy in UC Studies

In Study SC-3027, 6% (6 of 106) of subjects receiving vedolizumab SC developed AVA; 4 subjects (4%) were persistently positive, and 3 subjects (3%) developed neutralizing antibodies (Module 2.7.2 Table 4.b).

As seen in the vedolizumab IV program, 2 induction doses of vedolizumab IV in the placebo group appears to cause a higher AVA rate than in subjects who continued to receive vedolizumab in the maintenance phase. This group had 17 (30%) AVA-positive subjects (out of 56) at any time during study treatment compared with 6% of subjects who received vedolizumab in the induction and maintenance phase (SC and IV group). The rate of AVA-positive subjects was similar in both vedolizumab groups during the maintenance phase of Study SC-3027 (6% for vedolizumab SC; 3 of 54 subjects [6%] for vedolizumab IV) (Module 2.7.2 Table 4.b).

Development of AVA had an impact on efficacy as assessed by clinical remission and mucosal healing. None of the 6 subjects in the vedolizumab SC group who developed AVA achieved clinical remission or mucosal healing at Week 52 (Module 2.7.2 Table 4.j and Table 4.k). The impact of AVA on efficacy was similar for the SC and IV arms. Most of the subjects who were AVA positive were persistently positive and developed neutralizing antibodies.

Additional details related to AVA effects on PK, safety, and efficacy are provided in Module 2.7.2 Section 4.

6.0 LITERATURE REFERENCES

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7.0 APPENDIX

Table 7.a Summary of Results of Vedolizumab Subcutaneous Efficacy Studies for Ulcerative Colitis

Controlled Study						
SC-3027: Pivotal Phase 3, Randomized, Double-Blind, Placebo-Controlled Study						
Endpoints	**PBO N = 56**	**VDZ SC 108 mg N = 106**	**VDZ IV 300 mg N = 54**	**Difference Vedolizumab SC Versus Placebo**	**95% CI**	**P-value**
Primary Endpoint						
Number (%) of subjects achieving clinical remission at Week 52 [a]	8 (14.3)	49 (46.2)	23 (42.6)	32.3	(19.7, 45.0) [b]	<0.001 [c]
Secondary Endpoints						
Number (%) of subjects achieving mucosal healing at Week 52 [d]	12 (21.4)	60 (56.6)	29 (53.7)	35.7	(22.1, 49.3) [b]	<0.001 [c]
Number (%) of subjects achieving durable clinical response [e]	16 (28.6)	68 (64.2)	39 (72.2)	36.1	(21.2, 50.9) [b]	<0.001 [c]
Number (%) of subjects achieving durable clinical remission [f]	3 (5.4)	16 (15.1)	9 (16.7)	9.7	(-6.6, 25.7) [g]	0.076 [h]
Number (%) of subjects achieving corticosteroid-free clinical remission [i,j]	2 (8.3)	13 (28.9)	6 (28.6)	20.6	(-4.5, 43.7) [g]	0.067 [h]

Footnotes on last table page.

Table 7.a Summary of Results of Vedolizumab Subcutaneous Efficacy Studies for Ulcerative Colitis (continued)

Other Pertinent Study With Efficacy Data

Study SC-3030: Phase 3, Open-label, Long-term Safety Study With Exploratory Efficacy Endpoints

	MLN002SC-3027 Randomized Completer Subjects			MLN002SC-3027 Randomized Early Terminator Subjects		
Exploratory Efficacy Endpoints	**Placebo N = 20**	**Vedolizumab SC 108 mg N = 68**	**Vedolizumab IV 300 mg N = 35**	**Placebo N = 32**	**Vedolizumab SC 108 mg N = 21**	**Vedolizumab IV 300 mg N = 4**
N at Week 24	7	24	13	24	18	4
Number (%) of subjects achieving clinical remission at Week 24 [k]	6 (85.7)	16 (66.7)	10 (76.9)	13 (54.2)	5 (27.8)	0
N at Week 24	7	24	13	24	18	4
Number (%) of subjects achieving clinical response at Week 24 [l]	6 (85.7)	17 (70.8)	10 (76.9)	16 (66.7)	7 (38.9)	0

Sources: SC-3027 Table 15.2.1.1.1 (clinical remission), 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); SC-3030 Table 15.2.2.2 (clinical remission); 15.2.1.2 (clinical response); and 15.2.14.1.1 (combined analysis).
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.
[b] The 95% CI of the 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 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 remissions in either treatment group was ≤5.
[d] Mucosal healing, defined as a Mayo endoscopic subscore of ≤1 point, at Week 52 was the first secondary efficacy endpoint.
[e] Durable clinical response (response at both Weeks 6 and 52) was the second secondary efficacy endpoint.
[f] Durable clinical remission, defined as remission at both Week 6 and Week 52, was the third secondary efficacy endpoint.
[g] The 95% CI of the difference was based on the exact method.
[h] 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.
[i] Corticosteroid-free remission, defined as subjects using oral corticosteroids at baseline (determined by interactive web response system at time of randomization) who had discontinued oral corticosteroids and were in clinical remission based on the complete Mayo score at Week 52, was the fourth secondary efficacy endpoint.
[j] PBO: N = 24; VDZ SC: N = 45; VDZ IV: N = 21.
[k] Clinical remission was defined as a partial Mayo score of ≤2 and no individual subscore >1 point.
[l] Clinical response was 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.