27 February 2020
EMA/220524/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entyvio

International non-proprietary name: **vedolizumab**

Procedure No. EMEA/H/C/002782/X/0040

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
Act-1	murine homolog to vedolizumab antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	autoinjector/pen
AVA	anti-vedolizumab antibodies
AZA	azathioprine
BLA	Biologics License Application
BMI	body mass index
Cavg	average concentration during a dosing interval
Cavg,ss	average concentration during a dosing interval at steady state
CCDS	Company Core Data Sheet
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CLL	clearance of linear elimination pathway
Cmax	maximum concentration
CSR	clinical study report
Ctrough	concentration at the end of dosing interval
Ctrough,ss	concentration at the end of dosing interval at steady state
DSMB	Data Safety Monitoring Board
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EQ-5D	Euro Quality of Life-5D
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GI	gastrointestinal
HBI	Harvey-Bradshaw index
HCP	health care provider
HLT	High Level Term
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IFU	Instructions for Use
IgG1	immunoglobulin G1
ISS	Integrated Summary of Safety
IV	intravenous(ly)
JAK	Janus kinase
JC	John Cunningham
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PD	Pharmacodynamic(s)
PFS	prefilled syringe
PFS + AI	prefilled syringe in an autoinjector/pen
PFS + NSD	prefilled syringe with needle safety device
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPS	Per protocol set
PT	Preferred Term
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
QRG	Quick Reference Guide
QW	once weekly
RAMP	Risk Minimization Action Plan for PML
SAE	serious adverse event

SAF	safety analysis set
SC	subcutaneous(ly)
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
US	United States
WPAI	Work Productivity and Activity Impairment

1. Background information on the procedure

1.1. Submission of the dossier

Takeda Pharma A/S submitted on 7 March 2019 extensions of the marketing authorisation.
Extension application to introduce a new pharmaceutical form (solution for injection), associated with a new strength (108 mg) and a new route of administration (subcutaneous use).

The MAH applied for the following indications for Entyvio to be treated with the new strength associated with the new pharmaceutical form and route of administration:

Ulcerative colitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's disease

Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Furthermore, the PI is brought in line with the latest QRD template.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) (e) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0109/2018 on the agreement of a paediatric investigation plan (PIP) for ulcerative colitis (UC) and Crohn's disease (CD) (EMEA-000645-PIP01-09).

At the time of submission of the application, the PIP (EMEA-000645-PIP01-09) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on the development for the indication from the CHMP on 23 October 2014 (EMEA/H/SA/765/1/FU/3/2014/III). The Scientific Advice pertained to the following *quality and clinical* aspects:

Quality development:

- the proposed drug substance and drug product specification
- specifications for phase 3, function secondary packaging, testing approach to particulates, the proposed range of overfill

Clinical development:

- The proposed phase 3 study with vedolizumab SC
    - the proposed primary and secondary efficacy endpoints and corresponding analyses
    - the proposed patient population
    - the approach to selecting the vedolizumab SC dosing regimen
    - proposed choice of placebo as comparator
    - the proposal for administration
    - the proposed approach to assess immunogenicity
    - scale of the proposed safety data
- the proposed development program for the specific line extension, including aspects relating to the prefilled syringe and autoinjector
- the overall clinical development strategy and considerations regarding labelling

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	7 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	n/a
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 June 2019
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	04 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 July 2019

The MAH submitted the responses to the CHMP consolidated List of Questions on	10 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	19 November 2019
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC members on	15 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 June 2019
The CHMP Rapporteur circulated the updated Assessment Report to all CHMP members on	05 December 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	12 December 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 February 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 February 2020
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	n/a
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Entyvio on	27 February 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Vedolizumab SC has been developed as a maintenance treatment for UC and CD in patients who achieved clinical benefit after at least 2 infusions with vedolizumab IV therapy. No change to the approved indication for vedolizumab (ENTYVIO) powder for concentrate for solution for infusion is proposed with the introduction of vedolizumab SC:

Ulcerative Colitis:
Vedolizumab is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Crohn's Disease:
Vedolizumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

2.1.2. Epidemiology

Inflammatory bowel disease (IBD) affects 1.4 million of people in the United States and 2.2 million of people in Europe, and its peak onset is in persons 15 to 30 years of age. IBD is comprised of 2 major disorders: UC and CD. These disorders have both distinct and overlapping pathologic and clinical characteristics. UC is characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon. CD can involve any component of the gastrointestinal (GI) tract from the oral cavity to the anus and is characterized by transmural inflammation.

UC affects approximately 50 to 100 of every 100,000 people, corresponding to a prevalence of 150,000 to 300,000 people. The prevalence of CD is approximately 150/100,000 of the US population, approximately 125/100,000 of the population in Western Europe, and 21.2/100,000 of the population in Japan. Most patients with UC or CD are diagnosed in their teens or in 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.

2.1.3. Biologic features / Aetiology and pathogenesis

Inflammatory Bowel Disease (IBD) is a set of chronic, relapsing inflammatory diseases of the intestine. IBDs comprise two types of intestinal disorders: ulcerative colitis (UC) and Crohn's disease (CD), which are clinically distinguished by intestinal localization, local features of inflammation, profile of complications and familial aggregation. Both UC and CD are considered urbanized Western lifestyle associated diseases of unknown aetiology, despite the accumulating evidences suggest that these pathologies result from the interaction of genetic and environmental factors that ultimately promote an excessive and poorly controlled mucosal immune response that is directed against a component of the normal flora.

Intestinal immune system has a pivotal role in the pathogenesis of IBD. Both Innate and adaptive immune system are implicated in the development of the aberrant immune response that lead to the intestinal tissue damaging. In healthy subjects the immune response to the vast number of dietary and microbial antigens present in the lumen, is typically non-inflammatory, favouring a state of immune hypo-responsiveness. This adaptation is crucial for the maintenance of health. In mammals, intestinal homeostasis is controlled by the interplay between the epithelial cells and immune cells and this adjusts the host response to the daily charge of antigens derived from the microbiota and food proteins. Otherwise when an infection mediated by pathogen occurs, the immune response become inflammatory.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

UC involves the rectum and may affect part of the colon or the entire colon in an uninterrupted pattern (pancolitis) while CD generally involves the ileum and the colon, but it can affect any region of the intestine, often discontinuously. Since IBD are chronic diseases, patients will go through periods in which the disease flares up and causes symptoms. These periods may be followed by remission, in which symptoms disappear or decrease. Patients are often afflicted by abdominal cramps and pain, bloody diarrhea, severe urgency to have a bowel movement, lack of appetite, weight loss and anaemia due to the intestinal bleeding. Moreover, patients with IBD could develop some extra-intestinal manifestation such as primary sclerosing cholangitis, ankylosing spondylitis and psoriasis. Further clinical complications in CD may include the development of fistulae and perianal diseases or the formation of strictures and obstructions, whereas the most serious complication of UC is an acute non-

obstructive dilatation of the colon called "toxic mega-colon". Moreover, both UC and CD patients have increased risk of developing colon cancer.

The recognition of luminal antigens is particularly mediated by dendritic cells (DCs), a specialized class of antigen presenting cells (APCs) that orchestrate innate and adaptive immune responses. DCs migrate from peripheral tissues to secondary lymphoid organs, where they present antigen to T cells, leading to the activation of T cells. These latter express T cell receptor (TCR), and can be divided into two major sub-groups, T helper (Th) expressing CD4, and T cytotoxic (Tc) expressing CD8. CD4+ T cells become activated when they encounter DC that express antigen bound to MHC class II. Once activated, they divide rapidly and secrete cytokines that regulate the active immune response. Activated CD4+ T cells can differentiate into one of several subtypes, including Th1, Th2, Th17, T regulatory (Treg) or T follicular helper (TFH), which secrete different cytokines to facilitate a different type of immune response. CD8+ T cells recognize antigen in the context of MHC CLASS i and normally have a major role in the destruction of tumour and viral-infected cells and have been implicated as pathogenic cell type in autoimmune diseases.

In IBD CD4+ T cells play a major role in the activation/regulation of the inflammatory response. For many years, it has been assumed that CD is mainly mediated by Th1 cells, while UC is a Th2-like type of inflammation. This has been supported by increased levels of Th1 cytokines such as Interferon (IFN) alpha and interleukin (IL-) 12 in CD and increased expression of Th2 related cytokines such as IL-13 and IL-4 in UC. Th1 cells have a major role in the protection against intracellular microbes, while Th2 cells are involved in the allergic responses and in the protection against extracellular parasites. Development of both Th1 and Th2 cells subsets are controlled by certain transcription factors such as T box expressed in T cells (T-bet) and signal transducer and activator transcription factor (STAT) 4 in Th1 cells, and GATA-binding protein (GATA-) 3 and STAT6 for Th2 cells. Th1 differentiation is driven by IL-12 and IFN-alpha secreted by DCs after the binding/identification of the specific antigen, while IL-4 (in the absence of IL-12) drives Th2 differentiation. However, more recently, emerging evidences have contributed to show that the inflamed gut of patients with CD and with UC is also massively infiltrated with another subset of Th cells, namely Th17 and characterized by the production of high levels of cytokines such as IL-17A, IL-17F and IL-22.

Once activated, antigen-primed T cells relocate to peripheral sites and exert effector activities upon renewed antigen challenge. To achieve this, lymphocytes must travel between lymphoid and non-lymphoid organs via the blood and then exit the circulation to enter antigen-containing tissues. An essential step in this migration process is the adhesion of circulating lymphocytes to the endothelium of post capillary venules, which is a multistep process. In the first step, which is mediated by selectins, T cells are captured ("tethering") and weakly interact with the endothelial cells ("rolling"). Once they are rolling, they can undergo "activation," which is usually mediated by chemokines presented on the venular endothelium. Chemokines bind to specific G-protein-coupled receptors and trigger intracellular signals that lead to activation of integrins and the lymphocytes arrest ("sticking") on the endothelial surface. Only when all steps are completed lymphocytes can transmigrate into a tissue.

2.1.5. Management

About the product

The goal of therapy for both UC and CD is to induce and maintain clinical remission, with the optimal outcome of maintaining steroid-free remission, induction and maintenance of mucosal healing, and reduction of complications and the need for hospitalizations and surgery. The standard approach to therapy for UC and CD is generally step-wise and directed, based on disease activity and the extent

and location of disease. Treatment of mild disease includes anti-inflammatory agents, progressing to more potent therapies for patients who have more severe disease.

Pharmacological treatments for UC and/or CD vary depending upon the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission. Conventional therapies that are used for IBD include oral 5-aminosalicylates (5-ASAs; eg, sulfasalazine, mesalamine), glucocorticoids (eg, prednisone, budesonide), and immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate). Recently, an orally administered Janus kinase (JAK) inhibitor (tofacitinib) has been approved for the treatment of UC. Biologic treatments approved for IBD include TNF-α antagonists (eg, infliximab, adalimumab, certolizumab), interleukin antagonists (eg, ustekinumab), and integrin antagonists (eg, natalizumab, vedolizumab).

Vedolizumab IV has demonstrated statistically significant and clinically relevant effectiveness in multiple clinical trials in subjects with moderately to severely active UC or CD with clinically important endpoints of durable clinical response, durable clinical remission, mucosal healing, and corticosteroid-free remission, including subjects who have failed previous therapies such as corticosteroids, immunomodulators, or TNF-α antagonists. Pharmacological treatments with SC routes of administration provide convenience for patients, HCPs, and caregivers by removing the time, logistics, and burden to the health care system required for IV infusion and allows for patient preference. As a result, the sponsor has pursued development of vedolizumab SC to allow patients and HCPs the option to choose between IV infusion or SC injection for long-term maintenance therapy for UC or CD.

Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7.

Vedolizumab specifically inhibits the activity of the α4β7 integrin by selectively antagonizing binding and adhesion to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and to the extracellular matrix glycoprotein fibronectin but does not antagonize binding to vascular cell adhesion molecule-1. By antagonizing both the α4β7 MAdCAM-1 interaction and the associated migration of leukocytes into GI mucosa, vedolizumab reduces inflammation. Vedolizumab does not bind to, nor inhibit the function of, the $\alpha_4\beta_1$ and $\alpha_E\beta_7$ integrins.

In clinical studies, vedolizumab IV did not elevate neutrophils, basophils, eosinophils, cytotoxic T lymphocytes, total memory T helper lymphocytes, monocytes or natural killer cells in the peripheral blood of healthy subjects or subjects with UC or CD.

Vedolizumab did not affect immune surveillance and inflammation of the central nervous system in experimental autoimmune encephalomyelitis in nonhuman primates, a model of multiple sclerosis. Consistent with these results, vedolizumab IV did not alter the ratio of CD4+ to CD8+ cells or the number of T cells in the cerebrospinal fluid of healthy subjects. Vedolizumab IV did not inhibit the adaptive immune response to intramuscular antigen challenge with hepatitis B vaccine in healthy subjects but did inhibit an adaptive immune response to oral antigen challenge with killed cholera toxin vaccine due to the fact that cholera is localised to the GI. These results support the conclusion that vedolizumab selectively inhibits a gut mucosal immune response, but not the systemic adaptive immune response in humans.

Type of Application and aspects on development

The clinical development program for vedolizumab SC was discussed with regulatory authorities including the US Food and Drug Administration (FDA) and EU regulatory authorities. Takeda incorporated advice from these regulatory interactions into the clinical development program.

The clinical development program of vedolizumab SC in UC and CD was discussed with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). Takeda proposed a program including a phase 1 single dose pharmacokinetics (PK)/bioavailability study, a phase 3 placebo-controlled study in UC and a long-term OLE study. Given that vedolizumab has the same mechanism of action in the treatment of UC and CD, Takeda proposed that positive efficacy results from the planned phase 3 study in UC, together with similar PK and safety profiles compared with the vedolizumab IV program, are sufficient to support the registration of vedolizumab SC for maintenance treatment in both the UC and CD indications. The Agency recommended inclusion of an active vedolizumab IV arm in the study, to prospectively contextualize the comparative efficacy and safety of vedolizumab IV and SC (but not requiring a formal non-inferiority analysis), as well as several other changes, including the design of the OLE study. With regard to this vedolizumab SC program in UC supporting registration in CD, the Agency acknowledged that patients with UC and CD share a common pathway in the pathogenesis of the diseases and that, based on the results of the vedolizumab IV phase 3 studies, vedolizumab has a clinically relevant effect in induction and maintenance of remission in both conditions, but also noted a few differences to be taken into account, such as strength of evidence of PK/pharmacodynamic (PD) correlation in UC versus CD patients and possible differences in length of induction of remission. Overall, the Agency agreed that provided the efficacy and safety of SC vedolizumab are convincingly shown in the treatment of UC patients in the proposed study, the results may also support an indication for CD; noting however, that the efficacy and safety of SC vedolizumab in CD may need to be studied further in the post-approval setting. In addition, the Agency concurred that, provided vedolizumab SC dosing resulted in exposures comparable to those from vedolizumab IV, safety data from the vedolizumab IV safety data base could be supportive for vedolizumab SC, with the exception of potential adverse events (AEs) concerning administration-site reactions.

During Takeda interactions with the US FDA, agreement was reached on the overall registration strategy for vedolizumab SC. The development program includes 2 well-controlled, randomized phase 3 studies (1 each for the UC and CD indications, with inclusion of a vedolizumab IV reference arm in the UC study) to characterize the safety and efficacy of vedolizumab SC as maintenance therapy.

2.2. Quality aspects

2.2.1. Introduction

Vedolizumab IV, powder for concentrate for solution for infusion, 300 mg/vial (or MLN0002 IV) is a lyophilised formulation of vedolizumab intended for intravenous infusion (IV) which has been granted marketing authorisation in 2014.

The scope of this line extension application is the addition of a new pharmaceutical form (solution for injection), associated with a new strength (108 mg) and a new route of administration (subcutaneous use) intended for administration via a single-use prefilled syringe with a needle safety device (PFS + NSD) or a prefilled syringe in an autoinjector/pen (PFS + AI).

Vedolizumab in these new presentations, also referred to as Vedolizumab SC (MLN0002 SC), is formulated with citric acid monohydrate, sodium citrate dihydrate, L histidine, L histidine monohydrochloride, L arginine hydrochloride, polysorbate 80 and water for injections (WFI).

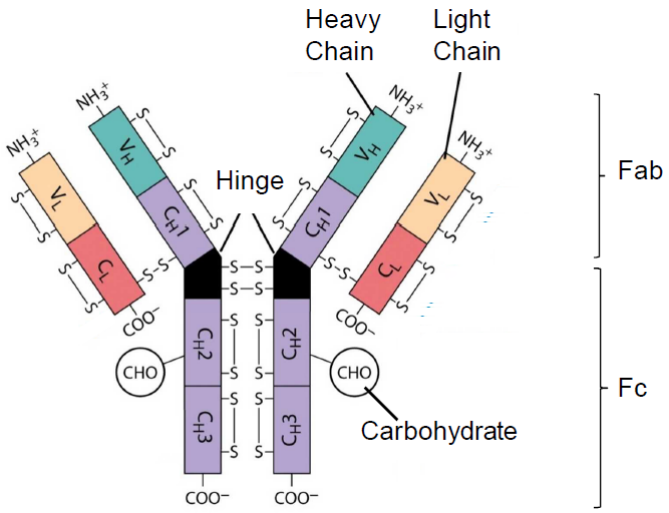
2.2.2. Active Substance

General information

Vedolizumab (MLN0002) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7. It is composed of two light chains of the kappa subclass and two heavy chains linked together by two disulfide bridges to form a Y-shaped molecule that is typical of IgG1 immunoglobulins as shown below in Figure 1. Each molecule contains 2 heavy chains and 2 light chains, 12 homologous domains, 12 intra-chain and 4 inter-chain disulfide bonds, and an asparagine-linked glycosylation site on each heavy chain at residue 301.

The stylized domain structure of MLN0002 is depicted in Figure 1.

Figure 1: ***Schematic Diagram of Vedolizumab***



Manufacture, characterisation and process controls

Vedolizumab subcutaneous (SC) active substance (AS) is manufactured at AbbVie Bioresearch Center (ABC), and at Lonza Biologics, Inc. (Lonza) in accordance with current Good Manufacturing Practices. Vedolizumab active substance is manufactured using recombinant Chinese hamster ovary (CHO) cells that secrete the antibody into the surrounding culture medium.

The manufacturing process for Vedolizumab IV (Process C-IV) and Vedolizumab SC (Process C-SC) are identical up to the penultimate process step. Information regarding the manufacturing process and process controls for the shared portions of the Vedolizumab manufacturing process are presented in the approved Entyvio (vedolizumab) IV assessment report.

The operating parameters for Process C-IV and Process C-SC have been adequately discussed and justified. The two processes are almost identical, apart from some differences that have been adequately discussed and justified.

The cell culture process including the inoculum expansion, the production phase, the media and supplemental feeds as well as all associated process parameters and in-process controls are shared with vedolizumab IV and information for these process steps was presented.

The two new raw materials, citric acid monohydrate and sodium citrate monohydrate used in the SC formulation, are of Ph. Eur. grade and adequately justified.

Control of critical steps and intermediates

Adequate process controls are used to monitor the vedolizumab SC active substance (AS) commercial manufacturing process. Critical process controls have been identified for process parameters that have a direct and significant influence on the product quality attributes.

In-process testing and monitoring of process parameters are used to ensure the safety and quality of the vedolizumab SC AS commercial manufacturing process. Results from process characterisation studies, combined with clinical and commercial manufacturing-scale experience, were used to establish the critical steps, critical process parameters or critical in-process controls, and their associated normal operating ranges (NORs) or in-process control limits.

Process validation

The process validation performed at ABC is considered adequate. Results from operations to concentrate, formulate, bottle and store vedolizumab SC AS produced from consecutive batches at ABC executed per the process performance qualification (PPQ) protocols met the protocol's acceptance criteria, providing evidence of the reproducibility and robust nature of the vedolizumab SC purification operations and associated equipment.

Systematic controls were performed to ensure that none of the process parameters had a negative impact on the product quality and overall ensure that a robust process is in place which yields a product of consistent quality.

Additionally, the downstream unit operations were validated for their impact to product related impurities through the inclusion of testing in the validation protocols.

The process validation performed at Lonza is overall considered adequate. The validation results for the unit operations shared with vedolizumab IV were provided in the approved Entyvio (vedolizumab IV) dossier.

An extractables and leachables assessment, validation of active substance transport, and control of in-process hold times have been provided and did not raise any concern.

Comparability exercise

The Applicant has performed the comparability exercise on a limited number of batches. Extended characterisation has also been performed.

Characterisation of the molecule was performed previously on Vedolizumab intended for IV administration. An extended characterisation of vedolizumab SC has been performed to evaluate the impact of the new formulation. No differences have been reported and this is acceptable.

The approach and comparability acceptance criteria are considered sufficient for the comparability demonstration. Nonetheless, in order to have a full representativeness of batches used to this purpose, the Applicant was recommended to further investigate on this point.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specification for the active substance includes appearance, identity, potency, purity, bacterial endotoxins, bioburden.

The specifications for active substance, analytical methods, method validation and batch analysis have been provided.

Upon request some specifications were revised and are considered acceptable. The proposed tests and acceptance criteria for routine active substance release and stability are acceptable.

Analytical procedures

Adequate descriptions of analytical methods, including their system suitability criteria and evaluation have been provided. All analytical methods are considered suitable for the control of the active substance.

Batch analysis

Results from several batches of active substance from each manufacturing site were provided. The proposed specifications were met. Batch-to-batch consistency is also demonstrated across all batches.

Reference standards

The Applicant has submitted the qualification protocol for future primary and working reference standards and these are acceptable. Extensive characterization of the reference standard was performed. The use of this reference standard in the release of both vedolizumab IV and SC is considered acceptable.

Container closure system

The container closure system for active substance has been described in detail and the choice of materials appropriately justified in terms of suitability, compatibility with active substance, and shipping conditions. The container closure system has been properly evaluated as part of stability studies and together with the filling, storage and shipment operations, provides adequate protection against microbial contamination.

Stability

Stability studies based on ICH guidelines have been conducted for Vedolizumab active substance. Relevant parameters were selected to study the stability profile of the active substance. The analytical methods were validated and are described in the relevant sections of the dossier.
The data from primary stability and supporting stability studies support the proposed shelf life at the designated storage condition in the proposed container closure system.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Vedolizumab SC finished product is a sterile finished product containing 108 mg of vedolizumab as active substance with citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80 and water for injections (WFI).

The excipients have been justified based on formulation development studies and are in compliance with the Ph. Eur. and USP.

Vedolizumab injection, for subcutaneous use (vedolizumab SC) finished product (FP) is presented as a sterile, liquid formulation in a single use pre-filled syringe (PFS) intended for subcutaneous injection. The commercial presentation is assembled into a Needle Safety Device (PFS+NSD) or Autoinjector (PFS+AI) format with 108 mg Vedolizumab and both are intended for subcutaneous injection.

Vedolizumab SC is intended for administration via a single-use, prefilled syringe with a needle safety device (PFS + NSD) or a prefilled syringe in an autoinjector/pen (PFS + AI).

The finished product solution does not come into direct contact with any of the device components.

Formulation development

Formulation knowledge gained from the development of vedolizumab IV active substance and finished product was utilised in the development of the vedolizumab SC finished product formulation.

Comparison of vedolizumab IV active substance and finished product and vedolizumab SC active substance and finished product formulations has been provided. A comparability assessment of the vedolizumab IV and SC formulations was conducted which showed that they are comparable.

Manufacturing process development

The manufacturing process of active substance has been adequately described.

Sufficient information and assembly process development for NSD (PFS+NSD) or AI (PFS+AI) has been provided.

Manufacture of the product and process controls

The finished product manufacturing process is a standard process and also includes aseptic filling and stoppering. The stoppered pre-filled syringes (PFS) are visually inspected, bulk packaged, and shipped for assembly with the needle safety device (PFS+NSD) or with the autoinjector (PFS+AI).

Adequate in-process controls (IPC) are monitored during manufacturing.

The container closure system for finished product is accurately described both for the primary closure system, which is the pre-filled syringe (PFS), and for the autoinjector (AI) and needle safety devise (NSD).

The choice of the container/closure is adequate.

The long-term stability studies and the container closure integrity studies demonstrated the primary container closure compatibility with the finished product solution and the ability of the container closure system to protect the finished product solution from microbial contamination.

The container closure systems for finished product are adequate for its intended use.

Process validation

A description of the process validation strategy has been provided, and in-process testing results and final product release testing results have also been provided. Overall the data demonstrate that for all validation batches the predefined parameters were met and confirmed that the process is capable of producing bulk finished product in prefilled syringes in a robust manner and providing a sterile product in a reproducible manner.

Process validation of the PFS+NSD and PFS+AI assembly process demonstrates that the assembly process is reproducible and consistent for commercial production.

The impact of transport on product quality and integrity was adequately assessed.

Product specification, analytical procedures, batch analysis

Vedolizumab SC finished product is not described in a pharmacopoeia monograph and is controlled using in-house established specifications. The panel of release tests are in line with ICH Q6B and it covers appearance, identity, purity and impurities, potency, quantity, and microbial quality.

Analytical procedures

Summaries of method descriptions specific for the finished product have been provided. Methods also used for active substance are described in the active substance section. Validation of all compendial methods were performed to demonstrate suitability of use.

Batch analysis

The proposed specifications were met on the batches analysed. Batch-to-batch consistency has been also demonstrated across all batches.

Reference standards

The same reference standard is used as for the analysis of the active substance. This is acceptable.

