



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 March 2014
EMA/CHMP/676643/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entyvio

International non-proprietary name: vedolizumab

Procedure No.: EMEA/H/C/002782/0000

Note

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



Product information

Name of the medicinal product:	Entyvio
Applicant:	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup Denmark
Active substance:	vedolizumab
International Nonproprietary Name	vedolizumab
Pharmaco-therapeutic group (ATC Code):	L04AA33
Therapeutic indication(s):	<ul style="list-style-type: none"> - 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. - 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.
Pharmaceutical form:	Powder for concentrate for solution for infusion
Strength:	300 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

Table of contents

1. Background information on the procedure	7
1.1. Submission of the dossier	7
1.2. Manufacturers	8
1.3. Steps taken for the assessment of the product	8
2. Scientific discussion	9
2.1 Introduction	9
2.2 Quality aspects	15
2.2.1 Introduction	15
2.2.2 Active Substance	16
2.2.3 Finished Medicinal Product	18
2.2.4 Discussion on chemical, pharmaceutical and biological aspects	20
2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects	20
2.3 Non-clinical aspects	20
2.3.1 Introduction	20
2.3.2 Pharmacology	21
2.3.3 Pharmacokinetics	28
2.3.4 Toxicology	30
2.3.5 Ecotoxicity/environmental risk assessment	40
2.3.6 Discussion on non-clinical aspects	40
2.3.7 Conclusion on the non-clinical aspects	46
2.4 Clinical aspects	47
2.4.1 Introduction	47
2.4.2 Pharmacokinetics	49
2.4.3 Pharmacodynamics	57
2.4.4 Discussion on clinical pharmacology	64
2.4.5 Conclusions on clinical pharmacology	66
2.5. Clinical efficacy	67
2.5.1. Dose response studies	67
2.5.2 Main studies	68
2.5.3 Discussion on clinical efficacy	116
2.5.4 Conclusions on the clinical efficacy	127
2.6 Clinical safety	128
2.6.1 Discussion on clinical safety	142
2.6.2 Conclusions on the clinical safety	147
3. Benefit-Risk Balance	157
4. Recommendations	162
APPENDIX 1	165

List of abbreviations

ADHOC1	unscheduled
Act-1	murine monoclonal antibody homologue of MLN0002, from which MLN0002 was derived by complementarity determining regions grafting and Fc mutation
5-ASAs	5-aminosalicylates
6-MP	6-mercaptopurine
AS	Active Substance
AEs	adverse events
ADCC	Antibody-dependent cellular cytotoxicity
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area under the concentration-versus-time curve
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CD	crohn's disease
CDAI	crohn's Disease Activity Index
CDC	complement-Dependent Cytotoxicity
CDR	complementarity-determining regions
CEX	cation exchange chromatography
CFR	code of Federal Regulations
CHO	chinese hamster ovary (cell line)
CIOMS	council for International Organizations of Medical Sciences
CI	confidence interval
CL	clearance
CLL	linear pathway clearance
C _{max}	single-dose maximum (peak) concentration
CMH	cochran-Mantel-Haenszel
CNS	central nervous system
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
CV	coefficient of variation
CVA	cerebrovascular accident
%CV	Coefficient of Variance
DC	discontinued
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
DTH	delayed type hyper-sensitivity
EAE	experimental autoimmune Encephalomyelitis
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ET	early Termination
FP	Finished Product
GALT	gut-associated lymphoid tissue
GI	gastrointestinal
GLP	good laboratory practice
GPI	generic product identifier
HAHA	human anti-human antibodies
HBI	Harvey Bradshaw Index
HBV	hepatitis B virus

HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high level term
HPLC	High Performance Liquid Chromatography
HRQOL	health-related quality of life
HRP	horseradish Peroxidase
HUSE	human serum
IAC	independent Adjudication Committee
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IC50	50% inhibition
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IEF	isoelectric focusing
IM	Intramuscular
IRB	institutional review board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous(ly)
IVRS	interactive voice response system
JCV	JC virus; a neurotropic DNA polyomavirus
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MAA	marketing authorisation application
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MAP	mean arterial pressure
MCB	Master cell bank
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
MFI	mean Fluorescence Intensity
Millennium	millennium Pharmaceuticals Inc., and its affiliates
MRD	minimum Required Dilution
MRI	magnetic resonance imaging
MLN0002	vedolizumab, formerly LDP-02 and MLN02
MS	multiple sclerosis
N/A	not applicable
NC	negative Control
NEC	not elsewhere classified
ND	not determined
nHAHA	neutralising HAHA
NHP	non-human primate
NK	natural killer
NMSC	Non-Melanoma Skin Cancer
NOAEL	no observed adverse effect level
NOR	Normal Operating Ranges
NSAID	nonsteroidal anti-inflammatory drug
OD	Optical Density
PAHA	primate antihuman antibodies
Ph. Eur.	European Pharmacopoeia
PALS	Periarteriolar lymphoid sheaths
PASS	Post Authorisation Safety Study
PBMC	Peripheral Blood Mononuclear Cells
PC	Positive Control
PCR	polymerase chain reaction
PD	pharmacodynamics(s)
PE	pulmonary embolism
PHA	Phytohemagglutinin

PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PLA	placebo
PML	progressive multifocal leukoencephalopathy
PPCB	Post-Production Cell Bank
PSUR	Periodic Safety Update Report
PT	preferred term
Q4W	every 4 week dosing
Q8W	every 8 week dosing
QOL	quality of life
RAHA	rabbit antihuman antibodies
RAMP	risk Assessment and Minimization for PML
RBC	red blood cell
RLVPs	retrovirus-like particles
RMP	risk management plan
SAEs	serious adverse events
SC	subcutaneous
SD	Standard Deviation
SDS-PAGE	Sodium dodecyl sulfate-Polyacrylamide gel electrophoresis
SE	standard error
SEC-HPLC	Size-exclusion chromatography-High Performance Liquid Chromatography
SF-36	Short Form-36
sMAdCAM-1	soluble mucosal addressin cell adhesion molecule 1
SNPs	single nucleotide polymorphisms
SOC	system organ class
SOP	Standard Operating Procedure
sTNFRI	soluble tumor necrosis factor receptor I
sTNFRII	soluble tumor necrosis factor receptor II
t _{1/2}	half-life
TB	tuberculosis
TDAR	T cell-dependent antibody response
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TK	toxicokinetics
TMB	3,3',5, 5'-tetramethylbenzidine
TNF α	tumor necrosis factor α
TPY	total person-time in years
TSE	transmissible spongiform encephalopathy
TT	tetanus toxoid
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
UV	UltraViolet
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1
VDZ	vedolizumab
V _{ss}	volume of distribution
VTE	venous thromboembolism
W	Week
WBC	white blood cell
WCB	Working Cell Bank
WFI	Water for Injections
WLW	method Wei, Lin, and Weissfeld method

1. Background information on the procedure

1.1. *Submission of the dossier*

The applicant Takeda Pharma A/S submitted on 6 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Entyvio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2012.

The applicant applied for the following indication:

Ulcerative Colitis

Vedolizumab Takeda 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 (TNF α) antagonist.

Crohn's Disease

Vedolizumab Takeda 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 (TNF α) antagonist".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that vedolizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/145/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/145/2010 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 applicant 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.

New active Substance status

The applicant requested the active substance vedolizumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not

a constituent of a product previously authorised within the Union

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 October 2006, 18 February 2010 and 22 July 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: US. The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

AbbVie Bioresearch Center
100 Research Drive
Worcester
01605-4314
USA

Manufacturer responsible for batch release

Takeda Italia S.p.A.
Via Crosa, 86
28065
Cerano (NO)
Italy

1.3. Steps taken for the assessment of the product

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

Rapporteur: Greg Markey Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 6 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2013.
- During the meeting on 25 July 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 November 2013.
- During the CHMP meeting on 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 January 2014.
- During the CHMP meeting on 18 February 2014, outstanding issues were addressed by the applicant during an oral explanation in front of the CHMP.
- During the meeting on 20 March 2014, 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.