Stability of the product

A shelf life of 18 months for the finished product PFS assembled into either PFS+NSD or PFS+AI is claimed when stored at 2°C-8°C. The assignment of shelf life for the PFS + NSD and PFS + AI has been based on the PFS manufacturing date and is limited by the PFS shelf life period.

Based on the stability results provided a shelf life of 18 months for the finished product PFS assembled into either PFS+NSD or PFS+AI when stored at 2 °C-8 °C is acceptable.

Stability data supports the storage the PFS+NSD (prefilled syringe) and PFS+AI (prefilled pen) left out of the refrigerator in its original carton at room temperature (up to 25 °C) for up to 7 days. The prefilled syringe or prefilled pen should not be used if left out of the refrigerator for more than 7 days.

Adventitious agents

The active substance manufacturing process for vedolizumab injection for subcutaneous use (MLN0002 SC) is essentially the same manufacturing process as the active substance manufacturing process for vedolizumab for intravenous infusion (MLN0002 IV). Two steps have been modified for the manufacturing of MLN0002 SC, neither of the two modified steps is considered to contribute to viral clearance or inactivation. As a result, the viral clearance studies performed with MLN0002 IV are also applicable for MLN0002 SC. All information pertaining to the adventitious agents safety evaluation for the process steps shared between MLN0002 SC and MLN0002 IV can be found in the approved Entyvio (vedolizumab) IV dossier and this is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In relation to the PFS Functional Test Results in the Design Verification Study, reporting data from accelerated aging, needle clogging was reported in several aged samples.

The supporting stability study data for Vedolizumab SC finished product did not show any out-of-specification for the syringe functional parameters results when tested beyond the proposed shelf-life.

Moreover, the reported clogging is specifically related to higher storage temperature of the accelerated aging study and thus not relevant for the product stored at the recommended storage conditions, even if for longer time. Finally, the proposed shelf life of the PFS assembled into either PFS+NSD or PFS+AI is 18 months when stored at 2—8°C, further reassuring on the maintenance of the quality of the product during storage.

Thus, the aspect of clogging was not considered critical during the assessment. The Applicant was requested to provide a list of all the reported clogging events, specifying the context in which they were observed and discussing the impact of these events on the quality and safety of the product. The Applicant provided the requested information, where it was clear that that the clogging everts were observed very rarely.

It is emphasized that the clogging events registered up to date do not pose any concern, since they were very rare and occurred mainly during storage in accelerated conditions that are much different from the claimed storage conditions in terms of time and temperature.

The overall quality documentation provided for Entyvio in this line extension application is of adequate quality. No major objections were identified during the assessment. There is a good control strategy in place to guarantee consistent quality of the finished product. The overall quality of Entyvio SC is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the data provided, this line extension application for Entyvio is considered approvable from a quality point of view.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

No new studies were submitted with the current application. The vedolizumab primary structure is the same in SC and IV drug products and no changes were made that would impact the primary structure of the protein. Moreover, comparable biochemical properties and in vitro functional activity between the two formulations have been demonstrated (please refer to quality part of this assessment report). Therefore, the nonclinical pharmacodynamic, pharmacokinetic, and toxicity studies conducted in support of the vedolizumab IV development program are considered applicable to the proposed vedolizumab SC formulation. A previously submitted GLP local tolerance study with vedolizumab SC in rabbits was cross referred in this application and showed that the formulation was well tolerated.

2.3.1. Ecotoxicity/environmental risk assessment

A justification for not performing a formal ERA was submitted by the Applicant, in line with guideline EMEA/CHMP/SWP/4447/00 Rev.1. The drug substance is a protein that will be catabolized into naturally occurring amino acids and is not expected to result in any significant risk to the environment.

2.3.2. Conclusion on the non-clinical aspects

This application is approvable from a non-clinical viewpoint.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: ***Tabular overview of clinical studies with SC and/or IV***

Table 1.a Clinical Studies With Vedolizumab SC and IV in Healthy Subjects and Patients With UC and CD

Study Identifier	Design/Population	Dosing Regimen, Formulation	Subjects Enrolled/ Subjects With PK	Key PK, E-R Objectives
Phase 1 Studies with Vedolizumab SC in Healthy Subjects				
C13010*	Phase 1, open-label, single-dose study to determine the absolute bioavailability following SC and IM administration. Healthy subjects (aged 18-60 years)	Single dose, 180 mg SC (n = 12) 180 mg IM (n = 11) 180 mg IV (n = 11) Lyophilized powder for Injection – 60 mg/mL SC and IM -1.5mL x 2	Total = 42 PK = 34	Determine vedolizumab bioavailability when administered SC and IM (relative to IV administration).
SC-101	Phase 1, open-label, single-dose study to assess the absolute bioavailability of vedolizumab following SC administration. Healthy subjects (aged 18-60 years for non-Japanese, or 20-60 years for Japanese)	Single dose, 300 mg IV (n = 12) 54 mg SC (n = 12) 108 mg SC (n = 12) 160 mg SC (n = 12) Vedolizumab IV -300 mg/vial. Lyophilized powder Vedolizumab SC 108 mg liquid formulation in a prefilled syringe	Total = 48 PK = 48	Assess absolute bioavailability and PK of vedolizumab SC.
SC-1017	Phase 1, open-label, randomized, pilot study to compare the PK of single SC injections of vedolizumab administered in PFS versus prefilled syringe in PFS+NSD. Healthy subjects (aged 18-65 years)	Single dose, 108 mg SC PFS (n = 12) 108 mg SC PFS+NSD (n = 12) Vedolizumab SC 108 mg liquid formulation in a prefilled syringe	Total = 24 PK = 24	Compare PK of vedolizumab SC administered as PFS vs PFS+NSD.

Table 1.a Clinical Studies With Vedolizumab SC and IV in Healthy Subjects and Patients With UC and CD

Study Identifier	Design/Population	Dosing Regimen, Formulation	Subjects Enrolled/ Subjects With PK	Key PK, E-R Objectives
SC-1018	Phase 1, open-label, randomized study to compare the PK of single SC injections of vedolizumab administered in PFS versus PFS+NSD. Healthy subjects (aged 18-65 years)	Single dose, 108 mg SC PFS (n = 51) 108 mg SC PFS+NSD (n = 51) Vedolizumab SC 108 mg liquid formulation in a prefilled syringe	Total = 102 PK = 102	Compare PK of vedolizumab SC administered as PFS vs PFS+NSD.
SC-1021	Phase 1, open-label, randomized, pilot study to compare the PK of single SC injections of vedolizumab administered in PFS versus PFS+AI. Healthy subjects (aged 18-65 years)	Single dose, 108 mg SC PFS (n = 12) 108 mg SC PFS+AI (n = 12) Vedolizumab SC 108 mg liquid formulation in a prefilled syringe	Total = 24 PK = 24	Compare PK of vedolizumab SC administered as PFS vs PFS+AI.
SC-1022	Phase 1, open-label, randomized study to compare the PK of single SC injections of vedolizumab administered in PFS versus PFS+AI. Healthy subjects (aged 18-65 years)	Single dose, 108 mg SC PFS (n = 102) 108 mg SC PFS+AI (n = 102) Vedolizumab SC 108 mg liquid formulation in a prefilled syringe	Total = 204 PK = 204	Compare PK of vedolizumab SC administered as PFS vs PFS+AI.

Study No. No. of Sites-Country Study Start-End Dates	Study Type Status (Type of Report)	Study Design Primary Objective (Endpoint)	Population [a] Sex and Race (n [%]) Mean Age (Min-Max)	Healthy Subjects or Diagnosis of Patients	Treatment(s) (Randomized/ Completed Study Drug) Treatment Duration
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication					
MLN0002SC-3027 141 sites in 29 countries 18 Dec 2015-21 Aug 2018	Safety and efficacy Completed (Full)	Phase 3, pivotal, multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled study with a VDZ IV reference arm To assess the effect of VDZ SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active UC who achieved clinical response at Week 6 following administration of VDZ IV at Weeks 0 and 2 (safety and efficacy)	383 subjects – induction phase 216 subjects – randomized into maintenance phase 130 (60.2%) men, 86 (39.8%) women 181 (83.8%) White, 32 (14.8%) Asian, 2 (0.9%) Black or African American, 1 (0.5%) American Indian or Alaskan Native 39.3 (18-69) years	UC	Placebo (56/21) VDZ SC 108 mg (106/77) VDZ IV 300 mg (54/41) 6-week open-label IV induction phase, 46-week placebo-controlled maintenance phase

Study No. No. of Sites-Country Study Start-End Dates	Study Type Status (Type of Report)	Study Design Primary Objective (Endpoint)	Population [a] Sex and Race (n [%]) Mean Age (Min-Max)	Healthy Subjects or Diagnosis of Patients	Treatment(s) (Randomized/ Completed Study Drug) Treatment Duration
5.3.5.2 Study Reports of Uncontrolled Clinical Studies					
MLN0002SC-3030 [c] 164 sites in 30 countries 15 Apr 2016-Data cutoff 31 May 2018	Safety and efficacy Ongoing (Interim)	Phase 3b, open-label extension study of MLN0002SC-3027 and MLN0002SC-3031 To obtain data on long-term safety and tolerability of VDZ SC in subjects with UC or CD (safety and efficacy)	595 subjects total 285 UC subjects 166 (58.2%) men, 119 (41.8%) women 223 (78.2%) White, 2 (0.7%) Black or African American, 58 (20.4%) Asian, 2 (0.7%) American Indian or Alaska Native 40.8 (18-77) years 310 CD subjects 165 (53.2%) men, 145 (46.8%) women 279 (90%) White, 7 (2.3%) Black or African American, 20 (6.5%) Asian, 1 (0.3%) American Indian or Alaska Native, 1 (0.3%) Native Hawaiian or Other Pacific Islander, 1 (0.3%) multiracial [b], 1 (0.3%) missing 37.8 (18-76) years	UC, CD	VDZ SC 598 subjects enrolled (287 UC and 311 CD) 595 subjects dosed (285 UC and 310 CD) No subjects completed study drug at the time of data cutoff; 136 subjects early terminated (66 UC and 70 CD) Duration of VDZ SC treatment will vary by subject based on continued benefit, but could be up to a maximum of 5 years, unless the subject withdraws from the study, or the sponsor decides to close the study.

Study No. No. of Sites – Country(ies) Study Start-End Dates Status	Study Design Primary Objective (Endpoint)	Population [a] and Type (Criteria) Sex and Race (n [%]) Mean Age (Min-Max)	Healthy Subjects or Diagnosis of Patients	Treatment(s) (Randomized/ Completed Study Drug) Treatment Duration
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication				
MLN0002SC-3031 131 sites – 30 countries 14 Dec 2015-06 May 2019 Completed	Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled study To assess the effect of VDZ SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active CD who achieved clinical response at Week 6 following administration of VDZ IV at Weeks 0 and 2 (safety and efficacy)	644 subjects – induction phase 409 subjects – randomized into maintenance phase 223 (54.5%) men, 186 (45.5%) women 374 (91.4%) white, 8 (2%) black or African American, 23 (5.6%) Asian, 2 (0.5%) American Indian or Alaska Native, 1 (0.2%) Native Hawaiian or other Pacific Islander, 1 (0.2%) multiracial [b] 37.5 (18-76) years	CD	Placebo (135/73) VDZ SC 108 mg (275/168) 6-week open-label IV induction phase, 46-week placebo-controlled maintenance phase

2.4.2. Pharmacokinetics

The aim of the clinical pharmacology program for vedolizumab SC was to describe the PK and immunogenicity of single-dose SC vedolizumab in healthy subjects and repeat-dose SC vedolizumab in UC patients. Factors that affect any of these parameters were also assessed by population modelling of PK data from the phase 3 studies Population PK approaches using nonlinear mixed-effects modelling and graphical analyses were used on data from the phase 3 studies to understand the effects of demographics or baseline covariates on PK of vedolizumab. The characterization of the exposure-response (E-R) relationship for UC patients was also an aim of the clinical pharmacology program to support dose recommendation for marketing applications and to assess the impact of vedolizumab serum Ctrough and Cavg on efficacy endpoints. Finally, characterization of long-term immunogenicity from vedolizumab IV program was also presented.

In SC clinical studies, plasma concentrations of vedolizumab were determined using a validated direct capture PK assay. Two versions of the assay were used which had different lower limits of quantitation (LOQ). The assay with the higher LOQ was used for the SC phase 3 studies and the majority of the phase 1 studies. A concentration-dependent effect on the accuracy of measuring vedolizumab in lipemic serum has been found. Lipemia in serum pharmacokinetic samples was not monitored in studies MLN0002SC-3027, MLN0002SC-3031, Vedolizumab SC-1017, Vedolizumab SC-1018, Vedolizumab SC-1019, vedolizumab SC-1022. Therefore, the MAH was not able to provide data to support the percentage of samples analysed in the lipemic matrix condition. During validation, testing for the effect of lipemia on the ability to measure vedolizumab concentrations in serum was conducted at various concentrations of vedolizumab and triglycerides.

The MAH's conclusion that serum lipemia may be a problem only at vedolizumab concentrations below 3 µg/mL can be supported; although batches were not spiked with vedolizumab concentration above 3.00

µg/mL. However, the issue is considered minor as only 2.72% (range, 2.22% to 4.43% for the individual studies) of all samples analysed in the submitted studies had a vedolizumab concentration in the range 0.200 - 3.00 µg/mL concentration, and only a small percentage (<4%) of serum samples, according to MAH's data, can be expected to have lipid levels high enough to affect the vedolizumab measurement.

It can be thus concluded that, overall, lipemia could have had an effect on the measurement of vedolizumab only in an insignificant number of serum samples, and thus it is not expected to have affected the overall conclusions of the studies.

Study SC-101 showed that the bioavailability following a single SC injection of vedolizumab SC was 75.1%, independent of the doses evaluated (54, 108, or 160 mg). Vedolizumab reached maximum serum concentrations around 1 week after a single SC injection. Vedolizumab was eliminated by both linear and nonlinear pathways following SC injection, with more rapid elimination with decreasing dose/concentration. Compared with non-Japanese subjects, Japanese subjects generally showed similar or slightly higher exposure; however, ethnicity did not have an impact on CLL or V2 based on the population pharmacokinetic analysis, likely since weight was a covariate for various population pharmacokinetic parameters.

Results from study SC-1017 showed that the two curves, i.e. for PFS+NSD and PFS groups, are very similar until approximately 60 days after dosing but then there is a difference between the two curves. This could be the reason why the ratios of geometric LSMs for AUClast and AUCinf are below the unity and the lower end of the 90% CIs is out of the reference value. Considering that the administration of vedolizumab SC should be Q2W, this differences in the last part of the AUC curve could be considered not clinically significant.

Results from Study SC-1021 showed that serum vedolizumab AUCWeek2, AUClast, AUCinf, and Cmax were approximately 19%, 29%, 33%, and 20% higher, respectively, following PFS+AI than following PFS. Results from these two studies, i.e. SC-1017 and SC-1021, showed that the ratios of geometric LSMs for AUClast and AUCinf are far from the unity and also the 90% CIs are out of the reference value. However, these studies are considered as pilot studies and two more studies investigating the bioequivalence among the different formulation have been conducted.

Study SC-1022 showed that the PK of serum vedolizumab is similar following dosing with PFS+AI and PFS: the ratios of geometric LSMs for AUClast, AUCinf, and Cmax were close to unity and the 90% CIs were within 80.00% to 125.00%, In Study SC-1018 the statistical comparison of Cmax and AUC parameters for all sites combined confirmed bioequivalence of the 2 treatments, i.e. PFS+NSD than following PFS, with GMRs of approximately 100% and 90% CIs within the 80% to 125% limits. Overall, PFS+NSD and PFS+AI showed similar PK results to the PFS used in phase 3 trials.

The base population PK model developed for vedolizumab IV was updated to include an absorption component for SC administration. The updated base model was fit to IV data from studies C13002 and C13009 and IV/SC data from studies C13010 and MLN0002SC_101. Results from this model were used in the current analysis as prior information to selectively inform a subset of PK parameters during model development. Informative priors were defined for the fixed-effect parameters Vmax, Km, Vp, Q, Ka, and F, and for the interindividual random-effect parameter on Ka. The use of informative priors served to support estimation of these model parameters and allowed stable estimates to be obtained despite the sparse available PK data.

Given that only trough PK samples were collected following SC administration, there was very limited information to support estimating covariate effects on F. The same argument could be made for Ka, where injection site was also modelled as a covariate, but this did not result in as much model instability and the covariate estimates were plausible. No covariate effects were modelled on F for these reasons.

The objective of popPK and E-R analysis was to evaluate maintenance SC therapy as an alternative to IV maintenance therapy for UC patients. Covariate effects on CLL were of primary interest given the significant impact of this PK parameter on drug exposure. Body weight was a determinant of variability in CLL with an estimated power coefficient (95% CDI) of 0.471 (0.406, 0.531). Serum albumin was also a determinant of variability in CLL with an estimated power coefficient (95% CDI) of -1.19 (-1.29, -1.11). The effects of body weight and albumin on CLL were estimated with reasonable precision and the 95% CDIs were statistically different from the null effect of zero. There was no clinically important effect of IBD diagnosis on CLL; the effect was precisely estimated with a point estimate (95% CDI) indicating a decrease in CLL in CD subjects by a factor of 0.968 (0.943, 0.993) compared to UC patients. The 95% CDI was statistically different from the null effect of one. The effect of SC injection site was not precisely estimated with a point estimate (95% CDI) indicating a decrease in Ka for the thigh and upper arm by a factor of 0.510 (0.299, 0.882) and 0.416 (0.201, 0.921), respectively, compared to the abdomen. The 95% CDIs were statistically different from the null effect of one.

The presence of AVA was estimated to increase vedolizumab CLL. For a typical AVA-positive subject with a titer of 250, the point estimate and 95% CDI for CLL was 0.254 L/day (0.229, 0.281) compared to 0.169 L/day (0.164, 0.174) for the reference subject with a negative AVA. The 95%CDI for the power coefficient of the AVA titer effect was wide (0.0464, 0.104) but was statistically different from the null effect of zero.

Further evaluation of covariate effects on CLL was conducted via simulation given the Bayesian posterior distributions (or uncertainty) of the model parameters. Covariate effect sizes of 25% from the typical reference subject were used as a limit for clinically meaningful changes. Body weight and albumin appeared not to have a clinically meaningful impact across the range of values evaluated except at the extremes (i.e., observed 5th or 95th percentiles of the covariate). Extreme values of body weight (e.g., 106 kg) and albumin (e.g., 2.7 g/dL) and a positive AVA titer (>10) were identified as potentially clinically important predictors of CLL, as the 95% CDI for the covariate effect partially or completely fell outside of the 25% range.

As result of the population PK analysis, Ctrought,SS and Cavg,SS for subjects on IV Q8W, IV Q4W, SC Q2W, SC QW regimens were simulated and the relative values were reported. Comparing the proposed dosage 108 mg Q2W SC with the approved one, 300 mg Q8W IV, it could be observed that model predicted Ctrough,SS for vedolizumab 300 mg Q8W IV is lower compared to 108 mg Q2W SC, mean values of 8.46 µg/mL, 8.39 µg/mL and 11.1 µg/mL for the first and 34.6 µg/mL and 23.1 µg/mL for the latter. Predicted Cavg,SS for vedolizumab 300 mg Q8W IV seems to be more close to 108 mg Q2W SC, mean values of 28.3 µg/mL, 29.5 µg/mL and 32.2 µg/mL for the first and 39.8 µg/mL and 36.8 µg/mL for the latter.

Given the differences in the two routes of administration the difference in Ctrough,SS was expected. Considering that, as acknowledged by the MAH, it cannot be assumed that 108 mg Q2W SC would result in similar efficacy compared to 300 mg Q4W IV administration, only vedolizumab SC 108 mg Q2w and Vedolizumab 300 mg IV Q8W should be considered. From a PK point of view, these two curves cannot be considered overlapping by definition. Indeed, Cmax following administration of vedolizumab SC 108 mg was substantially lower than observed Cmax following administration of vedolizumab 300 mg IV; and SC regimen was associated with a narrow fluctuation compared to both the IV regimens as well as Vedolizumab 300 mg IV Q8W.

The AVA seropositivity rate was 6% during treatment with vedolizumab SC administration to UC subjects. The development of AVA decreases vedolizumab trough concentrations. Considering that the AVA rate following SC administration was similar to IV administration (6%) the clinical impact is the same.

2.4.3. Pharmacodynamics

Main results of the E-R analysis are summarised below. Week 6 results showed that for all the exposure parameters considered, quartiles of higher exposure are associated with greater probability of week 6 clinical remission and week 6 clinical response.

Steady-state exposure metrics at week 52 were calculated for the week 6 responders who were randomized to the maintenance phase. A positive ER trend for each exposure metric within each arm was observed. The amount of overlap of the model-predicted exposures between arms has been analysed, the SC and IV presentations show better results for model-predicted Cavgss compared to model-predicted Ctroughss, however a good overlap has not been observed for neither of them.

SC treatment, as compared with IV treatment, leads to a higher exposure to vedolizumab. Analysing the exposure quartiles within arm and relating them to probability of week 52 clinical remission and mucosal healing, it can be observed that in the most of cases the probability of week 52 clinical remission and the rate of week 52 mucosal healing are higher for the SC treatment.

Week 52 clinical remission. VPCs for the full model-predicted Cavgss model (interaction model) looks good suggesting good ability of the model to reproduce the observed data. Instead visual predictive checks for the week 52 clinical remission ER model of model-predicted Ctroughss (the full model, the same as the interaction model) indicates the model cannot replicate the observed data.

Week 52 mucosal healing. Baseline albumin was estimated to significantly modify the odds of week 52 mucosal healing in the full model. Visual predictive checks for the interaction model of model-predicted Cavgss shows good ability to reproduce the observed data. VPCs for the interaction model of model-predicted Ctroughss, however, show that the models is not reliable for its purpose. Predictions from the interaction model of model-predicted Cavgss at covariate settings of interest showed that higher response is predicted for patients who are TNF-naive relative to TNF-failures, but to a degree that decreases in increasing exposure. A small, non-significant increase in response is seen as albumin levels increase from 40 g/L to 45 g/L.

Performing the screening for confounders to a multivariate approach, a propensity score model relating probability of low within-arm exposure to TNF- baseline rectal bleeding scores, and baseline endoscopic scores was fitted. Patients with prior TNF-failures and patients with more severe disease at baseline were identified as having a higher propensity to fall in the lowest exposure quartile.

Overall it can be concluded that a general trend of increased rate of response for patients with higher vedolizumab exposure was observed and it seems that the SC administration leads to slightly higher exposure compared to IV administration. Low albumin concentration has the potential to be clinically relevant.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology program for the SC vedolizumab formulation consists of many studies, including bioequivalence studies among the different device delivery presentations, population and exposure-response analysis. The claim for the CD indication was initially based on a PK bridging between the approved Vedolizumab 300 mg IV Q8W maintenance dosing and the new 108 mg Q2W SC formulation.
Comparing 108 mg Q2W SC to Vedolizumab 300 mg IV Q8W, from a PK point of view, the two curves cannot be considered overlapping by definition. Indeed Cmax following administration of vedolizumab SC 108 mg was substantially lower than observed Cmax following administration of vedolizumab 300 mg IV and the SC regimen which was associated with a narrower fluctuation to that of Vedolizumab 300 mg IV Q8W. Considering the very different nature of the exposure curves after SC and IV

administration the comparison between the two appears to be limited. The applicant was therefore asked at D120 to justify further that the available PK data can support the extrapolation of efficacy and safety from IV to SC vedolizumab in patients with CD, considering also that a PK/PD correlation was evident in UC but not in CD patients, or to provide clinical data from CD patients. As the company provided clinical data on CD (study results from study SC-3031) at D150 of the procedure (see assessment of clinical efficacy) the extrapolation based on PK bridging was not further pursued and the evaluation of the efficacy profile maintains a pivotal role.