2. Scientific discussion

2.1 Introduction

Problem statement

Inflammatory bowel disease (IBD), comprising primarily of Ulcerative colitis (UC) and Crohn's disease (CD), is a relapsing remitting condition characterized by chronic inflammation at various sites in the gastrointestinal tract. UC and CD are chronic, lifelong diseases that cause considerable morbidity as well as increased mortality in a patient population with an average age in the early 40s.

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. CD generally involves the ileum and the colon, but it can affect any region of the intestine, often discontinuously. Otherwise UC involves the rectum and may affect part of the colon or the entire colon in an uninterrupted pattern (pancolitis). Since IBD are chronic diseases, patients will go through periods in which the disease flares up and causes symptoms. These periods are followed by remission, in which symptoms disappear or decrease. Patients are often afflicted by abdominal cramps and pain, bloody diarrhoea, 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. Clinical complications in CD may include the development of fistulae and perianal diseases or the formation of strictures and obstructions, whereas the most important complication of UC is an acute non-obstructive dilatation of the colon called "toxic mega-colon". Moreover, both CD and UC patients have increased risk of developing colon cancer.

The intestinal immune system has a pivotal role in the pathogenesis of IBD. Both innate and adaptive immune systems are implicated in the development of the aberrant immune response that leads to the intestinal tissue damage. 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 pathogens occurs, the immune response becomes inflammatory.

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 lymphocytes. 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-complexed to MHC class II molecule on the plasma membrane. 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. Similarly, CD8+ T cells are activated by cells expressing antigen in the context of MHC class I proteins and they have a major role in the destruction of tumour and viral-infected cells.

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) γ 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- γ 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 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 or integrins, lymphocytes are captured ("tethering") and poorly 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.

CD4 T cells that migrate to the small intestine lamina propria express the integrin $\alpha 4 \beta 7$ and the chemokine receptor CCR9. These traffic molecules, as well as their corresponding

ligands, are essential for efficient T-cell migration into the small bowel. The main $\alpha 4\beta 7$ ligand, MAdCAM-1, is expressed on intestinal lamina propria venules and the CCR9 ligand CCL25/TECK is strongly expressed by epithelial cells in the small intestine and in lamina propria venules. The integrin $\alpha 4\beta 7$ is also important for T-cell migration into the colon, even during inflammation. However, the large bowel is devoid of CCR9+ cells, and its ligand CCL25 is not expressed in this compartment. Consistently, CCR9 desensitization or CCL25 blockade decreased adhesion of T cells in small bowel, but not colon venules. Thus, other chemoattractant pathways may direct T cell migration to the colon mucosa.

The calculated annual mortality rate in IBD is 1.0% to 1.4%. Pharmacological treatments exist for the treatment of UC, but there remains a significant unmet medical need for more effective and safer treatments for both induction and maintenance of remission. Failure of medical therapy leads to colectomy in approximately 1 year in 17% of UC patients with moderately to severely active disease while taking concomitant medical therapy including corticosteroids and/or immunosuppressants. Colectomy rates range from 9% (distal colitis) to 35% (pancolitis) over 5 years, depending on the extent of colon involved. For CD, although pharmacological treatments exist, there remains a significant unmet medical need for more effective and safer treatments for both induction and maintenance of remission. For many CD patients, at some stage of their disease, approaches such as surgical removal of highly diseased, strictured, or stenotic segments of the bowel is the only option. However, for CD, surgery often is not curative as CD can recur in any part of the gastrointestinal tract; after bowel resection with primary anastomosis, CD recurs at the site of the anastomosis in essentially all patients. Further contributing to morbidity of CD is its unique tendency to cause fistulization, often resulting in fecal discharge through the skin, the vagina, or the urinary tract.

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. Initial treatment often begins with anti-inflammatory agents, progressing to more potent agents for patients who fail to demonstrate a response. Conventional pharmacologic treatments for these diseases include the 5-aminosalicylates (5-ASAs), corticosteroids, and immunomodulators (thiopurines such as azathioprine [AZA] and 6-mercaptopurine [6-MP]) for both UC and CD, along with methotrexate (MTX) for CD. In addition, standard practice often involves using these treatments in combination. Although these treatments are effective for some patients with UC or CD, many patients either do not respond adequately or become refractory to these conventional therapies, and some may become dependent on long-term corticosteroid therapy, increasing their risk of developing the serious toxicities associated with long-term corticosteroid use. In addition, long-term use of AZA and related immunosuppressants increases the risk of lymphoma and serious systemic infections. Monoclonal antibodies directed against TNF α (e.g. infliximab and adalimumab) have been approved for treatment of UC and CD in the European Union (EU). These agents have substantially improved the care of patients with UC and CD by inducing and maintaining remission and decreasing the need for hospitalizations and surgeries, and other complications. Although TNF α antagonists represent an important addition to the pharmacologic armamentarium for both UC and CD, they are effective in only a subset of patients, with roughly two-thirds of patients in controlled trials not in remission at the end of the first year of therapy. In addition, controlled studies have demonstrated that, after failure of 1 TNF α antagonist, a patient's response to a second TNF α antagonist is substantially lower. The TNF α antagonists are also associated with a number of serious safety concerns based on their suppression of systemic

immunity, including reactivation of tuberculosis (TB); various bacterial, viral, fungal, and opportunistic infections; and malignancies such as hepatosplenic T-cell lymphoma.

Because of the ineffectiveness and toxicities experienced with immunomodulating therapies for moderately to severely active UC and CD, there remains considerable need for safer and more effective therapies. Patients who fail both conventional and TNF α antagonist therapy typically have no other medical therapeutic options available to them and often progress to surgical remedies. Despite potent immunomodulating combination therapies (eg, AZA plus a TNF α antagonist), many patients continue to experience disease flares and complications of their disease that may require frequent hospitalizations, abdominal surgeries, and treatment of infections, including abscess drainage. These complications contribute to a substantial morbidity.

Thus, there is a pressing need for alternative therapy effective in patients who do not respond, lose response, or are intolerant to currently available treatments for UC and CD. In addition, given the toxicities associated with chronic immunosuppression of the immune system associated with corticosteroids, immunomodulators, and TNF α antagonists, there is a need for new targeted therapies, particularly one that reduces the gastrointestinal inflammatory process without increasing the risk for toxicities commonly seen with the currently available agents. Vedolizumab is a gut-selective anti-inflammatory agent that was developed to help fulfill this important unmet medical need.

About the product

Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against the human lymphocyte integrin $\alpha 4\beta 7$. The mechanism of action of vedolizumab is based upon its exclusive binding of the $\alpha 4\beta 7$ integrin, a key mediator of gastrointestinal inflammation. The $\alpha 4\beta 7$ integrin is expressed on the surfaces of both T and B lymphocyte subpopulations, including at the surface of a discrete subset of memory T lymphocytes, designated $\alpha 4\beta 7^{\text{hi}}$, that preferentially migrate into the gastrointestinal tract and cause the inflammation that is characteristic of UC and CD. Vedolizumab binds to the $\alpha 4\beta 7$ integrin and selectively inhibits adhesion of these cells to one of the $\alpha 4\beta 7$ ligands mucosal addressin cell adhesion molecule-1 (MAdCAM-1), thereby preventing these cells entering the gut lamina propria and gut associated lymphoid tissue (GALT).

Vedolizumab does not bind to, or inhibit function of, the $\alpha 4\beta 1$ and $\alpha E\beta 7$ integrins. The inhibition of $\alpha 4\beta 7$ integrin is a shared mechanism of action of both vedolizumab and natalizumab and has thus raised a question of whether or not vedolizumab may also increase the risk of PML. The gut-selective profile of vedolizumab is attributable to 2 distinct pharmacologic properties.