2.4.5. Conclusions on clinical pharmacology

This Line extension is approvable from a clinical pharmacology viewpoint. The proposed dosage regimen is considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

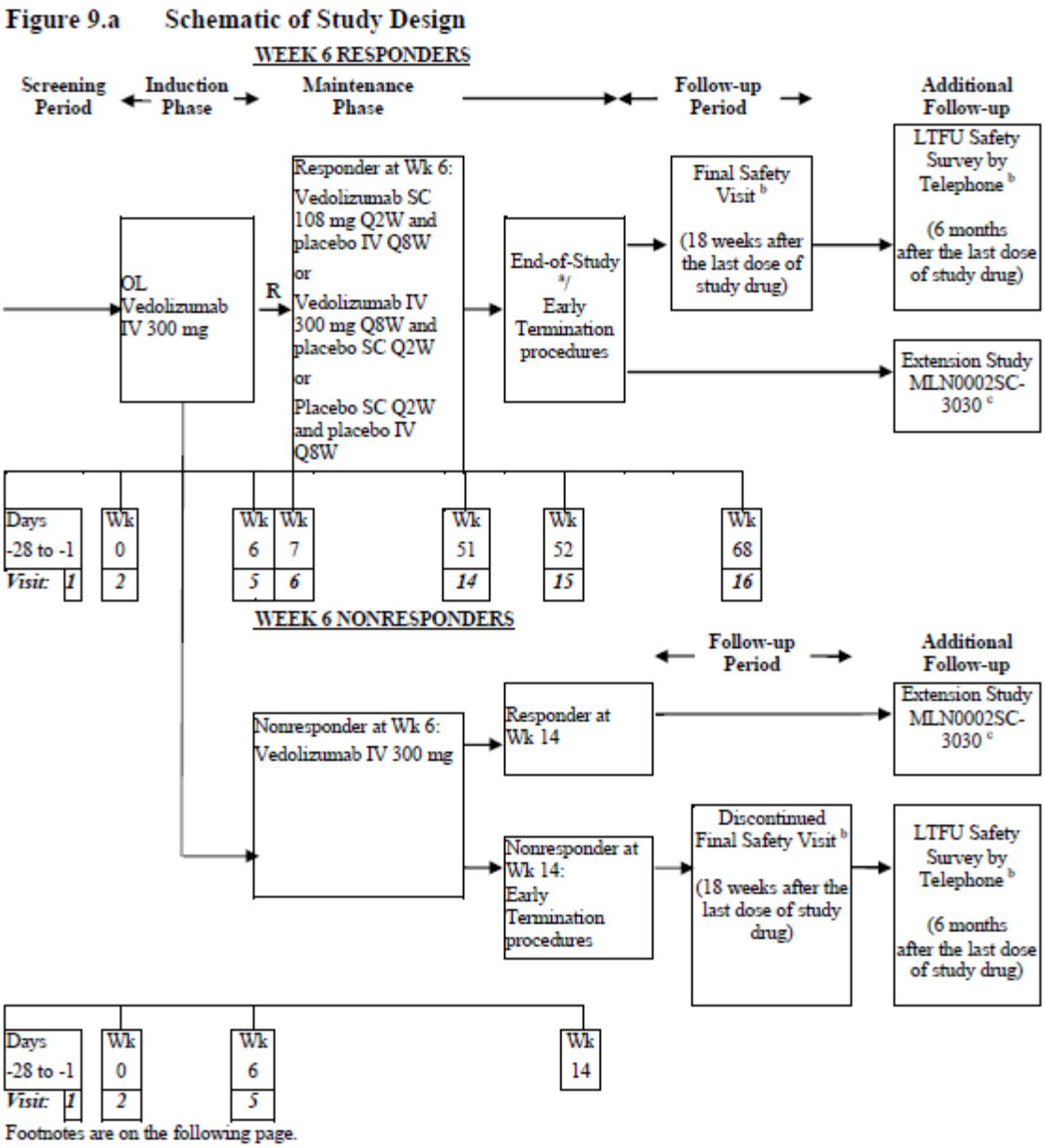
Please refer to above chapter on pharmacokinetics addressing popPK.

2.5.2. Main study

MLN0002SC-3027: 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 to 12 with an endoscopic subscore ≥2) who achieved clinical response following 2 doses (at Weeks 0 and 2) of open-label vedolizumab IV therapy.

Methods

Figure 2: ***Schematic of Study Design***



Study Participants

The key inclusion criteria included:

- adult patients with diagnosis of UC ≥6 months before screening with confirmatory histology;
- disease activity: moderately to severely active UC (Mayo score of 6-12 with endoscopic subscore ≥ 2) within 10 days before the first dose of study drug. Central reading of the endoscopy.
- evidence of UC extending proximal to the rectum (≥15 cm of involved Colon). 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.
- inadequate response or intolerance to at least 1 of the following therapies: immunomodulators, corticosteroids, and/or TNF-α antagonists.

The exclusion criteria were divided into 3 categories:

- GI exclusion criteria (extensive colonic resection, subtotal or total colectomy, abdominal abscess or toxic megacolon; extensive colonic resection; the subject had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine);
- Infectious disease (the common infectious diseases considered for biologic agents and for anti-integrin agents)
- General exclusions (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; diagnosis of Crohn's colitis or indeterminate colitis).

Treatments

Induction phase: patients received open-label infusions of vedolizumab IV 300 mg at **Weeks 0 and 2** and were assessed for clinical response at Week 6.

Subjects who achieved a **clinical response**, as assessed by full Mayo score (endoscopy score determined by central reading), were randomized at a 2:1:1 ratio in the double-blind, double-dummy **maintenance phase** in which participants in each treatment arm received both SC injections Q2W and IV infusions Q8W, beginning at Week 6 through Week 50, as follows:

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.

Subjects who did not achieve a clinical response at Week 6 were not randomized into the maintenance phase and instead received a **third infusion** of vedolizumab IV 300 mg, while Week 14 responders then had the chance to move to the OLE.

Permitted Medications and Treatments

Subjects were permitted to receive a therapeutic dose of the following drugs:

Oral 5-ASAs if stable dose for 2 weeks immediately before the first dose of study drug.

Oral corticosteroid therapy (prednisone at a stable dose ≤30 mg/d, budesonide at a stable dose ≤9 mg/d, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately

before the first dose of study drug if corticosteroids had just been initiated, or for the 2 weeks immediately before the first dose of study drug if corticosteroids were being tapered (according to defined guidelines).

Probiotics (eg, Culturelle, Saccharomyces boulardii) if stable dose for 2 weeks immediately before the first dose of study drug.

Antidiarrheals for control of chronic diarrhea.

Azathioprine or 6-mercaptopurine, provided the dose had been stable for 8 weeks immediately before first dose of study drug.

For immunosuppressives, oral 5-ASAs, probiotics and antibiotics for UC, dose reduction or discontinuation per label was allowed only due to adverse reactions.

For oral corticosteroids, dose reductions were made per the tapering schedule. For subjects who could not tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may have been increased up to the original dose at the start of induction therapy (should not have exceeded baseline dose). In such cases, the tapering regimen above must have been reinitiated within 2 weeks.

Among Excluded Medications and Treatment: all live vaccines from 30 days before screening to at least 6 months after the last dose of study drug.

Objectives

Primary Objective: To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active ulcerative colitis (UC) who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

Secondary Objectives:

- To determine the effect of vedolizumab SC maintenance treatment on mucosal healing at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on durable clinical response at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on durable clinical remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on corticosteroid free remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

Outcomes/endpoints

Primary Endpoint:

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

Secondary Endpoints:

- Proportion of subjects with mucosal healing, defined as Mayo endoscopic subscore of ≤1 point, at Week 52.
- Proportion of subjects with durable clinical response, defined as clinical response at Weeks 6 and 52, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
- Proportion of subjects with durable clinical remission, defined as clinical remission at Weeks 6 and 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.

Safety Assessments:

- Safety for maintenance therapy as assessed by adverse events (AEs), adverse events of special interest (AESIs) (including serious infections and opportunistic infection, such as progressive multifocal leukoencephalopathy [PML], liver injury, malignancies, infusion-related or injection site reactions or systemic reactions and hypersensitivity), serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and results of 12-lead electrocardiograms.

Sample size

Assuming a clinical remission rate of 42% for vedolizumab and 16% for placebo at Week 52, a sample size of 94 subjects in the vedolizumab SC group and 47 subjects in the placebo group is chosen, in order to provide 90% power at a 2-sided 0.05 level of significance. To ensure a randomized sample size of 188 subjects, assuming 47% of the subjects entering induction will achieve clinical response at Week 6, approximately 400 subjects are planned to be enrolled into the study. Assuming a mucosal healing rate of 52% for vedolizumab and 20% for placebo at Week 52, with a sample size of 94 subjects in the vedolizumab group and 47 subjects in the placebo group, the first secondary endpoint of mucosal healing at Week 52 is powered to at least 97% at a 2-sided 0.05 level of significance.

Randomisation

An interactive web response system (IWRS) system was used to randomly assign subjects with clinical response at Week 6 to receive injections of active vedolizumab or placebo.

Randomization was stratified by:

- concomitant use of oral corticosteroids,

- clinical remission status at Week 6,

- previous TNF-α antagonist failure or concomitant immunomodulator (azathioprine or 6 mercaptopurine) use.

Blinding (masking)

All study site personnel other than the investigational pharmacist or pharmacy designee were blinded to the treatment assignments for the duration of the study.

Statistical methods

Two populations (full analysis set [FAS] and per protocol set [PPS]) were analysed. All statistical testing was performed at 2-sided 0.05 level of significance. To control the overall type I error rate for the comparison between vedolizumab SC and placebo groups for the primary and secondary endpoints, a hierarchical approach was applied to the statistical testing. Analyses of additional endpoints were performed without adjustments for multiple comparisons, where nominal p-values were presented. A sensitivity analysis was conducted to assess the impact of dropouts for different missing mechanisms by using a hybrid approach in which discontinuation due to AE or lack of efficacy will be imputed as nonresponder and other discontinuation/missing was imputed using multiple imputation for primary and all secondary efficacy endpoints.

The primary statistical comparison of interest for all efficacy endpoints was between vedolizumab SC and placebo. The comparison of vedolizumab IV group vs placebo group was considered exploratory and hence was not included in the multiplicity control procedure. The descriptive statistics of treatment effects and corresponding 95% CI for the vedolizumab IV arm versus placebo were presented for the primary and secondary efficacy endpoints. The exact method is planned to be performed if the number of observations is too small (e.g., ≤5). Any p-values presented for vedolizumab IV versus placebo comparisons were nominal p-values. No statistical comparison was performed between the vedolizumab SC and vedolizumab IV treatment groups.

Results

Participant flow

Induction phase

*Table 2:**Subject Disposition (All Enrolled Subjects, Induction Phase): VDZ IV***

	VDZ IV 300 mg N = 383 n (%)
Enrolled and treated in open-label induction phase	383 (100.0)
Completed vedolizumab IV in open-label induction phase [a]	353 (92.2)
Prematurely discontinued vedolizumab IV in open-label induction phase	30 (7.8)
Reason for discontinuing vedolizumab IV in open-label induction phase (reason)	
Pretreatment event/adverse event	9 (30.0)
Significant protocol deviation	4 (13.3)
Lost to follow-up	0
Voluntary withdrawal	5 (16.7)
Study termination	0
Pregnancy	0
Lack of efficacy	9 (30.0)
Leukopenia or lymphopenia	0
Other	3 (10.0)

Source: Table 15.1.5.1.
IV: intravenous; VDZ: vedolizumab.
Percentages for reason for discontinuation of study drug are based on the total number of subjects who prematurely discontinued study drug.
[a] Subject completed induction if randomized or, if not randomized, completed the Week 14 visit or is 'Completed' per the End of Study Drug electronic case report form page.

Maintenance phase

Subject Disposition: Maintenance Phase (Full Analysis Set)

216 subjects were randomized into the maintenance phase (placebo: 56 subjects; vedolizumab SC: 106 subjects; and vedolizumab IV: 54 subjects).

Completed the study: 37.5% of the placebo subjects at Week 52, compared with 71.7% and 75.9% of subjects in the vedolizumab SC and vedolizumab IV treatment groups at Week 52, respectively.

The most frequent reason for discontinuation across all treatment groups was lack of efficacy, which was highest in the placebo group (80%) compared with 62.1% and 46.2% for vedolizumab SC and vedolizumab IV, respectively.

AEs leading to discontinuation occurred in 14.3% of placebo group, 17.2% in the vedolizumab SC group, and 15.4% in the vedolizumab IV group.

Recruitment

The study enrolled subjects at 105 sites worldwide for the maintenance phase (14 sites in the United States [US] and 91 sites ex-US). Date first subject signed informed consent form was on 18 December 2015. Date of last subject's last visit/contact was on 21 August 2018.

Conduct of the study

Through 16 February 2018, there were 5 protocol amendments to the original study protocol (26 February 2015). These were on adding exploratory objectives and endpoints, inclusion of an inclusion of a benefit risk assessment, clarifications on exclusion and inclusion criteria.

*Table 3:**Significant protocol deviations***

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

Source: Table 15.1.6.
FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; VDZ: vedolizumab.

Baseline data

Demographic

In the overall FAS 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 was 24.02 kg/m2. With respect to geographic distribution, 13.0% were enrolled at sites in North America and 87% were enrolled at sites outside of North America.

*Table 4:**Baseline UC Disease Characteristics (FAS)***

	PBO N = 56	VDZ SC 108 mg N = 106	VDZ IV 300 mg N = 54	Total N = 216
Duration of UC (years)				
n	56	106	54	216
Mean (SD)	7.36 (7.147)	7.96 (6.217)	8.18 (5.929)	7.86 (6.380)
Median	5.32	5.93	6.79	5.85
Minimum, maximum	0.6, 30.3	0.6, 29.8	0.5, 30.9	0.5, 30.9
Duration of UC categories, n (%)				
<1 year	5 (8.9)	6 (5.7)	1 (1.9)	12 (5.6)
≥1 to <3 years	14 (25.0)	16 (15.1)	10 (18.5)	40 (18.5)
≥3 to <7 years	16 (28.6)	37 (34.9)	16 (29.6)	69 (31.9)
≥7 years	21 (37.5)	47 (44.3)	27 (50.0)	95 (44.0)
Baseline disease activity, n (%)				
Mild (Mayo score <6)	0	0	0	0
Moderate (Mayo score = 6 to 8)	20 (35.7)	46 (43.4)	17 (31.5)	83 (38.4)
Severe (Mayo score = 9 to 12)	36 (64.3)	60 (56.6)	37 (68.5)	133 (61.6)
Baseline fecal calprotectin (µg/g)				
N	56	102	52	210
Mean (SD)	2393.4 (2859.66)	2607.2 (2908.67)	3173.5 (4785.48)	2690.4 (3451.64)
Median	1553.5	1734.5	1589.0	1638.5
Minimum, maximum	30, 13620	42, 15696	130, 28490	30, 28490
Categorical baseline fecal calprotectin categories, n (%)				
≤250 µg/g	5 (8.9)	9 (8.5)	2 (3.7)	16 (7.4)
>250 to ≤500 µg/g	7 (12.5)	6 (5.7)	4 (7.4)	17 (7.9)
>500 µg/g	44 (78.6)	87 (82.1)	46 (85.2)	177 (81.9)
Missing	0	4 (3.8)	2 (3.7)	6 (2.8)
Disease localization, n (%)				
Proctosigmoiditis	7 (12.5)	15 (14.2)	7 (13.0)	29 (13.4)
Left-sided colitis	24 (42.9)	46 (43.4)	21 (38.9)	91 (42.1)
Extensive colitis	4 (7.1)	7 (6.6)	7 (13.0)	18 (8.3)
Pancolitis	21 (37.5)	37 (34.9)	19 (35.2)	77 (35.6)

Source: Table 15.1.8.2.
FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.

*Table 5:**UC Prior Therapy History (FAS)***

	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)	Total N = 216 n (%)
Prior TNF-α antagonist use	20 (35.7)	40 (37.7)	24 (44.4)	84 (38.9)
No prior TNF-α antagonist use	36 (64.3)	66 (62.3)	30 (55.6)	132 (61.1)
Any prior TNF-α antagonist failure	20 (35.7)	40 (37.7)	24 (44.4)	84 (38.9)
Worst prior treatment failure [a]				
Prior TNF-α antagonist treatment failure	20 (35.7)	40 (37.7)	24 (44.4)	84 (38.9)
Inadequate response	9 (16.1)	21 (19.8)	13 (24.1)	43 (19.9)
Loss of response	8 (14.3)	17 (16.0)	9 (16.7)	34 (15.7)
Intolerance	3 (5.4)	2 (1.9)	2 (3.7)	7 (3.2)
Prior immunomodulator treatment failure	5 (8.9)	22 (20.8)	5 (9.3)	32 (14.8)
Inadequate response	1 (1.8)	6 (5.7)	2 (3.7)	9 (4.2)
Loss of response	0	3 (2.8)	0	3 (1.4)
Intolerance	4 (7.1)	13 (12.3)	3 (5.6)	20 (9.3)
Prior corticosteroid treatment failure	13 (23.2)	23 (21.7)	15 (27.8)	51 (23.6)
Inadequate response	5 (8.9)	14 (13.2)	5 (9.3)	24 (11.1)
Symptom recurrence upon tapering	4 (7.1)	6 (5.7)	9 (16.7)	19 (8.8)
Intolerance	4 (7.1)	3 (2.8)	1 (1.9)	8 (3.7)

FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; UC: ulcerative colitis; TNF-α: tumor necrosis factor-alpha; VDZ: vedolizumab.

a Subjects who had failure of multiple therapies were classified by the following hierarchy: TNF-α failure included all subjects who had failure of a TNF-α antagonist. Immunomodulator failure included all subjects who had failure of an immunomodulator but did not have failure of a TNF-α antagonist. Corticosteroid failure included all subjects who had failure of a corticosteroid and who did not have failure of a TNF-α antagonist nor an immunomodulator.

Each subject is counted only once within a medication class with their worst outcome being counted. Inadequate response is considered worse than loss of response, loss of response is considered worse than intolerance.

*Table 6:***Prior UC Therapy Use (FAS)**

	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)	Total N = 216 n (%)
Prior corticosteroids only				
Yes	22 (39.3)	28 (26.4)	21 (38.9)	71 (32.9)
No	34 (60.7)	78 (73.6)	33 (61.1)	145 (67.1)
Prior corticosteroids and immunomodulators				
Yes	32 (57.1)	71 (67.0)	32 (59.3)	135 (62.5)
No	24 (42.9)	35 (33.0)	22 (40.7)	81 (37.5)
Prior immunomodulators only				
Yes	1 (1.8)	6 (5.7)	1 (1.9)	8 (3.7)
No	55 (98.2)	100 (94.3)	53 (98.1)	208 (96.3)
No prior corticosteroids or immunomodulators				
Yes	1 (1.8)	1 (0.9)	0	2 (0.9)
No	55 (98.2)	105 (99.1)	54 (100.0)	214 (99.1)

Source: Table 15.1.8.2.
FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.

*Table 7:****Numbers analysed***

Table 11.a Summary of Analysis Populations (All Enrolled Subjects)

	Induction Phase n (%)	Maintenance Phase n (%)			
	VDZ IV 300 mg N = 383	PBO N = 56	VDZ SC 108 mg N = 106	VDZ IV 300 mg N = 54	Total N = 216
FAS [a]		56 (100.0)	106 (100.0)	54 (100.0)	216 (100.0)
PPS [b]		46 (82.1)	79 (74.5)	41 (75.9)	166 (76.9)
PK evaluable set [c]		56 (100.0)	106 (100.0)	54 (100.0)	216 (100.0)
SAF [d]		56 (100.0)	106 (100.0)	54 (100.0)	216 (100.0)
SAF-I [e]	167 (43.6)				
SAF-C [f]	383 (100.0)	56 (100.0)	106 (100.0)	54 (100.0)	216 (100.0)

Source: Table 15.1.7.
FAS: full analysis set; IV: intravenous; PBO: placebo; PK: pharmacokinetic; PPS: per protocol set; SAF: safety analysis set; SAF-C: safety analysis set–combined; SAF-I: safety analysis set–induction; SC: subcutaneous; VDZ: vedolizumab.
[a] All randomized subjects who received at least 1 dose of study drug. Subjects who only receive induction IV therapy and are not randomized into the maintenance phase were not included in the FAS; subjects were analyzed according to the randomized treatment assignment.
[b] All FAS subjects who did not violate the terms of the protocol in a way that would impact the study output significantly.
[c] All subjects who received at least 1 dose of study SC (placebo or vedolizumab) drug and had sufficient blood sampling to allow for PK evaluation.
[d] All subjects who received at least 1 dose of study SC (placebo or vedolizumab) drug; subjects were analyzed according to the treatment actually received.
[e] All subjects who received at least 1 induction dose, but were not randomized to the maintenance phase.
[f] All subjects who received at least 1 dose of vedolizumab IV.

Overall, 614 subjects were screened for enrollment, 383 subjects were enrolled into the open-label induction 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).

Outcomes and estimation

PRIMARY ENDPOINT

*Table 8:**Study SC-3027 Primary Efficacy Endpoint (FAS)***

Table 11.m Clinical Remission at Week 52 (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: 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 adjusted difference was based on the normal approximation method, or the exact method if the number of remissions in either treatment group was ≤5.
[c] The p-values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization strata (concomitant 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.

Sensitivity analyses

Analysis in the **PPS population** vedolizumab SC over placebo (adjusted difference 33.3 percentage points (p.p.) [18.4 p.p., 48.3 p.p], p<0.001).

Clinical remission analysis in the FAS population in accordance with the 2016 FDA draft UC guidance: a higher proportion of vedolizumab SC subjects achieved clinical remission than placebo subjects (adjusted difference: 32.3 p.p., 95% CI [20.3 p.p., 44.3 p.p.], p<0.001). For VDZ IV the adjusted difference was 29.7 p.p.

Exploratory analysis

Clinical remission in the FAS population at Week 52, defined by the complete Mayo score without PGA score, was also performed, vedolizumab SC was superior over placebo (adjusted difference, 37.0 p.p. [24.5 p.p., 49.6 p.p.], p<0.001).

SECONDARY ENDPOINTS

*Table 9:**Results on secondary endpoints***

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.

Note that durable clinical remission was not significant and formal testing stopped accordingly, i.e. no formal testing done for the 4th secondary endpoint of corticosteroid-free remission (only nominal p-values shown).

Ancillary analyses

*Table 10:**Exposure to TNF-α antagonist therapy (naïve versus experienced)***

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

	Subjects Without Prior TNF-α Antagonist Use			Subjects With Prior TNF-α Antagonist Failure		
Endpoint	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)	

Footnotes on last table page.

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

	Subjects Without Prior TNF-α Antagonist Use			Subjects With Prior TNF-α Antagonist Failure		
Endpoint	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.

The following table shows the results of inflammatory biomarkers in Study MLN0002-3027.

Table 11.cc 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: Table 15.2.12.2.
FAS: full analysis set; IV: intravenous; PBO: placebo; SC: subcutaneous; VDZ: vedolizumab.
[a] Baseline was defined as the last nonmissing measurement before or on the date of the first dose of study drug (Day 1).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial *MLN0002SC-3027*

Title: Study SC-3027	
Study identifier	
Design	a phase 3, multinational, randomized, double-blind, double-dummy, placebo-controlled study evaluating the efficacy and safety of vedolizumab SC as maintenance treatment after clinical response was achieved to vedolizumab IV induction therapy in subjects with moderately to severely active UC,demonstrate the efficacy of vedolizumab SC as maintenance treatment for patients with UC who responded to vedolizumab IV.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks
Hypothesis	Superiority VDZ SC versus PLB		
Treatments groups *(maintenance phase)*	vedolizumab SC 108 mg Q2W and placebo IV infusions Q8W.		
	vedolizumab IV 300 mg Q8W and placebo SC		
	Placebo SC injections Q2W and placebo IV infusions		
Endpoints and definitions	Primary endpoint	Clinical remission at Week 52	Complete Mayo score of ≤2 points and no individual subscore >1 point
	Secondary (hierarchy)	Mucosal healing at Week 52	Mayo endoscopic subscore of ≤1 point.
	Secondary	Durable clinical response	Clinical response at Weeks 6 and 52 where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
		Durable clinical remission	Clinical remission at Weeks 6 and 52.
		Corticosteroid-free remission at Week 52	Patients using oral corticosteroids at baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	VDZ SC 108 mg	VDZ IV 300 mg
	Number of subject	56	106	54
	Clinical remission at Week 52	14.3%	46.2%	46.2%

		P-value <0.001 Difference (95% CI) 32.3 (19.7, 45.0)		
	Mucosal healing at Week 52	21.4%	56.6%	53.7%
		P-value <0.001Difference (95% CI) 35.7 (22.1, 49.3)		
	Durable clinical response	28.6%	64.2%	72.2%
		P-value <0.001 Difference (95% CI) 36.1 (21.2, 50.9)		
	Durable clinical remission	5.4%	15.1%	16.7%
		P-value 0.076 Difference (95% CI) 9.7 (-6.6, 25.7)		
	Corticosteroid-free remission at Week 52	N = 24 8.3%	N = 45 28.9%	N = 21 28.6%
		P-value 0.067 [a] Difference (95% CI) 20.6 (-4.5, 43.7)		

[a] Note that hierarchical testing was done; because the first secondary endpoint was not significant, all further p-values are only nominal p-values.

Analysis performed across trials (pooled analyses and meta-analysis)

Comparison Across SC and IV Vedolizumab Maintenance Therapies (C13006 and SC-3027 studies)

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 SC-3027 was conducted as part of the vedolizumab SC clinical development program, and the CSR was submitted in the marketing applications for vedolizumab (ENTYVIO) for SC injection.

Baseline demographic characteristics were similar in both studies and across the treatment groups in each study, 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.

Below a comparison of results for primary and secondary endpoints:

*Table 11:**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)

	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

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; 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).

Supportive studies

MLN0002SC-3031

A phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled, 52-week study (SC-3031) that evaluated the efficacy and safety of vedolizumab SC as maintenance therapy in subjects with CD who responded to vedolizumab intravenous (IV) induction treatment.

Eligible subjects were enrolled into the induction phase at Week 0, received open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2, and were assessed for clinical response by Crohn's Disease Activity Index (CDAI) (defined as a ≥70-point decrease in CDAI score from baseline [Week 0]) at Week 6, as follows:

- Subjects who achieved a clinical response at Week 6 were randomized into the maintenance phase.

- Subjects who did not achieve a clinical response at Week 6 were not randomized into the maintenance phase and instead received a third infusion of open-label vedolizumab IV 300 mg at Week 6. Subjects who achieved a clinical response at Week 14 (by CDAI) were eligible to enrol into the OLE study (SC-3030), while subjects who did not achieve clinical response were discontinued.

In the maintenance phase, all subjects who received open-label vedolizumab IV treatment in the induction phase and demonstrated a clinical response at Week 6 were randomized in a 2:1 ratio to double-blind treatment with vedolizumab SC administered once every 2 weeks (Q2W) or placebo SC Q2W (Figure 3below).

- Randomization was stratified by 3 factors:
- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous treatment failure with or exposure to TNF-α antagonists or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

The last blinded SC injection in the maintenance phase was administered at Week 50 and the primary and secondary efficacy endpoints were assessed at Week 52. Subjects who completed or early terminated from the maintenance phase were eligible to enter into Study SC-3030 (unless withdrawn due to a study drug-related adverse event). Subjects who did not enroll into SC-3030 were to complete a final safety visit 18 weeks after the last dose of study drug in Study SC-3031 and a follow-up safety survey 6 months after the last dose.