Vedolizumab binds solely to the $\alpha 4\beta 7$ but not the $\alpha 4\beta 1$ integrin, unlike natalizumab, which binds to both. As a result, the binding of vedolizumab is specific for $\alpha 4\beta 7$ expressing cells including the gut-tropic subset of lymphocytes. The ability of natalizumab to bind to the $\alpha 4\beta 1$ integrin broadens its mechanism of action to modulate the systemic immune system as the $\alpha 4\beta 1$ integrin is more widely expressed by leukocytes than is the $\alpha 4\beta 7$ integrin, and the $\alpha 4\beta 1$ integrin mediates pleiotropic activities that are not regulated by the $\alpha 4\beta 7$ Integrin. Review of the scientific evidence published to date in peer-reviewed scientific journals supports the concept that PML associated with natalizumab results from antagonizing the $\alpha 4\beta 1$ integrin and not the $\alpha 4\beta 7$ integrin. The mechanism of action of vedolizumab represents a novel, selective intestinal-targeted approach relevant to the pathophysiology of both UC and CD. By virtue of this gut-selective mechanism of action, vedolizumab provides anti-inflammatory activity with the

potential for avoiding systemic immunosuppression and many of the side effects which are associated with existing UC and CD therapies. Hence, vedolizumab may offer a significant additional treatment option for the management of UC and CD patients who have failed conventional or TNF α antagonist therapy.

Type of application and aspect on development

The Union Marketing Authorisation Application (MAA) for Entyvio is being submitted under the centralized procedure in accordance with Article 3(1) of Regulation (EC) No 726/2004: mandatory scope for a Centralised Marketing Authorisation.

In addition, in line with the Clarification for Applicants in the Centralised Procedure: Chemical (Non-Biological) Products, and the Notice to Applicants Vol 2A, Chapter 1, Annex 3, vedolizumab, is considered a “new chemical active substance”.

The Applicant received scientific advice from CHMP on the following dates:

2006-10-18: EMEA/H/SA/765/1/2006/III

2010-02-18: EMEA/H/SA/765/1/FU/1/2010/I

2010-07-22: EMEA/H/SA/765/2/2010/III

2010-07-22: EMEA/H/SA/765/1/FU/2/2010/III

The applicant incorporated the scientific advice where possible and also provided a post-hoc analysis to address some of the points raised in the SA procedures.

The study design of the pivotal C13007/C13006 induction and maintenance studies deviated from the CHMP Guideline on the Development of New Medicinal Products for Ulcerative Colitis (CPMP/EWP/18463/2006 Rev. 1) and CD guideline (CHMP/EWP/2284/99 Rev.1) with regard to different issues. In order to address specific deviations from the CHMP Guidelines, the Applicant asked SA and conducted additional analyses in response to regulatory requests.

Deviations and SA are summarized below.

Deviations from EMA guidelines and additional analyses provided in order to address the deviations:

CD (CHMP/EWP/2284/99 Rev.1)

Maintenance Analyses Related to Deviations from CHMP Guideline (Study C13007)

Deviation	Analysis	Prespecified ^a or Post hoc ^b
Selection of C13007 Maintenance Study population	Effect of vedolizumab on clinical remission at Week 52 in the Week 6 Clinical Remission population, overall and by TNF α antagonist failure history	post hoc
	Effect of vedolizumab on corticosteroid-free clinical remission at Week 52 in the Week 6 Clinical Remission Population, overall and by TNF α antagonist failure history	post hoc
	Effect of vedolizumab on clinical remission at Week 52 in the Week 6 Enhanced Clinical Response population, overall and by TNF α antagonist failure history	prespecified

Deviation	Analysis	Prespecified ^a or Post hoc ^b
Study duration	Effect of vedolizumab on clinical remission after 52 weeks of maintenance therapy (ie, at the first study visit in C13008)	prespecified
	Effect of vedolizumab on clinical remission over time during 6-week induction therapy and 52-week maintenance therapy (including the first study visit in C13008)	prespecified
	Effect of vedolizumab on clinical remission over time during 6-week induction therapy and 52-week maintenance therapy (including the first study visit in C13008) in the Week 6 Clinical Remission population	post hoc

UC (CHMP/EWP/18463/2006)

INDUCTION STUDY

C13006 Induction Analysis Related to Deviations From CHMP Guideline

Deviation	Analysis	Prespecified ^a or Post hoc ^b
Duration of induction endpoint	Effect of vedolizumab following induction therapy on sustained clinical remission for 4 weeks (ie, clinical remission at both Weeks 6 and 10)	Post hoc

a Prespecified analyses were planned prior to study completion and study data unblinding and are described in the [C13006 SAP](#).

b Post hoc analyses were planned after the study was completed and study data were unblinded.

MAINTENANCE STUDY

C13006 Maintenance Analyses Related to Deviations from CHMP Guideline

Deviation	Analysis	Prespecified ^a or Post hoc ^b
Selection of C13006 Maintenance Study population	Effect of vedolizumab on clinical remission at Week 52 in the Week 6 Clinical Remission population	post hoc
	Effect of vedolizumab on mucosal healing at Week 52 in the Week 6 Clinical Remission population	post hoc
Maintenance of clinical remission throughout the study period	Effect of vedolizumab on corticosteroid-free clinical remission at Week 52 in the Week 6 Clinical Remission Population	post hoc
	Effect of vedolizumab on the durability of clinical remission during maintenance, where durability is defined as the proportion of patients who achieved clinical remission in at least 80% of study visits during the Maintenance Phase, in the Maintenance Study ITT population (Week 6 responders)	prespecified
	Effect of vedolizumab on the durability of clinical remission during maintenance, where durability is defined as the proportion of patients who achieved clinical remission in at least 80% of study visits during the Maintenance Phase, in the Week 6 Clinical Remission population	post hoc
	Effect of vedolizumab on the durability of clinical remission during maintenance, where durability is defined as the proportion of patients who achieved clinical remission in 100% of study visits during the Maintenance Phase, in the Maintenance Study ITT population (Week 6 responders)	post hoc
	Effect of vedolizumab on the durability of clinical remission during maintenance, where durability is defined as the proportion of patients who achieved clinical remission in 100% of study visits during the Maintenance Phase, in the Week 6 Clinical Remission population	post hoc
	Effect of vedolizumab on the durability of clinical remission during maintenance, where durability is defined as the proportion of patients who achieved clinical remission on the last 11 of 13 study visits, in the Maintenance Study ITT population (Week 6 responders)	post hoc

One year of maintenance therapy	Effect of vedolizumab on clinical remission after 52 weeks of maintenance therapy (ie, at the first study visit in C13008)	prespecified
	Effect of vedolizumab on clinical remission over time during 6-week induction therapy and 52-week maintenance therapy (including the first study visit in C13008)	prespecified
	Effect of vedolizumab on clinical remission after 52 weeks of maintenance therapy (ie, at the first study visit in C13008) in the Week 6 Clinical Remission population	post hoc
	Effect of vedolizumab on clinical remission over time during 6-week induction therapy and 52-week maintenance therapy (including the first study visit in C13008) in the Week 6 Clinical Remission population	post hoc

Source: C13006 EESA, Table 5-1.

a Prespecified analyses were planned prior to study completion and study data unblinding.

b Post hoc analyses were planned after the study was completed and study data were unblinded.

The Applicant deviated from the EMA guidelines for CD and UC with regard to different issues. Scientific advices have highlighted these discrepancies. In order to address these issues, the Applicant conducted additional analyses, mainly post-hoc.