The design of Study SC-3031 for CD was similar to that of the pivotal phase 3 study in subjects with ulcerative colitis (UC) (MLN0002SC-3027; hereafter referred to as SC-3027) with the exception of not having an IV reference arm in the double-blinded maintenance phase. The design and target population of Study SC-3031 were also similar to those of the maintenance phase of the GEMINI 2 (C13007) study [1] to allow cross-study comparison with vedolizumab IV Q8W maintenance treatment.

Figure 3: ***Study SC-3031 Study Design Schematic***

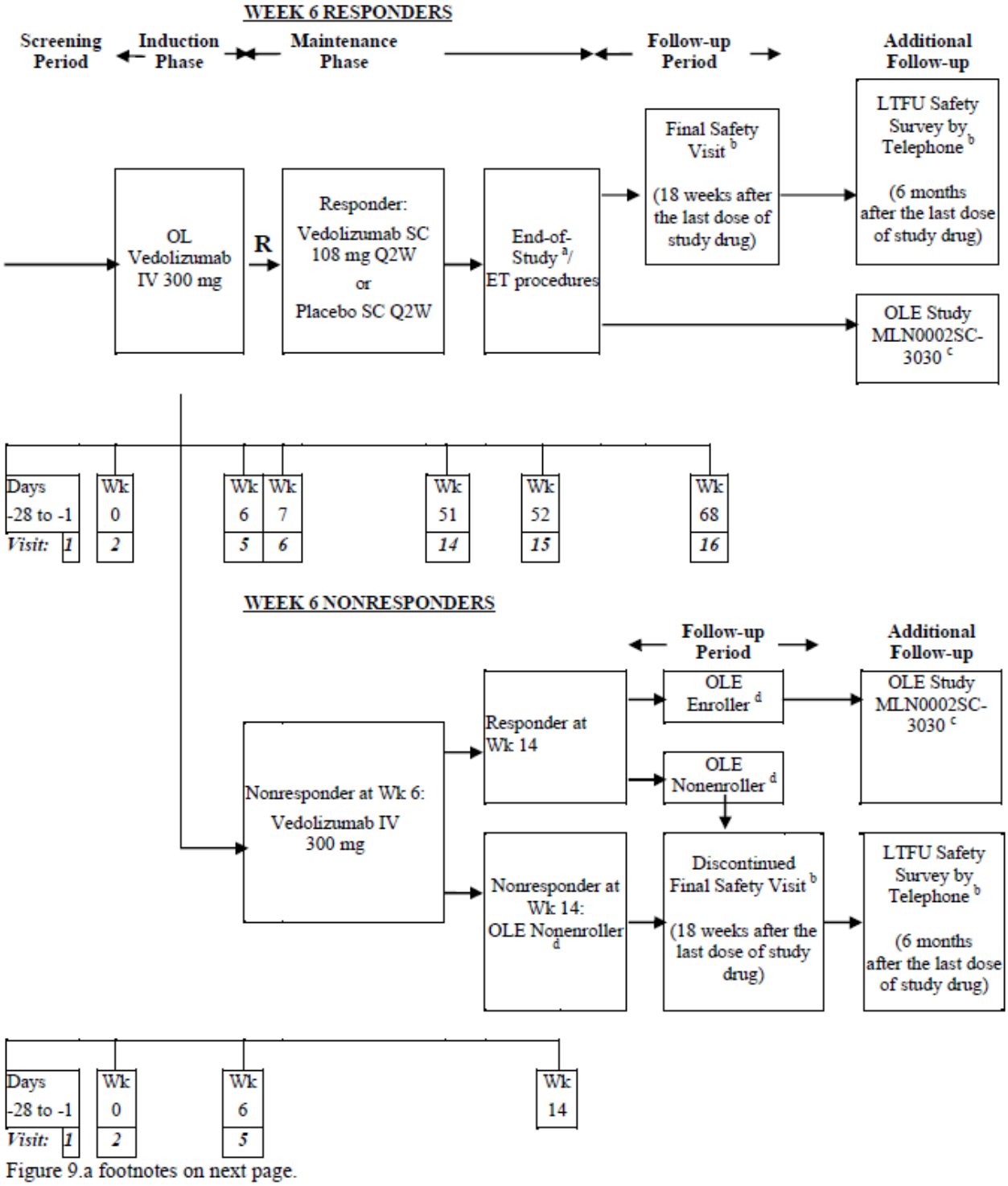


Figure 9.a footnotes on next page.

ET: early termination; IV: intravenous; LTFU: long-term follow-up; OL: open-label; OLE: open-label extension; Q2W: every 2 weeks; R: randomization; SC: subcutaneous.
a Maintenance phase: Subjects who discontinued the study early and consented to participate in the OLE Study SC-3030 entered the OLE study and began Study SC-3030 dosing after the Study SC-3031 end-of-study visit procedures have been completed.
b For subjects who do not enroll into the OLE Study SC-3030 (including early terminator subjects before Week 6 in the maintenance phase).

c First visit of OLE Study SC-3030 was within 4 weeks after last dose of study drug for Week 52 completer subjects/early terminator subjects or 1 week of Week 14 for Week 14 responders.
d Week 14 responders and nonresponders (OLE enroller/nonenroller) were to complete the procedures in accordance with the Schedule of Assessments.

In Study SC-3031, 644 subjects enrolled in the open-label vedolizumab IV induction period, and 410 were randomized into the double-blinded maintenance phase of the study.

Table 12:Primary Endpoint – Clinical Remission at Week 52 (FAS)

Clinical Remission [a]	**PBO N = 134**	**VDZ SC 108 mg N = 275**
Number (%) of subjects achieving clinical remission at Week 52	46 (34.3)	132 (48.0)
95% CI [b]	(26.3, 43.0)	(42.0, 54.1)
Treatment difference, vedolizumab vs placebo		13.7
95% CI [c]		(3.8, 23.7)
P-value, vedolizumab vs placebo [c]		0.008

CDAI: Crohn's Disease Activity Index; FAS: full analysis set; 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 nonremitters.
[a] Clinical remission, defined as CDAI score ≤150, at Week 52 was the primary efficacy endpoint.
[b] The 95% CIs of the percentages for each treatment group were based on the Copper-Pearson method.
[c] The treatment difference, the associated 95% CI, and p-value were obtained using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure/exposure or concomitant immunomodulator use) or Fisher's Exact test if the number of remitters or nonremitters in either treatment group was ≤5.

Table 13: ***Secondary Endpoints (FAS)***

	PBO	VDZ SC 108 mg
Enhanced Clinical Response [a]	**N = 134**	**N = 275**
Number (%) of subjects achieving enhanced clinical response at Week 52	60 (44.8)	143 (52.0)
95% CI [b]	(36.2, 53.6)	(45.9, 58.0)
Treatment difference, vedolizumab vs placebo		7.3
95% CI [c]		(-3.0, 17.5)
P-value, vedolizumab vs placebo [c]		0.167
Corticosteroid-Free Remission [d]	**N = 44**	**N = 95**
Number (%) of subjects achieving corticosteroid-free remission at Week 52	8 (18.2)	43 (45.3)
95% CI [b]	(8.2, 32.7)	(35.0, 55.8)
Treatment difference, vedolizumab vs placebo		27.1
95% CI [c]		(11.9, 42.3)
P-value, vedolizumab vs placebo [c,f]		0.002
Clinical Remission in Subjects Who Were Naïve to TNF-α Antagonists [e]	**N = 63**	**N = 107**
Number (%) of subjects achieving clinical remission at Week 52	27 (42.9)	52 (48.6)
95% CI [b]	(30.5, 56.0)	(38.8, 58.5)
Difference, vedolizumab vs placebo		4.3
95% CI [c]		(-11.6, 20.3)
P-value, vedolizumab vs placebo [c,f]		0.591

CDAI: Crohn's Disease Activity Index; FAS: full analysis set; 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/nonremitters.
[a] Enhanced clinical response, defined as ≥100-point decrease in CDAI score from baseline (Week 0), at Week 52 was the first secondary efficacy endpoint.
[b] The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.
[c] The treatment difference, the associated 95% CI, and p-value were obtained using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure/exposure or concomitant immunomodulator use) or Fisher's Exact test if the number of responders/remitters or nonresponder/nonremitters in either treatment group was ≤5.
[d] Corticosteroid-free remission, defined as subjects using oral corticosteroids at baseline (Week 0) who had discontinued oral corticosteroids and were in clinical remission at Week 52, was the second secondary efficacy endpoint.

[e] Clinical remission, defined as CDAI score ≤150, at Week 52 in subjects who were TNF-α antagonist naïve was the third secondary efficacy endpoint.
[f] Note that hierarchical testing was done; because the first secondary endpoint was not significant, all further p-values are only nominal p-values.

*Table 14:**Results on durable clinical remission (week 6 and week 52)(Exploratory endpoint in CD subjects)***

Table 11.cc Durable Clinical Remission (FAS)

Durable Clinical Remission [a]	PBO N = 134	VDZ SC 108 mg N = 275
Number (%) of subjects achieving durable clinical remission	30 (22.4)	77 (28.0)
95% CI [b]	(15.6, 30.4)	(22.8, 33.7)
Difference, vedolizumab vs placebo		5.6
95% CI [c]		(-2.7, 13.9)

Source: Table 15.2.1.1.
CMH: Cochran-Mantel-Haenszel; FAS: full analysis set; 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 nonremitters.
[a] Durable clinical remission was defined as clinical remission at both Weeks 6 and 52.
[b] The 95% CI of the percentages for each treatment group were based on the Clopper-Pearson method.
[c] The treatment difference and the associated 95% CI were obtained using a CMH test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure/exposure or concomitant immunomodulator use) or Fisher's Exact test if the number of remitters or nonremitters in either treatment group was ≤5.

*Table 15:**Results stratified by TNFalpha naïve or failure***

Table 11.s Key Endpoints in Subjects By Prior TNF-α Antagonist Use or Failure (FAS)

	Subjects Without Prior TNF-α Antagonist Use		Subjects With Prior Exposure to TNF-α Antagonists		Subjects With Prior TNF-α Antagonist Failure	
Endpoint	**PBO N = 134**	**VDZ SC 108 mg N = 275**	**PBO N = 134**	**VDZ SC 108 mg N = 275**	**PBO N = 134**	**VDZ SC 108 mg N = 275**
Clinical remission at Week 52 [a,b]						
N	63	107	12	17	59	151
Number (%) of subjects achieving clinical remission at Week 52	27 (42.9)	52 (48.6)	2 (16.7)	10 (58.8)	17 (28.8)	70 (46.4)
95% CI	(30.5, 56.0)	(38.8, 58.5)	(2.1, 48.4)	(32.9, 81.6)	(17.8, 42.1)	(38.2, 54.6)
Difference, vedolizumab vs placebo and 95% CI		4.3 (-11.6, 20.3)		42.2 (4.7, 72.3)		17.6 (3.8, 31.4)
P-value (nominal)		0.591		0.053		0.019
Enhanced clinical response [c]						
N	63	107	12	17	59	151
Number (%) of subjects achieving enhanced clinical response at Week 52	30 (47.6)	58 (54.2)	3 (25.0)	11 (64.7)	27 (45.8)	74 (49.0)
95% CI	(34.9, 60.6)	(44.3, 63.9)	(5.5, 57.2)	(38.3, 85.8)	(32.7, 59.2)	(40.8, 57.3)
Difference, vedolizumab vs placebo and 95% CI		4.4 (-11.6, 20.3)		39.7 (1.8, 69.2)		3.2 (-11.8, 18.2)
Corticosteroid-free remission [d,e]						
N	22	39	–	–	20	52
Number (%) of subjects achieving corticosteroid-free remission at Week 52	4 (18.2)	16 (41.0)			3 (15.0)	24 (46.2)
95% CI	(5.2, 40.3)	(25.6, 57.9)			(3.2, 37.9)	(32.2, 60.5)
Difference, vedolizumab vs placebo and 95% CI		22.8 (-3.2, 46.8)				31.2 (5.2, 54.5)

Footnotes are on the last table page.

Table 11.s Key Endpoints in Subjects By Prior TNF-α Antagonist Use or Failure (FAS) (continued)

Source: Table 15.2.3.1.10 (clinical remission); Table 15.2.3.2.10 (enhanced clinical response); Table 15.2.3.3.10 (corticosteroid-free remission).
CDAI: Crohn's Disease Activity Index; CMH: Cochran-Mantel-Haenszel; FAS: full analysis set; PBO: placebo; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha; VDZ: vedolizumab.
All subjects with missing data for the determination of endpoint status were categorized as nonremitters/nonresponders.
If the number of subjects in any subgroup was fewer than 10, that subgroup was not presented.
The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.
The treatment difference, the associated 95% CI, and p-values were obtained using a CMH test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission at Week 6, and previous TNF-α antagonist failure/exposure or concomitant immunomodulator use) or Fisher's Exact test if the number of remitters/responders or nonremitters/nonresponders in either treatment group was ≤5.
[a] Clinical remission, defined as CDAI score ≤150, at Week 52 was the primary efficacy endpoint.
[b] Clinical remission in TNF-α antagonist naïve subjects at Week 52 was the third key secondary efficacy endpoint.
[c] Enhanced clinical response, defined as ≥100-point decrease in CDAI score from baseline (Week 0), at Week 52 was the first secondary efficacy endpoint.
[d] Corticosteroid-free remission, defined as subjects using oral corticosteroids at baseline (Week 0) who had discontinued oral corticosteroids and were in clinical remission at Week 52, was the second secondary efficacy endpoint.
[e] N (PBO) = 44; N (VDZ SC) = 95.

*Table 16:**Inflammatory markers:***

Table 11.ee Proportion of Subjects With Elevated CRP Level at Baseline (Week 0) Who Have Reduction in CRP Level at Week 52, Subjects With Elevated CRP Levels at Baseline (>2.87 mg/L) (FAS)

CRP Level (mg/L) [a]	**PBO N = 80**	**VDZ SC 108 mg N = 168**
Number (%) of subjects with reduction in CRP level at Week 52	14 (17.5)	39 (23.2)
95% CI [b]	(9.9, 27.6)	(17.1, 30.3)
Difference, vedolizumab vs placebo		5.5
95% CI [c]		(-5.1, 16.1)

Source: Table 15.2.5.1.11.
CMH: Cochran-Mantel-Haenszel; CRP: C-reactive protein; FAS: full analysis set; PBO: placebo; SC: subcutaneous; TNF-α: tumor necrosis factor-alpha; VDZ: vedolizumab.
All subjects with missing data for determination of endpoint status are categorized as nonresponders.
[a] Reduction in CRP level was defined as a reduction below the upper level of normal (<5 mg/L).
[b] The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.
[c] The treatment difference and the associated 95% CI were obtained using a CMH test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at Week 6, and previous TNF-α antagonist failure/exposure or concomitant immunomodulator use) or Fisher's Exact test if the number of responders or nonresponders in either treatment group was ≤5.

Table 11.ff Summary of Fecal Calprotectin (µg/g) by Visit (FAS)

	PBO N = 134		VDZ SC 108 mg N = 275	
Study Visit	**Observed Value at Visit**	**Change From Baseline**	**Observed Value at Visit**	**Change From Baseline**
Baseline [a]				
N	132		274	
Mean (SD)	1434.2 (1955.83)		1309.7 (1696.76)	
Week 6				
N	124	122	246	246
Mean (SD)	1251.7 (2451.20)	-230.2 (2093.76)	1135.2 (1748.20)	-182.3 (2107.91)
Week 30				
N	87	87	175	175

PRO The recent 2018 revision to the Committee for Medicinal Products for Human Use (CHMP) *Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease* (CPMP/EWP/2284/99 Rev. 2) recommends that symptomatic relief be evaluated by patient reported outcomes (PRO). Until a validated PRO has been developed, the patient reported outcomes derived from CDAI diary items may be appropriate.

In Study SC-3031, an evaluation based on patient-reported items from the CDAI diary (PRO2, a 2-item PRO that includes stool frequency and abdominal pain CDAI components and PRO3, a 3-item PRO that included stool frequency, abdominal pain and general well-being CDAI components) showed a positive

trend in favour of vedolizumab. Health-related quality of life (HRQOL) was assessed by IBDQ, a disease specific instrument, and EQ-5D, which is a generic measure. Subjects treated with vedolizumab SC maintained improvements in IBDQ and EQ-5D scores at Week 52 to a greater extent than subjects who received placebo. Work productivity was assessed by WPAI-CD. Subjects treated with vedolizumab SC maintained improvements in WPAI-CD scores at Week 52 to a greater extent than patients who received placebo.

UC and CD indication long term

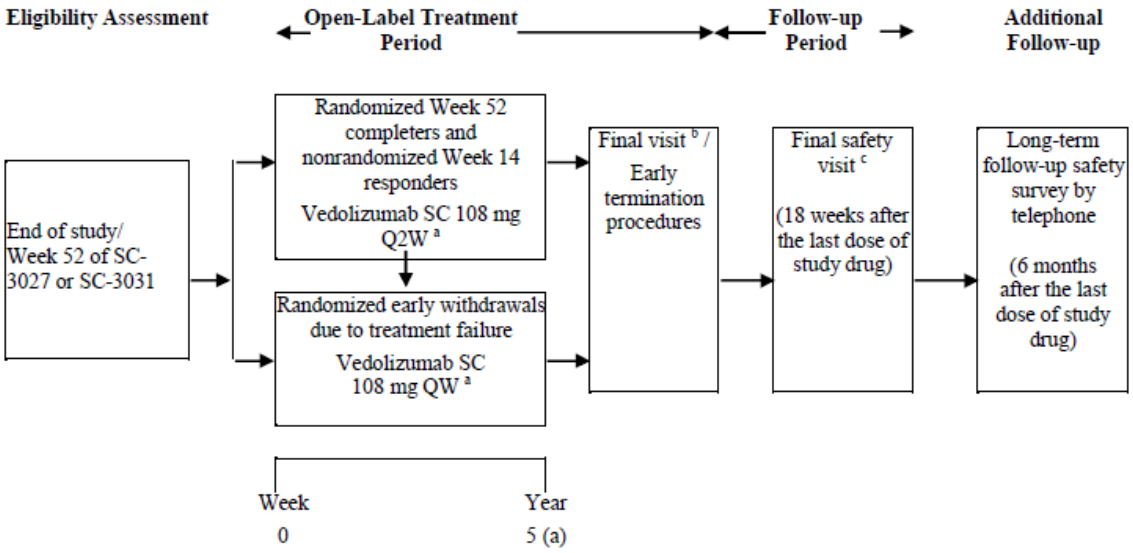
Study MLN0002SC-3030

Study MLN0002SC-3030 (hereafter Study SC-3030) is a phase 3b ongoing OLE study to gather long-term safety and efficacy data for vedolizumab SC, including eligible subjects from Studies SC-3027 (UC subject population) and SC-3031 (CD subject population). All enrolled subjects received vedolizumab SC 108 mg.

In this study, the duration of vedolizumab SC treatment will vary by subject based on continued benefit but could be 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.

An interim clinical study report (CSR) for SC-3030, based on a 31 May 2018 data cutoff date, is provided with this submission.

Figure 4: ***Schematic of Study Design***



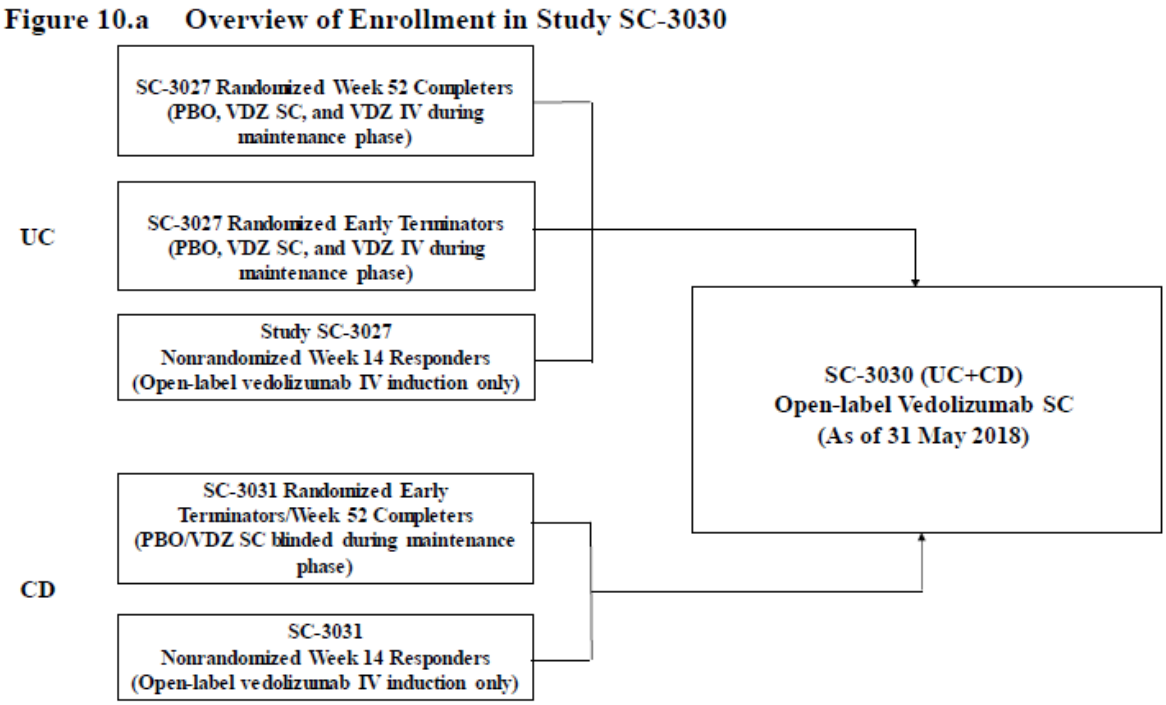
AI: autoinjector; ET: early termination; NSD: needle safety device; OLE: open-label extension; PFS: prefilled syringe; Q2W: once every 2 weeks; QW: once per week; SC: subcutaneous.

[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 OLE 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 ET visit.

Figure 5: ***Study participants***



Source: Tables 15.1.5.1 and Table 15.1.5.2.
CD: Crohn's disease; IV: intravenous; PBO: placebo; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.

Inclusion criteria
Subjects previously participating in Study MLN0002SC-3027 or MLN0002SC-3031, and, in the opinion of the investigator, tolerated the study drug well. Subjects who withdrew early from Study MLN0002SC-3027 or MLN0002SC-3031 must have withdrawn due to treatment failure (ie, as determined by disease worsening or need for rescue medications from Week 14 of the respective study) during the maintenance phase.

*Table 17:****Details of subjects who were permitted to enroll in the OLE Study MLN0002SC-3030***

	Time Point		
Reason for Withdrawal	**Before Week 6**	**Weeks 6-14**	**Beyond Week 14**
Disease worsening [a]	Not applicable	Eligible	Eligible
Requires rescue medication but does not meet criteria for disease worsening	Not applicable	Not eligible	Eligible
AE related to study drug leading to discontinuation of study drug	Not eligible	Not eligible	Not eligible
Requires surgical intervention for UC	Not eligible	Not eligible	Not eligible

AE: adverse event; UC: ulcerative colitis.
[a] See Section 4.2 for study definitions.

*Table 18:**Subject's disposition (UC, CD)***

Table 10.a Disposition of Subjects by Previous Treatment Group (FAS-UC) - Interim Analysis Through 31 May 2018

	NR Week 14 Responders N = 107	PBO N = 52	VDZ SC 108 mg N = 89	VDZ IV 300 mg N = 39	Total N = 287
Early termination from previous study [a]		32	21	4	57
Completed previous study at Week 52 [b]		20	68	35	123
Completed Study SC-3030	0	0	0	0	0
Ongoing (Study SC-3030)	70 (65.4)	44 (84.6)	73 (82.0)	34 (87.2)	221 (77.0)
ET from Study SC-3030	37 (34.6)	8 (15.4)	16 (18.0)	5 (12.8)	66 (23.0)
Primary reason for ET from Study SC-3030:					
PTE/AE	5 (13.5)	1 (12.5)	1 (6.3)	1 (20.0)	8 (12.1)
Significant protocol deviation	0	0	0	0	0
Lost to follow-up	0	0	1 (6.3)	0	1 (1.5)
Voluntary withdrawal	11 (29.7)	0	2 (12.5)	0	13 (19.7)
Study termination	0	0	0	0	0
Pregnancy	0	0	1 (6.3)	0	1 (1.5)
Lack of efficacy	20 (54.1)	6 (75.0)	9 (56.3)	4 (80.0)	39 (59.1)
Leukopenia or lymphopenia	0	0	1 (6.3)	0	1 (1.5)
Other	1 (2.7)	1 (12.5)	1 (6.3)	0	3 (4.5)

Source: Table 15.1.5.1 and Table 15.1.5.2
AE: adverse event; ET: early termination; FAS-UC: full analysis set-ulcerative colitis; IV: intravenous; NR: nonresponder; PBO: placebo; PTE: pretreatment event; SC: subcutaneous; VDZ: vedolizumab.
[a] Included randomized subjects who withdrew between Week 6 and Week 52 of the maintenance phase of Study SC-3027 and were eligible to enroll in Study SC-3030 (Study SC-3030 Week 0 as baseline).
[b] Included randomized subjects who completed Week 52 study drug/placebo of the maintenance phase of Study SC-3027 (Study SC-3027 Week 0 as baseline).
Percentages for reason for discontinuation of study drug were based on the total number of subjects who prematurely discontinued study drug.
Percentages for reason for discontinuation of study visits were based on the total number of subjects who did not complete all planned study visits.
Percentage was based on the number of subjects in each column except specified otherwise.
Pretreatment event was defined as any untoward medical occurrence in a clinical investigation subject who had signed the informed consent to participate in a study but before administration of any study medication.