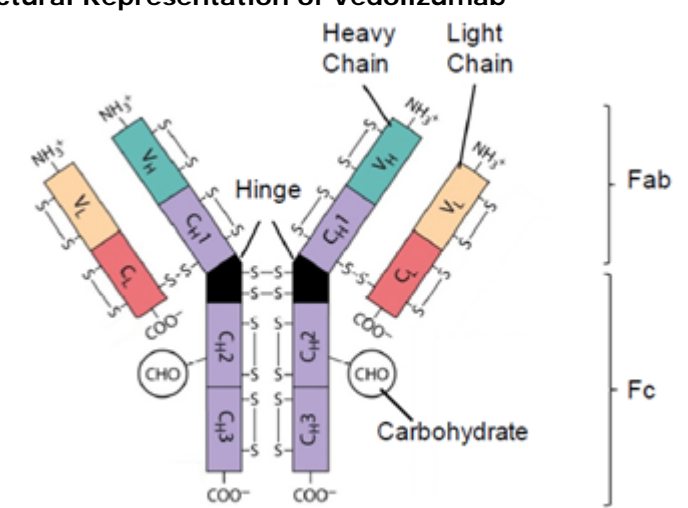
During the procedure, the Applicant has changed the proposed invented name from vedolizumab Takeda to Entyvio.

2.2 Quality aspects

2.2.1 Introduction

Vedolizumab is a recombinant humanized IgG1 monoclonal antibody to the human $\alpha 4\beta 7$ integrin. 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 in the figure below. Each molecule contains twelve intra-chain and four inter-chain disulfide bonds and an asparagine-linked glycosylation site on each heavy chain at residue 301 (see Figure 1).

Figure 1: Structural Representation of Vedolizumab



The mechanism of action of Vedolizumab is to selectively block the adhesion of $\alpha 4\beta 7$ + T cells and B cells to their natural ligand MAdCAM-1.

The isoelectric point is 7.6-8.3, the predicted mass for unmodified protein is 146,837 Da.

2.2.2 Active Substance

Manufacture

Manufacturing

The manufacturing of Vedolizumab active substance is performed by AbbVie Bioresearch Center.

The fermentation and harvesting process

Vedolizumab active substance (AS) is manufactured using recombinant Chinese hamster ovary (CHO) cells that secrete the antibody into the culture medium.

The inoculum expansion starts with the thawing of one Working Cell Bank (WCB) ampoule followed by culturing the cells at increasing volumes and, finally, into the production bioreactor. Vedolizumab antibody is harvested from the production bioreactor.

The purification process

An affinity column selectively captures the Vedolizumab antibody from the clarified harvest. After further purification and filtration steps to separate Vedolizumab antibody from process-related impurities, the antibody is brought to the target concentration.

The active substance is, bottled, and stored at the designated temperature until shipment to the finished product manufacturing site.

Process Control / Process Validation

The manufacturing process is controlled using process parameters and process controls.

The applicant has defined Normal Operating Ranges (NORs) and the control limits are acceptable.

The use of animal derived materials in the manufacturing process is minimized. The BSE/TSE contamination risk from animal-derived materials used in the manufacturing process is considered very low.

Manufacturing development

The manufacturing process used to produce the AS has been changed twice, evolving from process A to process B, and then to process C, a further adjustment of process C was carried out, scaling it up.

Comparability

Comparability between the different processes was evaluated. No indication of significant differences between processes B and C are evident. Process C clinical scale is considered comparable to Process C commercial scale.

Control of materials

All raw materials used in the production of the active substance are either of compendial quality or tested according to internal specifications.

No raw materials of human or animal origin are used.

Cell Banks

The Master Cell Bank and Working Cell Bank were prepared under cGMP conditions, and have been described.

The Post-Production Cell Bank (PPCB) was prepared from cells obtained from a cGMP production culture. The cell banks were verified to be acceptable for use with regard to adventitious agents.

Cell Line Generation and Cell banking

A CHO cell line was utilized as the host cell line in the generation of the production cell line. After adaptation to growth in suspension, a serum-free, suspension bank of host CHO-cells was established. This host cell bank was then transfected, amplified, and the final production cell line was selected.

After their adaptation to suspension growth, the bank of CHO cells underwent testing for virus and other adventitious agents, to ensure that they were suitable for use as host cells for creation of the production cell lines.