Table 10.b Disposition of Subjects by Previous Treatment Group (FAS-CD) - Interim Analysis Through 31 May 2018

	NR Week 14 Responders N = 97	Randomized PBO/VDZ SC N = 214	Total N=311
Completed Study SC-3030	0	0	0
Ongoing (Study SC-3030)	69 (71.1)	172 (80.4)	241 (77.5)
ET from Study SC-3030	28 (28.9)	42 (19.6)	70 (22.5)
Primary reason for ET from Study SC-3030:			
PTE/AE	4 (14.3)	2 (4.8)	6 (8.6)
Significant protocol deviation	0	0	0
Lost to follow-up	1 (3.6)	0	1 (1.4)
Voluntary withdrawal	4 (14.3)	9 (21.4)	13 (18.6)
Study termination	0	0	0
Pregnancy	0	1 (2.4)	1 (1.4)
Lack of efficacy	18 (64.3)	29 (69.0)	47 (67.1)
Leukopenia or lymphopenia	0	0	0
Other	1 (3.6)	1 (2.4)	2 (2.9)

Source: Table 15.1.5.1.
AE: adverse event; CD: Crohn's disease; ET: early termination; FAS-UC: full analysis set-ulcerative colitis; IV: intravenous; NR: nonresponder; PBO: placebo; PTE: pretreatment event; SC: subcutaneous; VDZ: vedolizumab.
Percentages for reason for discontinuation of study drug were based on the total number of subjects who prematurely discontinued study drug.
Percentages for reason for discontinuation of study visits were based on the total number of subjects who did not complete all planned study visits.
Pretreatment event was defined as any untoward medical occurrence in a clinical investigation subject who had signed the informed consent to participate in a study but before administration of any study medication.
Percentage was based on the number of subjects in each column except specified otherwise.
[a] Subjects who discontinued early from the maintenance phase of Study SC-3031.
[b] Subjects who completed the Week 52 assessment of the maintenance phase of Study SC-3031.

Sample size

No formal sample size calculations were performed. Approximately 692 subjects were expected to enter this study, including 242 UC subjects from Study MLN0002SC-3027 and 450 CD subjects from Study MLN0002SC-3031.

Analysis of efficacy variables is conducted in the full analysis set (FAS), defined as all enrolled UC subjects (FAS-UC) and all enrolled CD subjects (FAS-CD) of SC-3030.

Interim Results

For **subjects with UC** (FAS-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, randomized early terminators, and nonrandomized Week 14 responders.

- 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**.

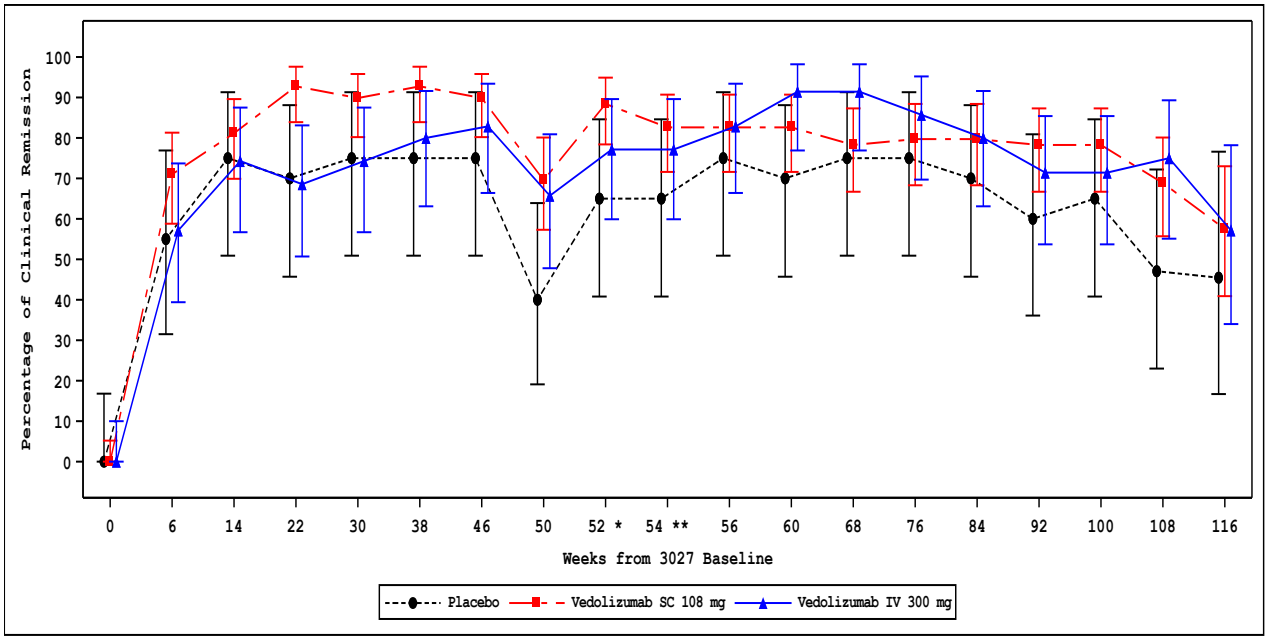
- Randomized early terminator subjects received vedolizumab IV during the induction phase of Study SC-3027, achieved clinical response at Week 6, and were subsequently randomized to the maintenance phase of Study SC-3027 to receive vedolizumab SC 108 mg Q2W, vedolizumab IV 300 mg Q8W, or placebo, but 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**.

Clinical remission rates over time in subjects with UC who completed 52 weeks of treatment in Study SC-3027 and rolled over to Study SC-3030 (randomized completers)

Long-term clinical remission rates were calculated for the population of randomized completer subjects in Study SC-3027 (ie, those subjects who completed the Week 52 assessment in Study SC-3027 and rolled over into Study SC-3030), who had a baseline (Week 0) assessment in Study SC-3030, and an assessment at the study visit of interest or had terminated prematurely from Study SC-3030 before that study visit.

The combined longitudinal results for clinical remission rates across Studies SC-3027 and SC-3030 are shown by visit up to Week 116 in Figure below. Randomized completer subjects are grouped according to their treatment assignment in Study SC-3027 (placebo, vedolizumab SC, or vedolizumab IV), noting that all subjects received open-label vedolizumab SC after Week 52 of Study SC-3027, when rolled over into the OLE study.

Figure 6: ***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): Interim Data up to 17 May 2019***



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 17 May 2019 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.

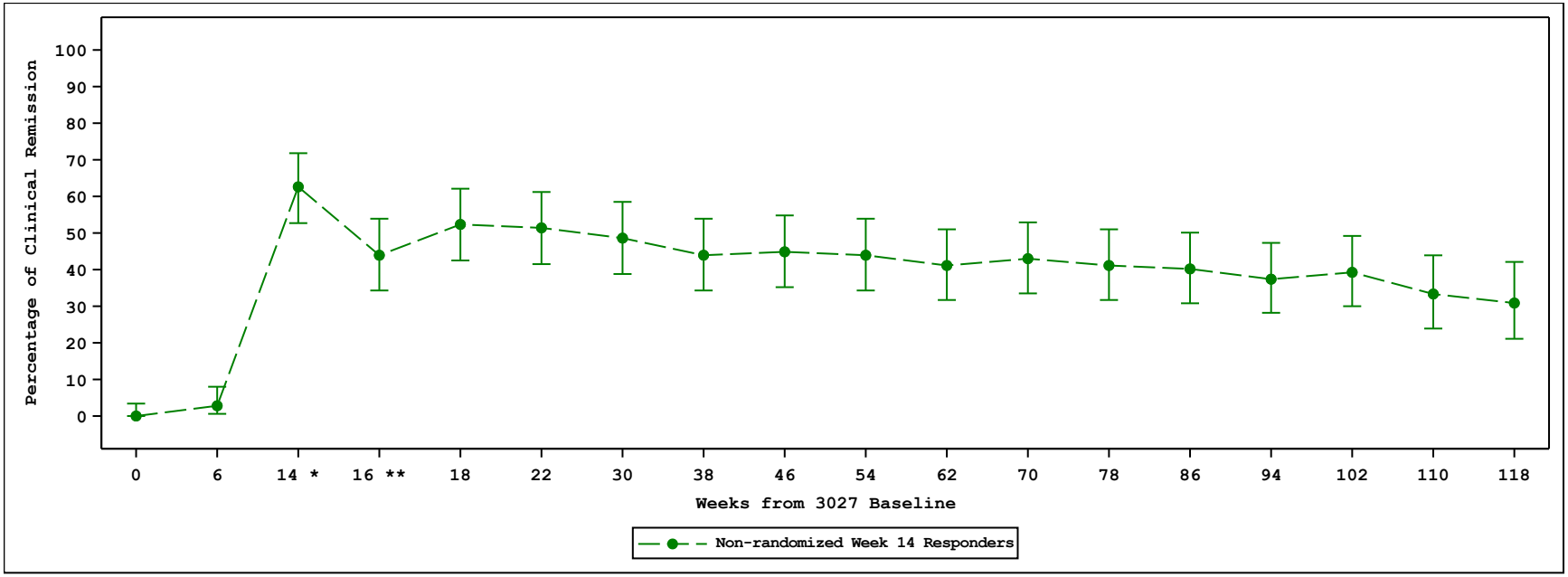
Clinical remission rate over time in nonrandomized Week 14 responder subjects with UC in Study SC-3027 who rolled over to Study SC-3030

The nonrandomized Week 14 responder subjects received open-label IV doses of vedolizumab induction treatment at Weeks 0 and 2 in Study SC-3027, were non-responders at Week 6 as assessed by a complete Mayo score, but did achieve a clinical response at Week 14 after receiving a third vedolizumab IV infusion at Week 6 in Study SC-3027. These subjects were eligible to enroll in Study SC-3030 (nonrandomized Week 14 responder UC subjects) and were treated with open-label vedolizumab SC on a once every 2 weeks (Q2W) dosing regimen.

Long-term clinical remission rates were calculated for the population of nonrandomized Week 14 responder subjects who had a baseline (Week 0) assessment in Study SC-3030, and an assessment at the study visit of interest or had terminated prematurely from Study SC-3030 before that study visit.

The combined longitudinal results for clinical remission rates across Studies SC-3027 and SC-3030 are shown by visit up to Week 118 in the below. Note that all subjects received open-label vedolizumab SC starting at Week 14 upon enrolling into OLE Study SC-3030. The figure shows that in general, nonrandomized Week-14 responder subjects who continued with open-label vedolizumab SC treatment in Study SC-3030 maintained high clinical remission rates over time. Interpretation of data beyond Week 118 is limited, because of the small number of subjects with evaluable data.

Figure 7: ***Proportion of Study SC-3030 UC Subjects With Clinical Remission Over Time Among Study SC-3027 Nonrandomized Week 14 Responder Subjects for Long-term Combined Efficacy (FAS-UC): Interim Data up to 17 May 2019***



FAS-UC: full analysis set–ulcerative colitis; Q2W: once every 2 weeks; 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 17 May 2019 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.

* Week 14 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 14 in this analysis visit window. Week 14 in this analysis combined Week 14 of SC-3027 and Week 0 of SC-3030.

** Week 16 for SC-3030 patients with Q2W dose.

Additional Long-term PRO Analyses

Long-term PRO analyses include the IBDQ, EQ-5D, and WPAI-UC questionnaires. PRO scores are collected every 24 weeks in ongoing Study SC-3030.

Long-term PRO analyses over time in subjects with UC who completed 52 weeks of treatment in Study SC-3027 and rolled over to Study SC-3030 (randomized completers)

IBDQ scores by study visit and by prior treatment group are summarized for randomized completer subjects up to Week 100 in

*Table 19:**Summary of IBDQ Total Scores for SC-3030 Subjects With UC by Study Visit Among SC-3027 Randomized Completers for Long-term Combined Efficacy (FAS-UC): Interim Data as of 17 May 2019***

Study Visit	Placebo N = 20	Vedolizumab SC 108 mg N = 69	Vedolizumab IV 300 mg N = 35
Baseline			
N	20	68	35
Mean (SD)	114.45 (36.720)	120.00 (32.619)	105.40 (34.266)
Median	118.00	119.00	97.00
Minimum, maximum	43.0, 180.0	53.3, 201.0	58.0, 181.0
Week 6 (LOCF)			
N	20	69	35
Mean (SD)	172.85 (38.322)	182.30 (25.596)	174.80 (28.060)
Median	181.50	189.00	175.00
Minimum, maximum	73.0, 212.0	103.0, 220.0	102.0, 215.0
Week 30 (LOCF)			
N	20	69	35
Mean (SD)	176.90 (38.272)	193.39 (22.149)	187.51 (24.539)
Median	190.00	201.00	194.00
Minimum, maximum	80.0, 221.0	108.0, 220.0	121.0, 222.0
Week 52 (LOCF) [a]			
N	20	69	35
Mean (SD)	166.45 (41.292)	198.00 (18.762)	185.86 (32.155)
Median	182.00	204.00	198.00
Minimum, maximum	91.0, 224.0	123.0, 224.0	97.0, 218.0

Footnotes are on the last table page.

*Table 20:**Summary of IBDQ Total Scores for SC-3030 Subjects with UC by Study Visit Among SC-3027 Randomized Completers for Long-term Combined Efficacy (FAS-UC): Interim Data as of 17 May 2019 (continued)***

Study Visit	Placebo N = 20	Vedolizumab SC 108 mg N = 69	Vedolizumab IV 300 mg N = 35
Week 76 (LOCF)			
N	20	69	35
Mean (SD)	176.40 (40.442)	196.77 (24.017)	194.37 (22.254)
Median	187.50	203.00	199.00
Minimum, maximum	80.0, 220.0	106.0, 224.0	126.0, 219.0
Week 100 (LOCF)			
N	20	69	35
Mean (SD)	170.80 (42.903)	189.66 (31.890)	191.57 (23.992)
Median	186.50	198.00	199.00
Minimum, maximum	60.0, 220.0	45.0, 222.0	133.0, 221.0

Source: Annex 1 SC-3030 Table 15.2.18.1.2.1 (combined analysis).
FAS-UC: full analysis set–ulcerative colitis; IBDQ: Inflammatory Bowel Disease Questionnaire; IV: intravenous; LOCF: last observation carried forward; SC: subcutaneous; UC: ulcerative colitis.
a Week 52 ends on the day of the first open-label extension SC dose of SC-3030. First dose of SC-3030 is assigned to Week 52 in this analysis visit window. Week 52 in this analysis combines the Week 52 of SC-3027 and Week 0 of SC-3030.

Long-term PRO analyses over time in nonrandomized Week 14 responder subjects with UC in Study SC-3027 who rolled over to Study SC-3030

IBDQ scores by study visit are summarized for nonrandomized Week 14 responder subjects up to Week 110. As shown in Table below, mean Total IBDQ scores during open-label, long-term vedolizumab SC treatment were maintained in Study SC-3030.

*Table 21:**Summary of Baseline in IBDQ Total Scores for SC-3030 Subjects With UC by Study Visit Among SC-3027 Nonrandomized Week 14 Responders for Long-term Combined Efficacy (FAS-UC): Interim Data as of 17 May 2019***

Study Visit	Nonrandomized Week 14 Responders N = 107
Baseline	
N	106
Mean (SD)	112.08 (33.460)
Median	109.50
Minimum, maximum	39.0, 212.0
Week 6 (LOCF)	
N	107
Mean (SD)	139.96 (37.767)
Median	139.00
Minimum, maximum	49.0, 217.0
Week 14 (LOCF) [a]	
N	107
Mean (SD)	142.24 (39.435)
Median	142.00
Minimum, maximum	49.0, 217.0
Week 38 (LOCF) [a]	
N	107
Mean (SD)	163.09 (38.757)
Median	171.00
Minimum, maximum	66.0, 224.0
Week 62 (LOCF)	
N	107
Mean (SD)	163.58 (39.952)
Median	172.00
Minimum, maximum	64.0, 224.0
Week 86 (LOCF)	
N	107
Mean (SD)	161.36 (40.795)
Median	167.00
Minimum, maximum	57.0, 221.0
Week 110 (LOCF)	
N	107
Mean (SD)	158.84 (42.973)
Median	165.00
Minimum, maximum	57.0, 224.0

FAS-UC: full analysis set–ulcerative colitis; IBDQ: Inflammatory Bowel Disease Questionnaire; LOCF: last observation carried forward; SC: subcutaneous; UC: ulcerative colitis.

a Week 14 ends on the day of the first open-label extension SC dose of SC-3030. First dose of SC-3030 is assigned

to Week 14 in this analysis visit window. Week 14 in this analysis combines the Week 14 of SC-3027 and Week 0 of SC-3030.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study MLN0002SC3027 was 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 to 12 with an endoscopic subscore ≥2) who achieved clinical response following 2 doses (at Weeks 0 and 2) of open-label vedolizumab IV therapy (induction phase). Responders at week 6 (clinical response defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline [Week 0]) at Week 6) were randomized in the maintenance phase including using vedolizumab SC 108mg Q2W or placebo (study powered for superiority of VDZ SC versus placebo) plus vedolizumab IV arm (within-study descriptive comparisons of efficacy, safety, and immunogenicity between vedolizumab IV and SC). An additional week 6 injection in patients non-responders at week 6 was allowed, response was assessed at week 14. Week 14 responders (assessed by partial Mayo score) were included into the long term extension 3030 OL study. Non-responders at week 14 entered into early termination.

The study design is acceptable. Inclusion and exclusion criteria reflect the target population. According to entry criteria, TNF-alpha naïve as well as TNF-alpha antagonist failed patients could have been enrolled.

The primary endpoint was clinical remission (defined as a complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52). The endoscopic endpoint (mucosal healing at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2) is included as first secondary endpoint applying a hierarchical approach. Although the updated EMA guideline refers to a primary endpoint meant as co-primary including both clinical remission as well as endoscopic remission the selection is acceptable for a line extension. The study is powered for the primary and first secondary endpoints and the sample size calculation is considered adequate. Secondary endpoints are acceptable as well as those defined as exploratory.

It is of note that the MAH has included among exploratory endpoints some definition recommended by FDA within the draft guidance for industry (UC clinical trial endpoints) such as definition of remission by modified Mayo score and clinical remission by Mayo score without PGA assessment. To complement mucosal healing definition the MAH added a separate exploratory endpoint i.e. histological changes.

383 Subjects have been enrolled in the Induction Phase, 216 subjects achieved response at week 6 and were randomized into the maintenance phase (placebo: 56 subjects; vedolizumab SC: 106 subjects; and vedolizumab IV: 54 subjects) and 37.5% of the placebo subjects, 72.6% and 75.9% of subjects in the vedolizumab SC and vedolizumab IV treatment groups, respectively, completed the study. The most frequent reason for discontinuation across all treatment groups was lack of efficacy, which was highest in the placebo group (80%) compared with 62.1% and 46.2% for vedolizumab SC and vedolizumab IV, respectively. Moreover, It is of note that a total of 86% out of 383 subjects treated in the Induction Phase are responders at week 6 or week 14, of these half of subjects (56%) out of 383 treated in the Induction Phase were responders at week 6 (vedolizumab infusion at week 0 and 2) and roughly 30% of subjects much more (79.7%) were responders at week 14 (using one additional infusion). This supports the dosage regime reported in the SmPC of "at least 2 intravenous infusions", suggesting that an additional infusion could increase efficacy.

In the study conduct, significant protocol deviations were recorded in an important percentage of subjects ranging from 40 to 50% across groups, mainly affecting: i) procedures not performed per protocol (35 % in the total group) and ii) entry criteria (11%). Overall the high number of significant deviations could have affected study results and is not in support of quality standards of trial conduct. The PPS population (All FAS subjects who did not violate the terms of the protocol in a way that would impact the study output significantly) which is the 77% of the total, and the sensitivity analysis using this population is therefore deemed important.

Enrolled population: Demographic characteristics reflect the target population. Roughly 60% of subjects had severe UC (ie, Mayo score of 9 to 12) and 40% had moderate disease according to Mayo score grading.

Baseline disease activity, as assessed by the complete Mayo score, was slightly imbalanced among study groups in favour of PLB and VDZ IV arms (severe Mayo: 64%, 57%, 68.5% in the PLB, VDZ SC and VDZ IV, respectively). Most subjects had left-sided colitis (42.1%) or pancolitis (35.6%). The great majority (82%) of the studied population was in the category of baseline fecal calprotectin >500 mg/g. Previous treatments: 62,5% had previous treatment with IMM and CCs. 61% of subjects didn't have previous TNF-alpha use (naïve) and 39% had previous treatment failure (20% inadequate response and 15%, loss of response and only 3.2% intolerance).

The aim of study MLN0002SC3031 was to evaluate the efficacy and safety of vedolizumab SC as maintenance therapy in subjects with moderate to severe Crohn's Disease who responded to vedolizumab intravenous (IV) induction treatment (vedolizumab IV 300 mg at Weeks 0 and 2). Only subjects who achieved a clinical response at Week 6 were randomized into the maintenance phase (randomization 2:1 ratio to double-blind treatment with vedolizumab SC administered once every 2 weeks (Q2W) or placebo SC Q2W). The study design was broadly similar to the design of the study in UC but no internal control arm using vedolizumab IV was included, hampering a direct comparison. Therefore, the only possible indirect comparison is the IV arm of the GEMINI 2 (C13007) study.

Efficacy data and additional analyses

In **UC subjects** (study MLN0002SC3027), administration of SC vedolizumab resulted in maintenance of clinical remission/response with amelioration of endoscopic scores, such as mucosal healing, compared to placebo. Results are considered clinically significant.

The primary endpoint (clinical remission defined as a complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52) 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 (delta 31.9). Clinical remission at week 52 was slightly higher in subjects randomized to vedolizumab SC 108mg Q2W than in the vedolizumab IV 300mg Q8W (32.3% versus 27.9%). Sensitivity analyses and exploratory analysis using FDA modified definitions as well as a PPS analysis showed consistent results.

Subgroup analyses overall favour VDZ over PLB; subgroups of interest: baseline disease activity (risk difference estimate moderate 39.3 vs severe 26); clinical remission at week 6 (risk difference estimate yes 37.4 and no 27.6); prior anti-TNF alpha failure (risk difference estimate yes 28.1 no 32.1).

Endoscopic response, evaluated by Mucosal healing (a Mayo endoscopic subscore of ≤1 point) at week 52, was the first secondary endpoint according to the applied ranking. The percentage of subjects achieving mucosal healing was statistically higher in vedolizumab SC subjects (56.6%) as compared with subjects who received placebo 21.4%, and the magnitude of effect was clinically relevant. Vedolizumab SC treatment showed similar results as the vedolizumab IV treatment.

The proportion of subjects with mucosal healing at Week 52 in the PPS population was similar to the FAS population. A consistent treatment difference was observed between the placebo and vedolizumab SC (adjusted difference from placebo: 36.2 [95% CI: 20.5, 51.9], p<0.001).

Different endpoints have been assessed with the aim of evaluating the durability of the effect (response/remission) being the treatment meant for chronic use and for an autoinflammatory/autoimmune disease. Below the results are summarized according to the different applied definitions:

Durable (both Weeks 6 and 52) clinical response (according to total Mayo score) was statistically significantly higher in vedolizumab SC subjects versus PLB (difference from placebo 36.1%). Vedolizumab IV showed slightly higher results to vedolizumab SC (44.5 versus 36.1). Consistent results were achieved in the PPS population.

As regards durable remission (defined as complete Mayo score of ≤2 points and no individual subscore >1 point at both Weeks 6 and 52), a more stringent endpoint, a numerical trend in favour of vedolizumab was observed (15.1%) compared with the placebo group (5.4%). Vedolizumab IV showed similar results.

At the CHMP request, 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 was evaluated as exploratory endpoint, in order to gain information on durability/sustainable remission. Of note, this definition was based on Partial Mayo Scores (defined as a partial Mayo score ≤2 and no individual subscore >1, excluding endoscopy. In the FAS population, a higher proportion of subjects treated with vedolizumab SC had sustained Maintenance of Efficacy (i.e. clinical remission in at least 80% of the study visits, delta from PLB 37.8 ; Clinical remission at ≥60% of study visits, delta from PLB 39.9; clinical response in at least of 60% of the study visits, delta from PLB 26.8) supporting the maintenance/persistence of the effect. Using alternative FDA definitions for remission, consistent results have been observed.

The CHMP considered that the results did not support a substantial corticosteroid sparing effect of VDZ treatment; there was a favorable trend towards VDZ SC but the results were not statistically significant. Approximately 41.7% of the FAS subjects were on corticosteroids at baseline. Corticosteroid-free clinical remission (as subjects using oral corticosteroids at baseline who had discontinued oral corticosteroids and were in clinical remission based on the complete Mayo score at Week 52) which is considered an important although difficult achievement in these patients, showed only numerically higher rates in VDZ SC with a treatment difference of 20.6 from placebo. A similar treatment difference from placebo was observed for the vedolizumab IV group (20.2). This result was statistically significant in data obtained from GEMINI 1 (VDZ IV initial MAA study treatment difference 17.6, IV Q8W dosing versus placebo), a possible reason for this difference could be the limited number of subjects in the subgroup evaluated for the corticosteroid sparing effect in the SC-3027 study.

Also, the proportion of subjects who achieved clinical remission and were corticosteroid free for 90 or for 180 days was only numerically higher in VDZ SC treated subjects as compared to PLB (vedolizumab SC group 26.7%, placebo group (8.3%).

Considering the two subgroups of interest (TNF-alpha naïve and failed subjects) similar results in the FAS analysis have been observed, with a magnitude of effect higher in the antiTNF-alpha naïve subjects.

Results on calprotectin, a biomarker of inflammation, further support efficacy, showing increase of subjects within the less severe calprotectin (<250 µg/g) category among VDZ treated subjects.

Of note, there seems to be a trend in reduction of hospitalization/surgery, which are important clinical goals, however numbers are limited to draw firm conclusions.

CD subjects (study MLN0002SC3031).

At D120 the MAH was asked to justify that the available PK data can support the extrapolation of efficacy and safety from IV to SC vedolizumab to patients with CD, considering that the PK/PD relationship may not be exactly the same in UC and CD or provide clinical data from CD patients. Accordingly results from study MLN0002SC3031 were provided to further support the indication.

644 subjects were enrolled in the open-label vedolizumab IV induction period, and 410 were randomized into the double-blinded maintenance phase of the study.

The primary endpoint clinical remission at Week 52, was met (VDZ 48.0% vs PLB 34.3%, respectively) (adjusted treatment difference 13.7 p.p.; 95% CI [3.8, 23.7, p = 0.008]). Of note, in the vedolizumab IV Q8W group of GEMINI 2 study, the treatment difference was similar: 17 p.p., PLB 22% and VDZ Q8W 39%.

When a more stringent and exploratory evaluation of remission (durable defined as remission at week 6 and 52) was considered the difference between PLB and VDZ SC arms was very limited (5.6%).

The first secondary efficacy endpoint, **enhanced clinical response**, was not statistically significant; placebo response is very high (44.8%) resulting in a very limited difference between the two arms (treatment difference 7.3, p=0.167). In the GEMINI 2 the treatment difference was higher (14%) and a PLB response of 30%.

Statistical inference was not conducted, and nominal p-values are reported for the second (corticosteroid-free clinical remission) and third (clinical remission at Week 52 in TNF-α antagonist naïve subjects) secondary endpoints.

Taking into account this methodological limit/failure, evaluation of the key secondary endpoint of corticosteroid-free remission at Week 52 suggested an effect of vedolizumab SC over placebo (vedolizumab SC, 45.3%; placebo, 18.2%; adjusted difference from placebo 27.1 p.p., 95% CI [11.9, 42.3]; nominal p = 0.002).

Looking at the endpoint of **clinical remission at Week 52 in the tumor necrosis factor-alpha (TNF-α) antagonist naïve subject population** (third secondary endpoint, 50% of the enrolled population) again a very high PLB response is observed leading to very limited treatment difference (42.9% PLB and 48.6% VDZ, treatment difference 4.3). In subjects with prior antiTNF-alpha failure a larger difference is seen (VDZ 45.4 PLB 28.8 difference 17.6%) due to a lower PLB response while a very similar response is seen in the treatment arm.

Reduction in **inflammatory markers** was observed for fecal calprotectin (increase of subjects having ≤250mg/g as compared to higher cut-off levels) but not for CRP reduction in subjects having high CPR level at baseline (≥2.87mg/L). A positive trend in favour of vedolizumab was reported for some PROs and HQL measures.

In conclusion, a high PLB response is seen across different endpoints negatively impacting the treatment difference and therefore study results. However, the subjective nature of CDAI as endpoint is acknowledged and heterogeneity of placebo response is seen across trials using drugs for the treatment of IBD and is reported in literature.

The MAH was asked during the procedure to further discuss the added value of Vedolizumab to background therapy (corticosteroids and immunomodulators). Analyses of study endpoints stratified by different background treatments were provided and did not suggest a significant impact of background therapy on vedolizumab efficacy results.

Stratified analyses were also provided by dose category and type of steroid, showing that the majority of patients were treated with low doses. A comprehensive discussion of the added value of Vedolizumab

to background therapy (corticosteroids and immunomodulators) from a clinical perspective was not provided; however, overall the added value of vedolizumab SC over background therapies seems limited, although in line with the results observed with the IV formulation in particular for the primary endpoint.

Supportive information is coming from the **SC-3030 Study**. As mentioned before, this study is an interim report and allows the inclusion of both UC and CD pts coming from these two studies. No patient completed the study, 77% of subjects are still ongoing, 23% terminated early (primary reason being lack of efficacy 59% of the total population of early terminators).

The MAH has provided an interim update of the in subjects with ulcerative colitis (UC) from Study SC-3030 (A Phase 3b Open-Label Study to Determine the Long-term Safety and Efficacy of Vedolizumab Subcutaneous in Subjects With Ulcerative Colitis and Crohn's Disease [CD]) through the data lock point (DLP) of 17 May 2019. Details about subjects' disposition across arms were provided. Lack of efficacy remains the main reason for study interruption in both UC and CD subjects, at the IA (cut-off May 2019). Considering the previous treatment group, subjects who interrupted study 3030 were similarly distributed.

Data up to week 116 on clinical remission in subjects with UC who completed 52 weeks of treatment in Study SC-3027 and rolled over to Study SC-3030 (randomized completers) and in nonrandomized Week 14 responder subjects who rolled over to Study SC-3030 support a trend in the maintenance of the effect although less pronounced in the nonrandomized week 14 responders.

Data on PRO analysis in both subjects' groups are supportive of a positive trend over time.

2.5.4. Conclusions on the clinical efficacy

The efficacy of subcutaneous vedolizumab treatment (108 mg administered by subcutaneous injection once every 2 weeks following at least 2 intravenous infusions) as maintenance treatment of patients with moderately to severely active Ulcerative Colitis and Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factoralpha (TNFα) antagonist is sufficiently demonstrated. Entyvio (either as IV or SC) seems less efficacious in Crohn's disease compared to ulcerative colitis. No direct comparison has been made between Entyvio SC and Entyvio IV in Crohn's disease. Indirect comparison with previous studies of Entyvio IV, suggest that the efficacy in both indications appears similar for Entyvio SC and Entyvio IV.

2.6. Clinical safety

The clinical safety assessment of vedolizumab SC includes safety data from 3 phase 3 studies and 5 phase 1 studies. The phase 3 studies include pivotal Study SC-3027 in subjects with UC, ongoing Study SC-3031 (blinded study in subjects with CD, week 52 database lock provided), and ongoing Study SC-3030 (OLE study from parent Studies SC-3027 [UC] and SC-3031 [CD]). Pivotal Study SC-3027 was assessed independently and as part of 2 pooled data sets listed below. Safety data from Study SC-3031 in subjects with CD have been provided within the responses to D120 LoQ.

*Table 22:**Study Groupings for Pooled Study Data***

Pools 1 and 2: Phase 3 Study SC-3027 and open-label extension Study SC-3030	
Pool 1: Study SC-3027/SC-3030 UC Subjects	Pool 2: Study SC-3027/SC-3030 UC/CD Subjects
Data collected in the maintenance phase of Study SC-3027 for subjects randomized to SC together with data collected in extension Study SC-3030 from subjects previously enrolled in Study SC-3027 (UC subjects). N = 303	Data collected in the maintenance phase of Study SC-3027 for subjects randomized to SC together with all data collected in extension Study SC-3030 regardless of previous enrollment in Study SC-3027 (UC subjects) or Study SC-3031 (CD subjects). N = 613
Pool 3: Phase 1 Studies SC-101, SC-1017, SC-1021, SC-1018 and SC-1022: single-dose PK studies	
Vedolizumab SC	
Studies SC-101 (SC subjects only), SC-1017, SC-1021, SC-1018, and SC-1022; N = 390	

*Table 23:**Patient exposure***

Table 1.d Duration of Exposure to Vedolizumab SC: Phase 3 Studies

Duration	Pool 1 (UC) [a] VDZ SC 108 mg	Pool 2 (UC/CD) [b] VDZ SC 108 mg
At least 1 dose	(N = 303)	(N = 613)
Duration of SC exposure (days) [c]		
N	303	613
Mean (SD)	420.9 (174.57)	358.3 (167.47)
Median	433.0	336.0
Min, max	127, 899	127, 899
Total number of SC injections		
N	303	613
Mean (SD)	24.3 (15.51)	19.9 (15.27)
Median	23.0	17.0
Min, max	1, 88	1, 92
Duration of SC exposure (months)		
≥1 dose	303 (100.0)	613 (100.0)
≥6 months	269 (88.8)	523 (85.3)
≥12 months	193 (63.7)	273 (44.5)
≥18 months	68 (22.4)	88 (14.4)
≥24 months	13 (4.3)	16 (2.6)

Source: Pool 1 (UC), ISS Table 1.1.3, Pool 2 (UC/CD), ISS Table 1.2.3.
CD: Crohn's disease; ISS: Integrated Summary of Safety; max: maximum; min: minimum; SC: subcutaneous; UC: ulcerative colitis; VDZ: vedolizumab.
[a] Pool 1 (UC) includes subjects enrolled in the maintenance phase of Study SC-3027 and randomized to SC, and subjects enrolled in the extension study (Study SC-3030) who were previously enrolled in Study SC-3027.
[b] Pool 2 (UC/CD) includes subjects enrolled in the maintenance phase of Study SC-3027 and randomized to SC, and all subjects enrolled in the extension study (Study SC-3030) regardless of previous enrollment in Study SC-3027 or Study SC-3031.
[c] Duration of exposure = (date of last dose of study drug - date of first dose of study drug) + 127.

Demographic Characteristics:

The majority of patients were male, white and <65 years old. Previous therapies included corticosteroids and immunomodulators for more than half of subjects in pool1 and pool 2 and TNF-α antagonist in 42% and 52% of subjects, respectively, in pool 1 and 2. Overall, demographic baseline characteristics seem to be well balanced among placebo and treatment arms in Study SC-3027. However, it was noted that a higher proportion of Asian were included in placebo arm (23.2%) compared to Vedolizumab SC (13.2%) and IV (9.3%) arms.

*Table 24:*Baseline Disease Characteristics: Study SC-3027, Pool 1 (UC), and Pool 2 (UC/CD)

	Study SC-3027 [a]				Pool 1 (UC) [b]	Pool 2 (UC/CD) [c]
	Placebo N = 56	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Overall N = 216	Vedolizumab SC 108 mg N = 303	Vedolizumab SC 108 mg N = 613
Indication						
UC	56	106	54	216	303 (100.0)	303 (49.4)
CD	NA	NA	NA	NA	NA	310 (50.6)
Baseline disease activity, n (%) [d]						
Mild	0	0	0	0	ND	ND
Moderate	20 (35.7)	46 (43.4)	17 (31.5)	83 (38.4)	ND	ND
Severe	36 (64.3)	60 (56.6)	37 (68.5)	133 (61.6)	ND	ND
Disease localization (UC)						
Proctosigmoiditis	7 (12.5)	15 (14.2)	7 (13.0)	29 (13.4)	42 (13.9)	42 (6.9)
Left sided colitis	24 (42.9)	46 (43.4)	21 (38.9)	91 (42.1)	126 (41.6)	126 (20.6)
Extensive colitis	4 (7.1)	7 (6.6)	7 (13.0)	18 (8.3)	27 (8.9)	27 (4.4)
Pancolitis	21 (37.5)	37 (34.9)	19 (35.2)	77 (35.6)	107 (35.3)	107 (17.5)
NA (subject is a CD patient)						310 (50.6)
Disease localization (CD)						
Colon only	NA	NA	NA	NA	NA	65 (10.6)
Ileum only	NA	NA	NA	NA	NA	71 (11.6)
Ileocolonic	NA	NA	NA	NA	NA	137 (22.3)
Other	NA	NA	NA	NA	NA	37 (6.0)
N/A (subject is a UC patient)						303 (49.4)
History of extraintestinal manifestations	5 (8.9)	13 (12.3)	7 (13.0)	25 (11.6)	45 (14.9)	237 (38.7)
Previous IBD therapy, n (%)						
TNF-α antagonist use	20 (35.7)	40 (37.7)	24 (44.4)	84 (38.9)	128 (42.2)	318 (51.9)
Corticosteroids only	22 (39.3)	28 (26.4)	21 (38.9)	71 (32.9)	93 (30.7)	163 (26.6)
Immunomodulators only	1 (1.8)	6 (5.7)	1 (1.9)	8 (3.7)	11 (3.6)	31 (5.1)
Corticosteroids and immunomodulators	32 (57.1)	71 (67.0)	32 (59.3)	135 (62.5)	196 (64.7)	412 (67.2)
No corticosteroids or immunomodulators	1 (1.8)	1 (0.9)	0	2 (0.9)	3 (1.0)	7 (1.1)

Source: SC-3027 Table 15.1.8.2; Pool 1 (UC), ISS Table 1.1.2; Pool 2 (UC/CD), ISS Table 1.2.2.

Adverse events

*Table 25:**Study SC-3027 Most Frequent (⩾5%) TEAEs by PT (Safety Analysis Set)***

SOC PT	Number of Subjects (%) PBO N = 56	VDZ SC 108 mg N = 106	VDZ IV 300 mg N = 54	Total N = 216
Subjects with any most frequent TEAEs	32 (57.1)	43 (40.6)	31 (57.4)	106 (49.1)
Blood and lymphatic system disorders	2 (3.6)	6 (5.7)	5 (9.3)	13 (6.0)
Anaemia	2 (3.6)	6 (5.7)	5 (9.3)	13 (6.0)
Gastrointestinal disorders	18 (32.1)	15 (14.2)	6 (11.1)	39 (18.1)
Colitis ulcerative	18 (32.1)	15 (14.2)	6 (11.1)	39 (18.1)
Infections and infestations	14 (25.0)	21 (19.8)	15 (27.8)	50 (23.1)
Nasopharyngitis	11 (19.6)	11 (10.4)	10 (18.5)	32 (14.8)
Upper respiratory tract infection	1 (1.8)	10 (9.4)	2 (3.7)	13 (6.0)
Sinusitis	3 (5.4)	1 (0.9)	0	4 (1.9)
Urinary tract infection	2 (3.6)	0	4 (7.4)	6 (2.8)
Investigations	1 (1.8)	2 (1.9)	5 (9.3)	8 (3.7)
Alanine aminotransferase increased	0	1 (0.9)	3 (5.6)	4 (1.9)
Blood creatine phosphokinase increased	1 (1.8)	1 (0.9)	3 (5.6)	5 (2.3)
Musculoskeletal and connective tissue disorders	1 (1.8)	6 (5.7)	4 (7.4)	11 (5.1)
Arthralgia	1 (1.8)	6 (5.7)	4 (7.4)	11 (5.1)
Nervous system disorders	6 (10.7)	9 (8.5)	0	15 (6.9)
Headache	6 (10.7)	9 (8.5)	0	15 (6.9)
Psychiatric disorders	0	1 (0.9)	3 (5.6)	4 (1.9)
Insomnia	0	1 (0.9)	3 (5.6)	4 (1.9)
Skin and subcutaneous tissue disorders	1 (1.8)	1 (0.9)	3 (5.6)	5 (2.3)
Rash	1 (1.8)	1 (0.9)	3 (5.6)	5 (2.3)

Study SC-3031

73.5% of CD subjects, compared to 76.1 of subjects in the PLB arm, experienced TEAEs of which the majority were mild or moderate in intensity (32.8% and 34.3% of subjects, respectively for placebo and 32.4% and 36.0%, respectively for vedolizumab SC).

Pool 1 (UC)

Overall, 185 subjects (61.1%) reported any TEAE in Pool 1 (see Table below). UC, the condition under study, was the most common TEAE reported in 42 subjects (13.9%) followed by nasopharyngitis in 31 subjects (10.2%), upper respiratory infections in 21 subjects (6.9%), and anaemia in 20 subjects (6.6%).

Pool2 (UC/CD)

Overall, 367 subjects (59.9%) reported any TEAE in Pool 2 (see Table below). UC and CD, the conditions under study, were among the most commonly reported TEAEs, reported in 42 subjects (6.9%) and 28 subjects (4.6%), respectively. Nasopharyngitis was reported in 45 subjects (7.3%), followed by upper respiratory infection in 37 subjects (6%) and arthralgia in 28 subjects (4.6%). Abdominal pain, anaemia, diarrhoea, and headache were reported in ≥3% of subjects. Bronchitis, cough, nausea, back pain, blood creatine phosphokinase increased, influenza, and injection site reaction were reported in ≥2% subjects.

AEs by Intensity

Study SC-3027

Within each treatment group, most subjects developed AEs that were considered by the investigator to be mild or moderate in intensity (32.1% and 39.3% of subjects, respectively, for placebo; 25.5% and 34.0%, respectively, for vedolizumab SC; and 31.5% and 42.6%, respectively for vedolizumab IV). **Severe AEs** occurred in 5.4% of subjects in the placebo group, 5.7% in the vedolizumab SC group, and 1.9% in the vedolizumab IV group. Most of the severe cases in the placebo and vedolizumab SC groups were in the SOC of **gastrointestinal disorders**, mostly due to UC. One (0.5%) severe infection (peritonitis, in the vedolizumab SC group) was reported in the study.

Pool 1 (UC)

Most TEAEs were mild (31.7%) or moderate in intensity (24.1%). Severe TEAEs occurred in 16 subjects (5.3%). The most frequent severe AEs occurred in the gastrointestinal disorders SOC (10 subjects, 3.3%) with UC being the most commonly reported severe TEAE (9 subjects, 3.0%). Other severe TEAEs included anaemia in 3 (1.0%), blood creatine phosphokinase increased in 2 (0.7%), tachycardia in 1 (0.3%), acute abdomen in 1 (0.3%), large intestine perforation in 1 (0.3%), peritonitis in 1 (0.3%), appendicitis in 1 (0.3%), and alanine aminotransferase, gamma-glutamyl transferase, and blood alkaline phosphatase increased in 1 (0.3%) subject.

Pool 2

Most subjects develop ped TEAEs that were mild (30.3%) or moderate (24.1%) in intensity. Severe TEAEs occurred in 33 subjects (5.4%). Most severe TEAEs occurred in the gastrointestinal disorders SOC (21 subjects, 3.4%) with UC (9 subjects, 1.5%) and CD (7 subjects, 1.1%) being the most commonly reported severe TEAEs.

TRAEs

Study SC-3027

AEs considered related to study treatment were reported in a total of 47 subjects (21.8%) including 28 subjects (26.4%) in the vedolizumab SC group, 9 subjects (16.7%) in the vedolizumab IV group, and 10 subjects (17.9%) in the placebo group. Most AEs were in gastrointestinal disorders (5.6%), infections and infestations (5.6%), and general disorders and administration site conditions (6%) SOCs.

Study SC-3031

AEs considered related to study treatment were reported in 19.3% of subjects in the vedolizumab SC group and in 14.9% in the placebo group, mainly due to injection-site reactions, all of which were considered drug related in the vedolizumab SC group.

Pool 1 and Pool 2

Most Frequent (≥1%) TRAE by PT: Pool 1 (UC)

MedDRA PT	Number of Subjects (%) [Events per 100 Patient-Years] Pool 1 (UC) [a] (N = 303, Patient-Years = 349)
Subjects with any TRAEs	77 (25.4) [22.1]
Colitis ulcerative	15 (5.0) [4.3]
Injection site reaction	9 (3.0) [2.6]

Most Frequent (≥1%) TRAEs by PT: Pool 2 (UC/CD)

PT	Number of Subjects (%) [Events per 100 Patient-Years] Pool 2 (UC/CD) [a] (N = 613, Patient-Years = 601)
Subjects with any TRAEs	120 (19.6) [20.0]
Colitis ulcerative	15 (2.4) [2.5]
Injection site erythema	11 (1.8) [1.8]

Injection site erythema	8 (2.6) [2.3]	Injection site reaction	10 (1.6) [1.7]
Nasopharyngitis	5 (1.7) [1.4]	Arthralgia	6 (1.0) [1.0]
Injection site swelling	4 (1.3) [1.1]	Crohn's disease	6 (1.0) [1.0]
Arthralgia	3 (1.0) [0.9]	Headache	6 (1.0) [1.0]
Headache	3 (1.0) [0.9]	Pyrexia	6 (1.0) [1.0]
Injection site pruritus	3 (1.0) [0.9]	Upper respiratory tract infection	6 (1.0) [1.0]
Pain in extremity	3 (1.0) [0.9]		
Pruritus	3 (1.0) [0.9]		
Pyrexia	3 (1.0) [0.9]		
Upper respiratory tract infection	3 (1.0) [0.9]		

Serious adverse event/deaths/other significant events

Deaths

No deaths occurred neither in UC (including Study SC-3027 and Pool 1) nor in CD population. One death was reported during Study SC-3030 (pulmonary embolism) considered not related to study treatment by the investigator.

Other SAEs

Study SC-3027

In total, 23 subjects (10.6%) reported a SAE in the study. The frequency of SAEs was generally similar across all 3 treatment groups. The overall highest incidence (4.6%) of SAEs was reported in the **gastrointestinal disorders** SOC and occurred in **placebo** subjects more frequently (8.9%) than in the vedolizumab SC (3.8%) or vedolizumab IV (1.9%) groups. The only other SAE reported with a frequency of >1% was anaemia, with a similar incidence between the vedolizumab SC and placebo groups.

Study SC-3031

SAEs occurred in 8.4% of patients in VDZ SC arm and 10.4% in PLB arm

Most Frequent (≥1%) TESAEs by SOC PT: Pool 1 (UC)

MedDRA SOC PT	Number of Subjects (%) [Events per 100 Patient-Years] Pool 1 (UC) [a] (N = 303, Patient-Years = 349)
Subjects with any TESAEs	31 (10.2) [8.9]
Blood and lymphatic system disorders	10 (3.3) [2.9]
Anaemia	10 (3.3) [2.9]
Gastrointestinal disorders	16 (5.3) [4.6]
Colitis ulcerative	14 (4.6) [4.0]

Source: ISS Table 2.1.6.1.
ISS: Integrated Summary of Safety; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SC: subcutaneous; SOC: System Organ Class; TESAE: treatment-emergent serious adverse event; UC: ulcerative colitis.
[a] Pool 1 (UC) includes subjects enrolled in the maintenance phase of Study SC-3027 and randomized to SC, and subjects enrolled in the extension study (Study SC-3030) who were previously enrolled in Study SC-3027.

Most Frequent (≥1%) TESAEs by SOC and PT: Pool 2 (UC/CD)

SOC PT	Number of Subjects (%) [Events per 100 Patient-Years] Pool 2 (UC/CD) [a] (N = 613, Patient-Years = 601)
Subjects with any TESAEs	64 (10.4) [10.6]
Blood and lymphatic system disorders	12 (2.0) [2.0]
Anaemia	12 (2.0) [2.0]
Gastrointestinal disorders	33 (5.4) [5.5]
Colitis ulcerative	14 (2.3) [2.3]
Crohn's disease	10 (1.6) [1.7]

Source: ISS Table 2.2.6.1.
CD: Crohn's disease; ISS: Integrated Summary of Safety; PT: Preferred Term; SC: subcutaneous; SOC: System Organ Class; TESAE: treatment-emergent serious adverse event; UC: ulcerative colitis.
[a] Pool 2 (UC/CD) includes subjects enrolled in the maintenance phase of Study SC-3027 and randomized to SC, and all subjects enrolled in the extension study (Study SC-3030) regardless of previous enrollment in Study SC-3027 or Study SC-3031.

AESIs

Overall Summary of AESIs in Pool 1

AESI	Pool 1 (UC) [a] (N = 303, Patient-Years = 349) # of subjects with event (%) [per 100 Patient-Years]
Subjects with any AESI	127 (41.9) [36.4]
Hypersensitivity reactions	40 (13.2) [11.5]
Infections	105 (34.7) [30.1]
Injection site reactions	23 (7.6) [6.6]
Liver injury	4 (1.3) [1.1]
Neoplasms	3 (1.0) [0.9]

Overall Summary of AESIs in Pool 2

Adverse Event Special Interest (AESI)	Pool 2 (UC/CD) [a] (N = 613, Patient-Years = 601) # of subjects with event (%) [per 100 Patient-Years]
Subjects with any AESI	228 (37.2) [37.9]
Hypersensitivity reactions	59 (9.6) [9.8]
Infections	189 (30.8) [31.4]
Injection site reactions	29 (4.7) [4.8] [b]
Liver injury	11 (1.8) [1.8]
Neoplasms	6 (1.0) [1.0]

Infections

Study SC-3027

Infections were reported in 79 of 216 subjects (36.6%) in Study SC-3027 (35.7%, 36.8%, and 37.0% in the placebo, vedolizumab SC, and vedolizumab IV groups, respectively).

In the **vedolizumab SC group,** the most common PTs of infections were nasopharyngitis (10.4%) and upper respiratory tract infections (9.4%). Nasopharyngitis was reported in 19.6% of subjects in the placebo group and 18.5% of subjects in the IV groups. **Upper respiratory tract infection** was reported in 1.8%, 3.7% and **9.4%** of subject in the placebo, IV and SC groups, respectively. Pneumonia was reported with an overall frequency of 2.3% (2.8% in vedolizumab SC group, 1.8% and 1.9% in placebo and vedolizumab IV groups, respectively).

Study SC-3031

A slightly higher number of **infections** were reported in the placebo-treated subjects (34.3%) than in the vedolizumab SC–treated subjects (31.3%). The most frequently reported infection AESIs were in the HLT of upper respiratory tract infections (including PTs of nasopharyngitis, upper respiratory tract

infection, sinusitis, pharyngitis, tonsillitis, acute sinusitis, and rhinitis) and occurred more frequently in vedolizumab SC–treated subjects (17.8%) than in subjects treated with placebo (14.2%). The most common PTs of infection in both groups were nasopharyngitis and upper respiratory tract infections. These were more frequent in the vedolizumab SC group (9.1% and 6.2%, respectively) than in the placebo group (4.5% and 3.7%, respectively). Treatment-**related** AEs of infections in the vedolizumab SC group included abscess intestinal, anal abscess, *Clostridium difficile* infection, tongue fungal infection, bronchitis, pneumonia, tinea versicolour, nasopharyngitis, sinusitis, and upper respiratory tract infection (each in 1 subject, 0.4%).

Pool 1 and Pool 2

Summary of Infection AESIs in ≥2% of Subjects in Pool 1

PT	Pool 1 (UC) [a] (N = 303, Patient-Years = 349) # of subjects with event (%) [per 100 Patient-Years]
Subjects with at least 1 infection AESI	105 (34.7) [30.1]
Nasopharyngitis	31 (10.2) [8.9]
Upper respiratory tract infection	21 (6.9) [6.0]
Influenza	9 (3.0) [2.6]
Gastroenteritis	7 (2.3) [2.0]
Bronchitis	6 (2.0) [1.7]
Pharyngitis	6 (2.0) [1.7]

Summary of Infection AESIs in ≥2% of Subjects in Pool 2

PT	Pool 2 (UC/CD) [a] (N = 613, Patient-Years = 601) # of subjects with event (%) [per 100 Patient-Years]
Subjects with at least 1 infection AESI	189 (30.8) [31.4]
Nasopharyngitis	45 (7.3) [7.5]
Upper respiratory tract infection	37 (6.0) [6.2]
Bronchitis	18 (2.9) [3.0]
Influenza	12 (2.0) [2.0]

In Pool 2 **SAEs** of infection were reported in 13 subjects (2.1%), 5 UC and 8 CD. These included appendicitis in 2 subjects with UC (0.7%); pneumonia in 2 subjects with CD (0.3%); and abdominal abscess, abdominal wall abscess, anal abscess, peritonitis, rectal abscess, *Clostridium difficile* infection, herpes zoster, influenza, and tonsillitis in 1 subject (0.2%) each. Treatment-related infection SAEs were reported in only 2 subjects including 1 subject each with *Clostridium difficile* infection and influenza.

Malignancies

Six subjects (1.0%) reported 7 TEAEs in the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps) in Pool 2 (three UC patients and three CD patients). However, they were considered all not to be related to study treatment by the investigators.

Hypersensitivity (Including Injection Site Reactions and Infusion Reactions)

In Study SC-3027 all AEs were reported as **nonserious** and mild or moderate in severity. Treatment-**related** TEAEs were reported for 7 subjects (3.2%) overall, 6 from the vedolizumab SC group and 1 from the placebo group. Injection site rash and pruritus were reported in 2 subjects (1.9%), and all other AEs including peripheral swelling, eczema, erythema, and urticaria were reported in 1 subject (0.9%) each in the vedolizumab SC group. No subject reported any treatment-related TEAE of hypersensitivity in the vedolizumab IV group.

There was no case of anaphylaxis or severe allergic reaction**.** None of the AEs led to study discontinuation.

Injection-Related AEs: Overall, 12 subjects (5.6%) reported an injection site reaction, 11 (10.4%) subjects in the vedolizumab SC group and 1 subject in vedolizumab IV group.

In Study SC-3031, 37 subjects (9.0%) experienced a **hypersensitivity reaction** (13 subjects, 9.7% in placebo-treated subjects and 24 subjects, 8.7% in vedolizumab SC–treated subjects). Most AEs were mild or moderate in severity. An event of seasonal allergy, in a subject treated with vedolizumab SC, was considered severe. There were no cases of anaphylaxis during the maintenance phase. Overall, 10 of 409 subjects (2.4%) reported an **injection site reaction** and these reports were more frequent in the vedolizumab SC group (8 subjects, 2.9%) than in the placebo group (2 subjects, 1.5%).

In **Pool 2** hypersensitivity reactions were reported in 59 subjects (9.6%). The most frequently reported reactions were rash (9 subjects [1.5%]), pruritus (6 subjects [1.0%]), and eczema (6 subjects [1.0%]).

Summary of Injection Site Reaction AESIs in Pool 1 - Study SC-3027/3030 UC Subjects

PT	Pool 1 (UC) [a] (N = 303, Patient-Years = 349) # of subjects with event (%) [per 100 Patient-Years]
Subjects with at least 1 injection site reaction special interest TEAE	23 (7.6) [6.6] [b]
Injection site reaction	10 (3.3) [2.9]
Injection site erythema	8 (2.6) [2.3]
Injection site swelling	4 (1.3) [1.1]
Injection site pruritus	3 (1.0) [0.9]
Injection site rash	2 (0.7) [0.6]
Injection site bruising	1 (0.3) [0.3]
Injection site haematoma	1 (0.3) [0.3]
Pruritus	1 (0.3) [0.3] [b]
Erythema	1 (0.3) [0.3] [b]

Summary of Injection Site Reaction AESIs in Pool 2-Study SC-3027/3030 UC/CD Subjects

PT	Pool 2 (UC/CD) [a] (N = 613, Patient-Years = 601) # of subjects with event (%) [per 100 Patient-Years]
Subjects with any injection site reactions special interest TEAEs	29 (4.7) [4.8] [b]
Injection site reaction	12 (2.0) [2.0]
Injection site erythema	11 (1.8) [1.8]
Injection site swelling	4 (0.7) [0.7]
Injection site pruritus	3 (0.5) [0.5]
Injection site rash	2 (0.3) [0.3]
Injection site bruising	1 (0.2) [0.2]
Injection site haematoma	1 (0.2) [0.2]
Injection site pain	1 (0.2) [0.2]
Pruritus	1 (0.2) [0.2] [b]
Erythema	1 (0.2) [0.2] [b]

Liver injury

2 subjects in vedolizumab SC group in Study SC-3027 and 4 subjects in pool 1 reported liver injury AESIs. In Study SC-3031 there were 8 subjects (2.9%) with **liver injury** AESIs in the vedolizumab SC group. Treatment-related liver injury TEAEs (per the investigator) were reported for 2 subjects in the vedolizumab SC group.

The number increased in pool 2, where 11 subjects (1.8%) experienced liver injury with the most frequently reported AEs being gamma-glutamyl transferase increased (5 subjects [0.8%]).

Pool 2: Liver injury AESIs were reported in **11 subjects (1.8%)** in Pool 2 (UC/CD). The most frequently reported AEs were gamma-glutamyl transferase increased (5 subjects [0.8%]), LFT increased (3 subjects [0.5%]), and alanine aminotransferase increased (2 subjects [0.3%]). Aspartate aminotransferase increase, hepatic enzyme increased, and hyperbilirubinemia were reported in 1 subject each. Most of these were mild or moderate in intensity except for severe TEAEs of alanine aminotransferase increased, gamma-glutamyl transferase, and blood alkaline phosphatase increased in a single subject. All events were reported as nonserious. One event each of alanine aminotransferase increased and gamma-glutamyl transferase increased lead to study discontinuation. There were no cases of Hy's law abnormality.

PML

There were no subjects diagnosed with PML.

Laboratory findings

In Study SC-3027, as well as in pool 1 and pool 2, no clinically relevant differences between the treatment groups in mean changes from baseline at any time point were observed for any hematology and chemistry parameter.

*Table 26:**Summary of Marked Laboratory Abnormalities During Treatment (SAF) in Study Sc-3027***

Parameter [a]	PBO N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)
Erythrocytes <0.8 × LLN	2 (3.6)	4 (3.8)	2 (3.7)
Hemoglobin <0.8 × LLN	5 (8.9)	14 (13.2)	4 (7.4)
Hematocrit <0.8 × LLN	3 (5.4)	6 (5.7)	4 (7.4)
Leukocytes >1.5 × ULN	3 (5.4)	6 (5.7)	3 (5.6)
Platelets>600 × 10^3/µL	4 (7.1)	9 (8.5)	1 (1.9)
ALT >3 × ULN	0	1 (0.9)	3 (5.6)
AST >3 × ULN	0	1 (0.9)	2 (3.7)
Bilirubin >2.0 mg/dL	0	2 (1.9)	0
Alkaline phosphatase >3 × ULN	0	1 (0.9)	1 (1.9)
GGT >3 × ULN	1 (1.8)	2 (1.9)	5 (9.3)
Glucose ≥20 mmol/L	0	0	1 (1.9)
Phosphate <0.52 mmol/L	1 (1.8)	0	0
Creatine kinase >5 × ULN	3 (5.4)	6 (5.7)	3 (5.6)
Sodium <130 mEq/L	1 (1.8)	0	0
Sodium >150 mEq/L	0	0	1 (1.9)
Potassium <3.0 mEq/L	1 (1.8)	0	0
Potassium >6.0 mEq/L	0	4 (3.8)	1 (1.9)

Source: Table 15.3.4.1.6.1.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IV: intravenous; LLN: lower limit of normal; PBO: placebo; SAF: safety analysis set; SC: subcutaneous; ULN: upper limit of normal; VDZ: vedolizumab.
[a] At least 1 markedly abnormal result during treatment.

Safety in special populations

AEs by Age

Pool 2: A total of 18/23 subjects (78.3%) aged ≥65 years reported an AE. In subjects aged ≥65 years, bronchitis, nausea, abdominal pain, anaemia, arthralgia, pneumonia, vomiting, cough, diarrhoea, gastroenteritis, hyponatraemia, hypertension, large intestine polyp, oedema peripheral, and urinary tract infection were reported with higher frequencies that in subjects aged <65 years. However, the small sample size of subjects aged ≥65 years precludes an appropriate comparison between the age groups.

A incidence of AEs was observed, both in pool 1 and pool 2, in subjects between 65 and 74 years of age compared to subjects younger than 65 years, in particular in the infections and infestations (54.5% vs

32.9% in pool 1 and 48.4% vs 29.9% in pool 2) and gastrointestinal disorders SOCs (36.4% vs 26.4% in pool1 and 35.5% vs 25.9% in pool 2). The analysis in subjects ≥75 years of age is hampered by the very small numbers of patients. In a new/updated safety pool (pool B) with data cut-off of 17 May 2019, including all SC-3027/SC-3031 vedolizumab SC and all SC-3030 subjects with UC or CD, AEs in the infections and infestations SOC were confirmed to be more frequent in the elderly age group (55.6% [25 of 45]) than in the adult age group (41.5% [318 of 766]), even though the difference between groups has narrowed from that observed in the previous data cut and it was not confirmed by the long-term safety study (C13008).

AEs by BMI

Pool 2: TEAEs considered related to study medication were more frequent in subjects with a BMI of ≥30 kg/m^2 (24 [25.0%]) than in subjects with a BMI of <30 kg/m^2 (96 subjects [18.6%]). In contrast, the TESAEs that lead to treatment discontinuation in subjects with a BMI of <30 kg/m^2 were greater (9 subjects [1.7%]) than in subjects with a BMI of ≥30 kg/m^2 (0). However, these differences could be due to the smaller sample size of subjects with BMI of ≥30 kg/m^2.

The incidence of TEAEs was slightly higher in subjects with BMI ≥30 kg/m^2 compared with subjects with BMI <30 kg/m^2 in the infections and infestations (40% vs 34% in pool 1 and 37.5% vs 29.6% in pool 2) and gastrointestinal disorders SOCs (42.9% vs 25% in pool 1 and 32.3% vs 25.1% in pool 2) and it was also confirmed in the newly submitted recent data pool (Pool B: infection AEs 39.3% vs 58.1%) and by the long-term safety study (C13008). Therefore, this information has been added under the section 4.8 of the SmPCs.

AEs for Subjects with Previous TNF-α Antagonist Use

Overall, a slightly higher incidence of AEs was reported in anti-TNF-α experienced subjects compared to those without previous TNF-α antagonist use both in pool 1 (57.9 events per 100 P/Y vs 49.2 events per 100 P/Y) and pool 2 (66.7 events per 100 P/Y vs 55.3 events per 100 P/Y). The most common TEAEs (≥3%) that occurred more in anti-TNF-α-experienced subjects than anti-TNF-α-naïve subjects included UC, nasopharyngitis, cough, headache, diarrhoea, influenza, oropharyngeal pain, abdominal pain, chills, haemorrhoids, nausea, and pharyngitis.

The rate of **serious infections** was higher in anti–TNFα experienced group compared to anti–TNFα naïve subjects in both pool 1 (2.3% vs 1.1%) and pool 2 (3.1% vs 1%), including no gastrointestinal serious infections such as herpes zoster, influenza, pneumonia (2 reports) and tonsillitis.

The more recent data pool (pool B) confirms a more frequently reported SAEs in the Infections and infestations SOC in the anti–TNFα–experienced subjects (4.5% [19 of 420]) than in the anti–TNFα–naïve subjects (2.8% [11 of 391]), without a specific trend, even if the difference between groups has narrowed from that observed in the previous interim data cut. Moreover, a slight difference between groups was also observed in the vedolizumab IV data from the long-term safety Study C13008 (10% vs 8%).

Immunological events

*Table 27:**AVA** Status by Injection Site Reactions – Safety Population (SC-3027)*

AEs Defined as Injection Site Reactions (Yes/No) AVA Status	Induction IV + Placebo [a] N = 56	Induction IV + Vedolizumab SC 108 mg N = 106	Induction IV + Vedolizumab IV 300 mg N = 54
At least 1 non-missing AVA sample	56	105	53
Yes			
N	0	11 [b]	1
AVA negative (%)	0	10 (90.9) [b]	1 (100)
AVA positive (%)	0	1 (9.1) [b]	0
Transiently AVA positive (%)	0	1 (9.1) [b]	0
Persistently AVA positive (%)	0	0	0
Positive neutralizing AVA (%)	0	0	0
No			
N	56	94 [c]	52
AVA negative (%)	40 (71.4)	91 (96.8) [c]	49 (94.2)
AVA positive (%)	16 (28.6)	3 (3.2) [c]	3 (5.8)
Transiently AVA positive (%)	2 (3.6)	2 (2.1) [c]	0
Persistently AVA positive (%)	14 (25.0)	1 (1.1) [c]	3 (5.8)
Positive neutralizing AVA (%)	12 (21.4)	1 (1.1) [c]	3 (5.8)

AE: adverse event; AVA: anti-vedolizumab antibodies; IV: intravenous; SC: subcutaneous.

[a] Subjects received 2 doses of vedolizumab and were randomized to placebo at Week 6.

[b] Total includes 1 additional subject (31002-102) who had AEs originally reported as infusion-related reactions. A review of these events suggested that they were actually injection site reactions, and this subject tested negative for AVA; thus, this subject is included in this summary. Refer to SC-3027 CSR Sections 12.2.3.3.2.2 and 12.2.3.3.2.3 for additional information.

[c] The total number of subjects without injection-site reactions has been reduced by 1. This has been done to account for a subject with AEs that were originally reported as infusion reactions but were later determined to be injection site reactions. See footnote b for additional information.

*Table 28:**AVA Status by Hypersensitivity Reactions – Safety Population (SC-3027)***

Adverse Events Defined as Hypersensitivity Reactions (Yes/No) AVA Status	Induction IV + Placebo [a] N = 56	Induction IV + Vedolizumab SC 108 mg N = 106	Induction IV + Vedolizumab IV 300 mg N = 54
At least 1 non-missing AVA sample	56	105	53
Yes			
N	2	16	7
AVA negative (%)	2 (100.0)	16 (100.0)	7 (100.0)
AVA positive (%)	0	0	0
Transiently AVA positive (%)	0	0	0
Persistently AVA positive (%)	0	0	0
Positive neutralizing AVA (%)	0	0	0
No			
N	54	89	46
AVA negative (%)	38 (70.4)	85 (95.5)	43 (93.5)
AVA positive (%)	16 (29.6)	4 (4.5)	3 (6.5)
Transiently AVA positive (%)	2 (3.7)	3 (3.4)	0
Persistently AVA positive (%)	14 (25.9)	1 (1.1)	3 (6.5)
Positive neutralizing AVA (%)	12 (22.2)	1 (1.1)	3 (6.5)

AVA: anti-vedolizumab antibodies; IV: intravenous; SC: subcutaneous; TEAE: treatment-emergent adverse event.
Hypersensitivity TEAE criteria include Standardised Medical Dictionary for Regulatory Activities Queries for anaphylactic/anaphylactoid shock conditions, angioedema, and hypersensitivity.
[a] Subjects received 2 doses of vedolizumab and were randomized to placebo at Week 6.

Safety related to drug-drug interactions and other interactions

Vedolizumab is an antibody and does not modulate cytokine production; therefore, the potential to directly affect or be affected by cytochrome P450 enzymes is low. The potential for vedolizumab to be affected by other drugs commonly used to treat the IBD (azathioprine, methotrexate, 6-mercaptopurine, and aminosalicylates) was assessed through population PK modeling using data from phase 3 studies. Immunomodulator coadministration was not a predictor of clearance for vedolizumab. No dedicated drug-drug interaction studies were conducted before, or since, the IV submission.

Discontinuation due to adverse events

Study SC-3027

*Table 29:**AEs Leading to Study Discontinuation by SOC and PT (SAF)***

Primary SOC PT	Placebo N = 56 n (%)	VDZ SC 108 mg N = 106 n (%)	VDZ IV 300 mg N = 54 n (%)	Total N = 216 n (%)
Subjects with at least 1 AE leading to discontinuation of study drug	5 (8.9)	5 (4.7)	2 (3.7)	12 (5.6)
Gastrointestinal disorders	5 (8.9)	4 (3.8)	1 (1.9)	10 (4.6)
Colitis ulcerative	5 (8.9)	4 (3.8)	1 (1.9)	10 (4.6)
Injury, poisoning and procedural complications	0	0	1 (1.9)	1 (0.5)
Craniocerebral injury	0	0	1 (1.9)	1 (0.5)
Clavicle fracture	0	0	1 (1.9)	1 (0.5)
Scapula fracture	0	0	1 (1.9)	1 (0.5)
Road traffic accident	0	0	1 (1.9)	1 (0.5)
Rib fracture	0	0	1 (1.9)	1 (0.5)
Investigations	0	1 (0.9)	0	1 (0.5)
Alanine aminotransferase increased	0	1 (0.9)	0	1 (0.5)
Gamma-glutamyl transferase increased	0	1 (0.9)	0	1 (0.5)
Blood alkaline phosphatase increased	0	1 (0.9)	0	1 (0.5)

Source: Table 15.3.1.6.1.
AE: adverse event; IV: intravenous; SC: subcutaneous; PT: Preferred Term; SOC: System Organ Class; VDZ: vedolizumab.

Study SC-3031

The overall incidence of AEs leading to study **discontinuation** was 22 of 409 subjects (5.4%); of these 22 subjects, 10 discontinued because of CD disease worsening or exacerbation. This was higher in the placebo group than in the vedolizumab SC group (placebo: 7 subjects, 5.2%; vedolizumab SC: 3 subjects, 1.1%). Four of the remaining 12 subjects who discontinued study medication were in the placebo group. The remaining 8 subjects in the vedolizumab SC group discontinued the study because of ileal stenosis and abscess intestinal (both in 1 subject), anal fistula (2 subjects), subileus, blood creatinine increased, lymphopenia, white blood cell count increased, and hypersensitivity.

Pool 2

A total of 17 subjects (2.8%) discontinued from the studies included in Pool 2 because of a TEAE. UC and CD were the most common reason for discontinuation (11 subjects, 1.8%). Anaemia in 2 subjects (0.3%) and arthralgia, increased alanine aminotransferase, increased gamma-glutamyl transferase, increased blood alkaline phosphatase, B-cell lymphoma and diffuse large B-cell lymphoma, rapidly progressive glomerulonephritis, and headache (1 subject each) were the other reasons for discontinuation.

In total, **9** subjects (1.5%) were withdrawn from study treatment because of a **TRAE** mainly due to UC (4 subjects, 0.7%) and CD (2 subjects, 0.3%). The remaining 3 subjects discontinued treatment because of **arthralgia** (1 subject), **headache** (1 subject), and **increased alanine aminotransferase,** gamma-glutamyl transferase increased and blood alkaline phosphatase increased (1 subject).

Post marketing experience

There is no post-marketing experience with vedolizumab SC.

2.6.1. Discussion on clinical safety

The safety profile of subcutaneous vedolizumab is based on data from the pivotal phase 3 study SC-3027 in UC patients and the ongoing Study SC-3030 (OLE study from parent Studies SC-3027 [UC] and SC-3031 [CD]), which are presented in pool 1, including data only from UC patients, and pool 2, including data from both UC and CD patients (the latter only from the OLE Study SC-3030), supporting, the assessment of long term vedolizumab SC safety profile. Safety data from Study SC-3031 in subjects with CD have been provided within the responses to D120 LoQ.

Across studies SC-3027 and SC-3030 (Pool 2), most subjects [523 (85.3%)] were exposed to vedolizumab SC for ⩾6 months and only 44.5% of subjects were exposed for ⩾12 months. Updates on long term safety from the long-term study 3030 OL will be provided post authorisation as outlined in the RMP. Most patients were male, white and <65 years old. Previous therapies included corticosteroids and immunomodulators for more than half of subjects and TNF-α antagonist in 42% and 52% of subjects, respectively, in pool 1 and 2. Overall, demographic and disease baseline characteristics seem to be well balanced among placebo and treatment arms in Study SC-3027.

About 60% of subjects in Study SC-3027 SC group, pool 1 and pool 2 experienced TEAEs. The spectrum of vedolizumab SC AEs seems to be overall similar to that reported for vedolizumab IV formulation. The most frequently reported TEAE in Study SC-3027 was colitis ulcerative, which however was most common in the placebo arm. The next most common AEs were nasopharyngitis, headache, anaemia, and upper respiratory tract infection. The incidence of AEs between the vedolizumab SC and vedolizumab IV groups was generally similar, even if some differences were noted between the groups (for example, headache was reported in the 8.5% of subjects in the vedolizumab SC group but none in the IV group and upper respiratory tract infections was reported in the 9.4% of the SC group and 3.7% of the vedolizumab IV group), probably by chance. TEAEs did not changed in the long time, with reference to type and frequency, as observed in pool 1. Moreover, no clinically significant differences were observed between pool 1 and pool 2, where also CD patients were included, apart from a slightly higher incidence of abdominal pain and bronchitis (respectively, 4 and 3 events/100 patients-year in pool 1 compared to 2.3 and 1.7 events/100 patients-year in pool 2).

Most of the events were mild or moderate in intensity, however severe events were more frequent in vedolizumab SC arm (5.7%) compared to vedolizumab IV (1.9%) arm, but similar to placebo (5.4%). The majority of the severe cases in the vedolizumab SC groups were in the SOC of gastrointestinal disorders mostly due to UC, suggesting a potential lack of efficacy in about 5% of subjects in placebo and 3.8% of subjects in SC groups (refer also to efficacy section), which has not been observed in vedolizumab IV group. From Study SC-3031, 73.5% of CD subjects, compared to 76.1 of subjects in the PLB arm, experienced TEAEs of which the majority were mild or moderate in intensity (32.8% and 34.3% of subjects, respectively for placebo and 32.4% and 36.0%, respectively for vedolizumab SC).

Related TEAEs were observed in a higher rate of subjects in vedolizumab SC arm (26.4%) compared to placebo (17.9%) and vedolizumab IV (16.7%) arms in Study SC-3027. The majority of these events were in gastrointestinal disorders (5.6%), infections and infestations (5.6%), and general disorders and administration site conditions (6%) SOCs and the difference in TREAEs between SC and IV administration seems to be driven mainly by GI disorders (7.5% and 1.9% in vedolizumab SC and IV, respectively) and general disorders and administration site conditions (10.4% vs 1.9%, respectively). In the latter case it was expected due in particular to Injection site reactions. A higher percentage of CD subjects in Study SC-3031 had drug-related AEs in the vedolizumab SC group (19.3%) than in the placebo group (14.9%), mainly due to injection-site reactions, all of which were considered drug related in the vedolizumab SC group. In pool 1 and pool 2 a similar rate of subjects reported TRAEs (25.4% and 20%, respectively) with the most frequent being Colitis Ulcerative followed by injection site reactions and injection site erythema.

SAEs were reported in about 10% of subjects in the SC-3027 study and 8.4% of subjects in SC-3031 study, as well as in pool 1 and pool 2, with a similar frequency across groups. Gastrointestinal disorders by SOC, with UC by PT, was the most common reported TESAEs in SC-3027 study as well as in pool 1 and 2. Anaemia was also reported, with a similar incidence between the vedolizumab SC and placebo groups. Overall, 9 subjects in pool 2 experienced treatment-related SAEs. One death was reported during Study SC-3030 (pulmonary embolism) considered not related to study treatment by the investigator.

Overall, 127 subjects (41.9%) in Pool 1 reported an AESI of which Infections were the most common AESI (34.7%), followed by hypersensitivity reactions (13.2%) and injection site reactions (7.6%). A similar picture was observed in pool 2 with only a slight major number of liver injury increase (1.8 events P/Y) compared to pool 1 (1.1 events P/Y).

Infections: In Study SC-3027 infections were reported with a similar frequency across arms (35.7%, 36.8%, and 37.0% in the placebo, vedolizumab SC, and vedolizumab IV groups, respectively) with the most frequent being in the HLT of upper respiratory tract infections. Similar percentages were reported in CD subjects from SC-3031 Study. In the vedolizumab SC group, the most common PTs of infections were nasopharyngitis (10.4%) and upper respiratory tract infections (9.4%). Upper respiratory tract infection (as PT) and pneumonia were reported with a higher frequency of subjects in SC group (9.4% and 2.8%, respectively) compared to placebo (1.8% each) and the IV (3.7% and 1.9%) groups. However, infections were reported as related AEs only in 4 patients (3.8%) in the vedolizumab SC group (anal abscess, nasopharyngitis, pneumonia and ear infection, 0.9% each). No increases of frequencies in infections and infestations were observed in the long-term safety evaluation as reported in pool 1. In pool 2, bronchitis occurred more frequently, suggesting a possible higher incidence in CD patients. The majority of infections were mild or moderate in intensity and 2 subjects (0.7%) had severe infections. In Study SC-3031 2 infection AESIs led to discontinuation of study participation in the vedolizumab SC group, of which one was considered related to treatment (anal abscess). Treatment-related AEs of infections in the vedolizumab SC group from Study 3031 included abscess intestinal, anal abscess, Clostridium difficile infection, tongue fungal infection, bronchitis, pneumonia, tinea versicolour, nasopharyngitis, sinusitis, and upper respiratory tract infection (each in 1 subject, 0.4%). Treatment-related infection SAEs were reported in 2 subjects in Pool 2, including 1 subject each with Clostridium difficile infection and influenza. Overall, ADRs of infections and infestations are already reflected in the SmPC including SAEs of infection.

Malignancies: Overall, six subjects in pool 2 (three UC patients and three CD patients) experienced TEAEs in the SOC of neoplasms benign, malignant and unspecified. However, they were considered all not to be related to study treatment by the investigators. A wording on malignancies is included in 4.4 and 4.8 sections of the SmPC.

Hypersensitivity: 11.6% of subjects in Study SC-3027 and 9% in Study SC-3031 experienced at least 1 hypersensitivity TEAE. These AEs were more common in the vedolizumab-treated groups than in subjects treated with placebo and were comparable between the vedolizumab SC and IV groups (15.1% vs 13.0%, respectively). There was no case of anaphylaxis or severe allergic reaction. The most common reported TEAEs of hypersensitivity were in the SOC of skin and subcutaneous tissue disorders, which occurred more frequently in vedolizumab arms (9.4% and 13% in SC and IV vedolizumab arm, respectively) than in the placebo arm. Hypersensitivity reactions in the SOC of General disorders and administration site conditions (peripheral swelling, injection site rush and oedema peripheral by PT) were reported in vedolizumab SC group. Injection site reactions were reported also in Pool 1 (7.6% of subjects; 6.6 events per 100 P/Y) and pool 2 (4.7% of subjects; 4.8 events per 100 P/Y) with the most frequent event being Injection site erythema (2.3 and 1.8, respectively). Injection site reactions have been added and described in 4.8 section of the SmPC which is agreed, and some examples of injections site reactions have been added.

Liver injury: 2 subjects in vedolizumab SC group in Study SC-3027 and 4 subjects in pool 1 reported liver injury AESIs. The number increased in pool 2, where 11 subjects (1.8%) experienced liver injury with the most frequently reported AEs being gamma-glutamyl transferase increased (5 subjects [0.8%]). Severe TEAEs of alanine aminotransferase increased, gamma-glutamyl transferase, and blood alkaline phosphatase increased occurred in a single subject. Moreover, in pool 2 alanine aminotransferase increased and LFT increased in 2 subjects each, and hyperbilirubinemia, aspartate aminotransferase increased, gamma-glutamyl transferase increased, and hepatic enzyme increased in 1 subject each were considered related to the study treatment. At the request of the PRAC, a cumulative review of vedolizumab liver injury reports has been conducted by the Applicant, retrieving 438 case reports (530 AEs). However, for the 66.4% of these the causal association was in doubt due to the presence of confounding factors. This analysis was accepted by the PRAC and that liver injury cases will be further monitored with no request to include liver injuries in the product SmPC at this stage (Reference: EMA/PRAC/ 369233/2018).

PML: There were no subjects diagnosed with PML.

No clinically relevant differences between the treatment groups and across pooling in mean changes from baseline at any time point were observed for any hematology and chemistry parameter. However, decreased red blood cells, hemoglobin, and hematocrit were reported in some subjects in the vedolizumab SC group of Study SC-3027, Pool 1, and Pool 2. In particular, in Study SC-3027 was observed a marked reduction in hemoglobin in a slightly higher rate of subjects in vedolizumab SC group (13.2%) than in placebo (8.9%) and vedolizumab IV (7.4%) groups. Moreover, increased platelet counts were also more common in vedolizumab SC group (8,5%) than in placebo (7.1%) and in vedolizumab IV (1.9%) groups. However, no AEs related to abnormal coagulation were reported in these subjects. As stated by the Applicant, anaemia may be due to disease under study and thrombocytosis may be due to ongoing inflammation. Moreover, absolute lymphocyte counts <0.5 × 109/L has been observed in 2.6% of combined Study SC-3027 and SC-3030 subjects, and in 1.1% of Study SC-3031 subjects. However, at present a causal association between the reduction lymphocyte counts <0.5 × 109/L and the occurrence of infections has not been demonstrated.

A slightly higher frequency in the most common reported TEAEs (SOCs of infections and GI disorders) were noted in the elderly as well as in subjects with BMI ≥30 kg/m2.

Overall, a slightly higher incidence of AEs was reported in anti-TNF-α experienced subjects compared to those without previous TNF-α antagonist use both in pool 1 (57.9 events per 100 P/Y vs 49.2 events per 100 P/Y) and pool 2 (66.7 events per 100 P/Y vs 55.3 events per 100 P/Y). The most common TEAEs (≥3%) that occurred more in anti-TNF-α-experienced subjects than anti-TNF-α-naïve subjects included UC, nasopharyngitis, cough, headache, diarrhoea, influenza, oropharyngeal pain, abdominal pain, chills, haemorrhoids, nausea, and pharyngitis. Even though the small number of serious infection events makes difficult to drawn firm conclusion, a higher frequency of serious infections in anti–TNFα–experienced (rate of serious infections in pool 1: 2.3% and pool 2: 3.1%) compared to anti–TNFα–naïve subjects (pool 1: 1.1% and pool 2: 1%), was noted and confirmed in the more recent data pool (pool B) as well as in the vedolizumab IV data from the long-term safety Study C13008 (10% vs 8%). At present there is not sufficient evidence for the inclusion of a warning in 4.4 section of the SmPC advising on the higher potential risk of serious infection in the anti–TNFα–experienced population with vedolizumab use. However, information on this slightly higher incidence of serious infection was included in 4.8 section of the SmPC. Moreover, the Applicant states that will continue to monitor TEAEs of infections in the ongoing long-term safety study (SC-3030) and this is agreed.

Vedolizumab SC safety profile seems to be not negatively influenced by AVA positivity with regard to hypersensitivity reactions and injection site reactions.

Discontinuation due to AEs in Study SC-3027 occurred more frequently in the placebo group than in either vedolizumab group (placebo: 8.9%; vedolizumab SC: 3.8%; vedolizumab IV: 1.9%), because of UC disease worsening or exacerbation in the majority of cases. One subject (from the vedolizumab SC group) discontinued because of a severe, nonserious AE of increased liver enzymes, which was considered by the investigator as related to the study drug. The overall incidence of AEs leading to study discontinuation in Study SC-3031 was 22 of 409 subjects (5.4%); of these 22 subjects, 10 discontinued because of CD disease worsening or exacerbation. This was higher in the placebo group than in the vedolizumab SC group (placebo: 7 subjects, 5.2%; vedolizumab SC: 3 subjects, 1.1%). 8 subjects in the vedolizumab SC group discontinued the study because of ileal stenosis and abscess intestinal (both in 1 subject), anal fistula (2 subjects), subileus, blood creatinine increased, lymphopenia, white blood cell count increased, and hypersensitivity.

In pool 1 and pool 2 there was not an increase of discontinuation and the reasons were for the most part UC and CD and anemia.

From the D120 responses the MAH completed the second interim analysis of the long-term Study SC-3030, which seems to not show new safety signals compared to the previous analysis. Overall, the incidence of the majority of TEAEs were similar between UC and CD populations, even if some imbalances in frequency presentation were observed. The exposure–adjusted incidence rates for the most common TEAEs, decreased within the UC population and were quite similar (or slightly increased in some cases) for the CD population.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of vedolizumab SC as maintenance treatment in UC and CD subjects seems to be in line to that of IV administration, with nasopharyngitis, headache, anaemia, and upper respiratory tract infection being the most common AEs. However, injection site reactions were reported more frequently with SC administration, as expected, and therefore have been included in 4.8 of the SmPC. No clinically significant differences were noted between pool 1 and pool 2.

2.7. Risk Management Plan

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infusion-Related Reactions, Including Hypersensitivity Reactions	**Routine risk minimisation measures:** SmPC section 4.8 SmPC section 4.2 where advice is given on monitoring during and after infusion SmPC section 4.4 where advice is given on monitoring for acute hypersensitivity and infusion-related reactions PL sections 2 and 4	**Additional pharmacovigilance activities:** MLN-0002_401

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Upper Respiratory Tract Infections	**Routine risk minimisation measures:** SmPC section 4.8 PL section 4	**Additional pharmacovigilance activities:** MLN-0002_401

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infections: Gastrointestinal Infections and Systemic infections (Serious and Nonserious) Against Which the Gut Constitutes a Defensive Barrier Other Serious Infections, Including Opportunistic Infections Such as PML	**Routine risk minimisation measures:** SmPC section 4.8 SmPC section 4.4 where advice is giving on monitoring for infections and PML PL sections 2 and 4 **Additional risk minimisation measures:** Patient Alert Card Healthcare Professional Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for PML **Additional pharmacovigilance activities:** MLN-0002_401

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancies	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8	**Additional pharmacovigilance activities:** MLN-0002_401

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Liver Injury	**No risk minimisation measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for hepatic adverse events **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in Pregnancy and Lactation	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3	**Additional pharmacovigilance activities:** MLN-0002_401

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term Safety	**No risk minimisation measures**	**Additional pharmacovigilance activities:** MLN-0002_401 MLN0002SC-3030

Conclusion

The CHMP and PRAC considered that the risk management plan version 5.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

Please refer to the PI attachment. Apart from the addition of the new formulation changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guidelines [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Within this line extension the MAH is seeking approval for the Vedolizumab subcutaneous Solution for Injection in Pre-filled Syringe as a new liquid formulation for the treatment of Ulcerative Colitis and Crohn's Disease in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. 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.

3.1.2. Available therapies and unmet medical need

Vedolizumab intravenous (IV) is currently approved 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.

Subcutaneous vedolizumab has now been developed for the maintenance treatment of the same patient population for which vedolizumab IV is already approved.

Pharmacological treatments with SC routes of administration provide convenience for patients, HCPs, and caregivers by removing the time, logistics, and burden required for IV infusion.

At present there are alternative SC therapies available for vedolizumab second line indication.

3.1.3. Main clinical studies

The development program consists of pivotal study MLN0002SC-3027 and a roll-over long-term study MLN0002SC-3030. Furthermore, in support of the indication in Crohns Disease data from ongoing study MLN0002SC-3031 were provided.

MLN0002SC-3027: The efficacy and safety of subcutaneous vedolizumab for the treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopic sub score ≥ 2) was demonstrated in a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at week 52. Enrolled patients had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

The primary study endpoint clinical remission was defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point at 52 weeks in patients who had achieved a clinical response at week 6 of intravenous vedolizumab induction treatment. Clinical response was defined as a reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 2 points and no individual subscore >1 point.

Patients who achieved clinical response to open-label treatment with intravenous vedolizumab at week 6 were eligible to be randomised. For the evaluation of the week 52 endpoints, patients were randomised and treated in a double-blind fashion (2:1:1) to 1 of the following regimens: subcutaneous vedolizumab 108 mg every 2 weeks, intravenous vedolizumab 300 mg every 8 weeks, or placebo.

Study MLN0002SC-3031 is a phase 3, randomized, double-blind, placebo-controlled study in CD patients, which is currently ongoing and for which data from the week 52 database lock have been analyzed and presented within this submission in support of the CD indication.

Patients who completed study MLN0002SC-3027 or study MLN0002SC-3030 were eligible to enrol in the ongoing, open-label extension study MLN0002SC-3031 to evaluate long-term safety and efficacy of subcutaneous vedolizumab treatment in patients with ulcerative colitis or Crohn's disease. The duration of vedolizumab SC treatment in this study will vary by subject based on continued benefit, for up to a maximum of 5 years. An interim clinical study report (CSR) for SC-3030, based on a 17 May 2019 data cut-off date, was provided with this submission

3.2. Favourable effects

Remission/response in UC:

A statistically significant and clinically meaningful gain in clinical remission rate (defined as a complete Mayo score of ⩽2 points and no individual sub-score >1 point at Week 52) was shown for vedolizumab SC subjects (46.2%) compared to placebo subjects (14.3%).Clinical remission at week 52 was slightly higher in subjects randomized to vedolizumab SC 108mg Q2W than in the vedolizumab IV 300mg Q8W (32.3% versus 27.9%).

Results were confirmed by all sensitivity analyses as well as by an exploratory analysis using FDA modified definitions, and PPS analysis.

In addition, all subgroup analyses of clinical interest (i.e. baseline disease activity, naïve versus prior anti-TNF alpha failure) favoured VDZ over PLB. In particular, vedolizumab SC was proved effective both in anti-TNF-alpha naïve as well as in anti-TNF-alpha failed patients, although the magnitude of the effect was higher in the anti-TNF-alpha naïve subjects.

The durability of the effect in UC was explored by different endpoints, being the treatment meant for chronic use and for an autoinflammatory/autoimmune disease. Results on durable (both Weeks 6 and 52) clinical response (according to total Mayo score) confirmed the statistical superiority of VDZ SC over PLB (vedolizumab SC subjects 64.2% compared with subjects who received placebo 28.6%; difference from placebo 36.1%. Vedolizumab IV showed slightly higher results to vedolizumab SC (44.5% versus 36.1%).However, only a positive trend (15.1% VDZ SC vs 5.4% PLB), suggestive of a better performance over placebo, was shown for vedolizumab SC on the more stringent endpoint, durable remission defined as complete Mayo score of ⩽2 points and no individual sub-score >1 point at both Weeks 6 and 52). Vedolizumab SC showed a similar increase in the difference from placebo as vedolizumab IV (9.7% and 11.3%, respectively).

A statistically higher proportion of subjects treated with vedolizumab SC was also observed in favour of vedolizumab for the exploratory endpoints of the proportion of subjects who were in clinical remission (according to Partial Mayo Scores) in at least 80%/60% of clinic visits.

The superiority of VDZ SC versus PLB was also confirmed by endoscopic data (Mucosal healing, a Mayo endoscopic sub-score of ⩽1 point at week 52), and further supported by calprotectin data showing reduced inflammation following vedolizumab SC treatment.

Overall, in patients with UC, results obtained with Vedolizumab SC treatment were similar to those achieved with vedolizumab IV treatment.

Remission/response in CD:

The primary endpoint clinical remission at Week 52, was met (VDZ 48.0% vs PLB 34.3%, respectively [adjusted treatment difference 13.7%; 95% CI, 3.8, 23.7, p = 0.008]), with a similar treatment difference in GEMINI 2 (17%, PLB 22 and VDZ Q8W 39%). When a more stringent evaluation of remission (durable defined as remission at week 6 and 52) was considered the difference between PLB and VDZ SC arms was rather limited (5.6%).

However, evaluation of corticosteroid-free remission at Week 52 demonstrated an effect of vedolizumab SC over placebo (vedolizumab SC, 45.3%; placebo, 18.2%; adjusted difference from placebo 27.1% [95% CI, 11.9, 42.3]; nominal p = 0.002).

Reduction in inflammatory markers was observed for fecal calprotectin (increase of subjects having ⩽ 250mg/g as compared to higher cut-off levels) but not for CRP reduction in subjects having high CPR level at baseline (⩾2.87mg/L). A positive trend in favour of vedolizumab was reported for some PROs and HQL measures.

3.3. Uncertainties and limitations about favourable effects

UC

Corticosteroid sparing effect in UC is considered an important although difficult achievement in these patients. Approximately 41.7% of the FAS subjects were on corticosteroids at baseline. Corticosteroid-free clinical remission (based on the complete Mayo score at Week 52) showed only numerically higher rates in VDZ SC with a treatment difference of 20.6 from placebo. A similar treatment difference from placebo was observed for the vedolizumab IV group (20.2). Similar results were seen using the proportion of subjects who achieved clinical remission and were corticosteroid free for 90 or for 180 days.

More mature data on the **long-term maintenance** of the effect (after 52 weeks) are at present available from the 5-year 3030 study in the UC indication, supporting a favourable trend.

CD

The first secondary efficacy endpoint, **enhanced clinical response**, was not statistically significant; placebo response is very high (44.8%) resulting in a very limited difference between the two arms (treatment difference 7.3 p=0.167). In the GEMINI 2 the treatment difference was higher (14%) and a PLB response of 30%. For the second (corticosteroid-free clinical remission) and third (clinical remission at Week 52 in TNF-α antagonist naïve subjects) secondary endpoints nominal p-values are reported.

Evaluation of the key secondary endpoint of corticosteroid-free remission at Week 52 suggested an effect of vedolizumab SC over placebo (vedolizumab SC, 45.3%; placebo, 18.2%; adjusted difference from placebo 27.1% [95% CI, 11.9, 42.3]; nominal p = 0.002). However, the very limited number of subjects achieving the endpoint in the PLB arm (8 subjects) together with the outlier result (lower compared to the other ones having roughly 30-40%) makes it difficult to draw a firm conclusion.

Looking at the endpoint of **clinical remission at Week 52 in the tumor necrosis factor-alpha (TNF-α) antagonist naïve subject population** (third secondary endpoint, 50% of the enrolled population) again a very high PLB response is observed leading to very limited treatment difference (42.9% PLB and 48.6% VDZ, treatment difference 4.3). In subjects with prior antiTNF-alpha failure a larger difference is seen (VDZ 45.4 PLB 28.8 difference 17.6%) due to a lower PLB response while a very similar response is seen in the treatment arm.

A high PLB response is seen across different endpoints negatively impacting the treatment difference and therefore study results. However, the subjective nature of CDAI as endpoint is acknowledged and heterogeneity of placebo response is seen across trials using drugs for the treatment of IBD and is reported in literature.

Overall, efficacy in Crohn's disease appears similar for Entyvio SC and Entyvio IV (in particular for the primary endpoint and indirect comparison) as compared to Ulcerative Colitis.

3.4. Unfavourable effects

The spectrum of vedolizumab SC AEs seems to be overall similar to that reported for vedolizumab IV formulation.

The most frequently reported TEAE in Study SC-3027 was ulcerative colitis, which however was most common in the placebo arm. The next most common AEs were nasopharyngitis, headache, anaemia, and upper respiratory tract infection. Overall, type and frequency of TEAEs seem to not change in the long term. In Study SC-3031 the overall percentage of most-frequently reported (≥5%) AEs was similar in the placebo and vedolizumab SC groups (41.8% and 39.3%, respectively). Nasopharyngitis, upper respiratory tract infection, and headache were more common in the vedolizumab SC treatment group than in the placebo group, while nausea, vomiting, and abdominal pain were more common in placebo group than in the vedolizumab SC group.

In Study SC-3027 most of the events were mild or moderate in intensity, however severe events were more frequent in vedolizumab SC arm (5.7%) compared to vedolizumab IV (1.9%) arm, but similar to placebo (5.4%) and the majority were in the SOC of gastrointestinal disorders mostly due to UC. Related TEAEs were observed in a higher rate of subjects in vedolizumab SC arm (26.4%) compared to placebo (17.9%) and vedolizumab IV (16.7%) arms. The difference in TREAEs between SC and IV administration seems to be driven mainly by GI disorders (7.5% and 1.9% in vedolizumab SC and IV, respectively),

and injection site reactions and general disorders (10.4% SC vs 1.9% IV). However, the provided evidence does not allow to draw firm conclusions and a specific wording in the SmPC is at present not required.

In Study Sc-3031 a higher percentage of subjects had drug-related AEs in the vedolizumab SC group (19.3%) than in the placebo group (14.9%), mainly due to injection-site reactions. Infections and infestations, malignancies, hypersensitivity, liver injury and PML are confirmed AESIs and defined risks in the RMP. There were no subjects diagnosed with PML.

3.5. Uncertainties and limitations about unfavourable effects

Some differences in AEs were noted between anti-TNF-α-experienced subjects and anti-TNF-α-naïve subjects, in particular for serious infections which were slightly higher in anti–TNFα–experienced (rate of serious infections in pool 1: 2.3% and pool 2: 3.1%) compared to anti–TNFα–naïve subjects (pool 1: 1.1% and pool 2: 1%) as also confirmed in the more recent data pool (pool B) as well as in the vedolizumab IV data from the long-term safety Study C13008 (10% vs 8%). At present there is not sufficient evidence for the inclusion of a warning in 4.4 section of the SmPC advising on the higher potential risk of serious infection in the anti–TNFα–experienced population with vedolizumab use. However, information on this slightly higher incidence of serious infection was included in 4.8 section of the SmPC. Moreover, the Applicant will continue to monitor TEAEs of infections in the ongoing long-term safety study (SC-3030) as outlined in the RMP.

3.6. Effects Table

Effects Table for Vedolizumab s.c. in the treatment of Ulcerative Colitis and Crohn's disease

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical remission	complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52	Proportion of Subjects	46.2%	14.3%	Well supported by results obtained using different definitions	Pivotal study
Durable clinical response	Durable (both Weeks 6 and 52) clinical response (according to total Mayo score)	Proportion of Subjects	64.2%	28.6%	Well supported	Pivotal study
Mucosal healing	Mayo endoscopic subscore of ≤1 point) at week 52	Proportion of Subjects	56.6%	21.4%	Well supported	Pivotal study

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Durable clinical remission	Durable (both Weeks 6 and 52) clinical remission (according to total Mayo score)	Proportion of Subjects	15.1%	5.4%	Not statistically significant. However, supported by durable remission results calculated using the partial Mayo score and remission in 60% or 80% of study visits	Pivotal study
Corticosteroid-free clinical remission	subjects using oral corticosteroids at baseline who had discontinued oral corticosteroids and were in clinical remission based on the complete Mayo score at Week 52	Proportion of Subjects	8.3%	28.9%	Not statistically significant. Study limitations.	Pivotal study
Unfavourable Effects						
Injection site reactions including hypersensitivity	Injection site erythema, swelling, pruritus, rash, bruising, haematoma, pain	Proportion of Subjects	4.7% (pool 2)		Proposed as an important identified risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab SC clinical development program.	Safety database
Upper Respiratory Tract Infections	Study SC-3027: In the vedolizumab SC group the most common PTs of infections were nasopharyngitis (10.4%) and upper respiratory tract infections (9.4%).	Proportion of Subjects	pool 2: 1% among treatment-related infections		Upper respiratory tract infections are an important identified risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab SC clinical development program.	Safety database

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The availability of a SC formulation for vedolizumab is considered an important favourable effect, particularly in the maintenance therapy, as it decreases the burden for IV infusion.

UC indication:

Overall the efficacy of vedolizumab SC in the sought UC indication is considered sufficiently demonstrated and characterised as substantially similar to vedolizumab IV. No statistically significant difference was observed for corticosteroid sparing effect by VDZ SC, which is acceptable, considering that a particularly difficult-to-treat patient population is targeted by the drug. Maintenance of the effect in the long-term, after 52 weeks of treatment, is at present poorly characterised but not required for this marketing authorisation; a dedicated 5-year study is currently on-going and the MAH will report on this study as defined in the RMP. The safety profile of the SC formulation is clinically manageable and substantially similar to that already known for the IV formulation, with the exceptions of injection-site reactions that are obviously related to the route of administration, and GI disorders that are numerically higher with the SC formulation compared to IV, but a potential less optimal control of the UC pathology compared to the IV formulation is not further supported by efficacy data.

CD indication

Overall vedolizumab SC showed efficacy in the sought CD indication. A high PLB response across different endpoints was apparent, negatively impacting the difference in treatment effect between arms (Vedolizumab versus background therapy corticosteroids and immunomodulators). The added benefit of vedolizumab SC over background therapy is limited, although in line with what observed with the IV formulation, in particular for the primary endpoint.

Overall, the safety profile of vedolizumab SC in CD patients from Study 3031 seems to be consistent with that observed in UC subjects from Study SC-3027 and that already known from vedolizumab IV administration.

3.7.2. Balance of benefits and risks

The benefits observed with the SC formulation of vedolizumab in the UC and CD indications (patients who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist) outweigh the risks specific to this route of administration which are considered manageable with routine pharmacovigilance measures.

3.8. Conclusions

The overall B/R of Entyvio is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Entyvio 108 mg solution for injection for subcutaneous use is favourable in the following indications:

Ulcerative colitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's disease

Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Entyvio subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Entyvio are provided with a physician pack containing the following:

• Summary of Product Characteristics and Package Leaflet

• Physician's Educational Material

• Patient alert card,

The **Educational Material** for physicians should contain the following key messages:

- Consider the patient's full medical history, including any prior or concurrent biological medicine use
- There is no clinical trial experience with Entyvio in patients previously treated with natalizumab. Given the known risk of PML development in patients with previous natalizumab exposure, physicians should normally wait 12 weeks after the last natalizumab dose prior to initiating Entyvio treatment.
- Patients treated with Entyvio should be monitored for any new onset or worsening of neurological signs and symptoms such as those listed below:

  o Progressive weakness on one side of the body or clumsiness of limbs

  o Disturbance of vision

  o Changes in thinking, memory, and orientation, leading to confusion and personality changes
- Any patients with new onset or worsening signs and symptoms suggestive of PML should be considered for neurological referral at a center equipped to diagnose PML.