The MCB, WCB, and PPCB were more extensively tested for viruses and other adventitious agents. The cell banks were verified to be acceptable for use with regard to adventitious agents.

Specification

Characterisation

The characterisation of the active substance was satisfactory. The presented analytical results show that the AS has the expected primary, secondary and tertiary structures and physical-chemical properties. Moreover Vedolizumab has the expected biological properties.

Impurities

The impurity profile of Vedolizumab was studied, identifying process- and product-related impurities, extractables and leachables.

Control of active substance

The active pharmaceutical ingredient, Vedolizumab, is not described in a pharmacopoeia and is controlled using an in-house specification. This specification is used for active substance release testing and monitoring of stability.

The analytical methods specifically developed for release and stability testing of the active substance have been appropriately validated. A summary for the procedure and validation of each analytical method was provided.

The methods used evaluate Purity, Identity, Protein Concentration, and Potency.

Batch analysis data

The applicant provides an extensive justification of specifications. This justification is acceptable.

Reference standard

The primary active substance reference standard was manufactured using the commercial manufacturing process. Extensive characterization of the reference standard was performed.

Container closure system

The compatibility of the container closure system with the active substance formulation has been demonstrated through long-term stability studies. The potency, purity, and other quality attributes of the active substance are maintained following long term storage.

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

The Vedolizumab finished product (FP) is a sterile, lyophilised formulation provided in a single-use vial containing 300 mg of Vedolizumab antibody. Vedolizumab FP is filled into 20 mL Type I (Ph. Eur, USP) borosilicate glass vials. The vials are closed with a rubber stopper and sealed with a 20 mm aluminium seal with a plastic cap.

Sterile Water for Injections (WFI) is used as a diluent for reconstitution. This diluent is commercially available and is not supplied with the FP. The reconstituted FP is then diluted into commercially available 250 mL of normal saline (Sterile 0.9 % sodium chloride). When reconstituted with 4.8 mL of sterile WFI, the vial contains an overfill. This overfill is necessary to withdraw the 5 mL, 300 mg dose.

Pharmaceutical Development

The reconstituted FP contains 60 mg/mL of active Vedolizumab antibody, histidine (as L-histidine and L-histidine monohydrochloride), L-arginine hydrochloride, sucrose, and polysorbate 80.

The excipients were chosen to provide optimal buffering capacity, enhance stability, and protect the antibody during manufacture and storage. All excipients used in the FP formulation were determined to be compatible with each other and are appropriate for maintaining stability as demonstrated by the FP stability studies.

Manufacture of the product

Manufacturing development

The FP was produced using three different processes: Process A, Process B and Process C, the current, commercial lyophilised formulation.

An extensive analytical assessment was performed to support each new process and each change in manufacturer.

Manufacturing process

The FP manufacturing process is an aseptic process with a sterile filtration step and sterility assurance included as a release criterion. The manufacturing process involves sterile filtration, aseptic filling and partial stoppering, lyophilisation, stoppering, and sealing of the vials. The sealed vials are capped, inspected, and bulk packaged for shipment to the labelling/packaging facility where they are labelled, packaged, and stored for commercial distribution.

Process Validation

The finished product process includes formulation and freeze drying in the final container. The use of Normal Operating Ranges (NOR) to set specifications is acceptable.

Product specification

Control of the Finished Product

The finished product is not described in a pharmacopoeia and is controlled using an in-house specification. This specification is used for Finished Product release and shelf-life monitoring.

The analytical methods for release and stability testing of the finished product have been appropriately validated. A summary for the procedure and validation of each analytical method was provided.

The methods used evaluate Identity, Purity, Potency, and Protein concentration.

In addition, compendial methods are performed at release and during stability testing of the finished product.

Container closure system

The primary container closure system consists of a single-use 20 mL, untreated, clear Type I glass tubing vial with a rubber stopper and an aluminium seal with a plastic flip-off cap.

Compatibility of the primary packaging and the issue of leachables is sufficiently addressed in the dossier.

Stability of the product

Stability studies based on ICH guidelines were carried out for primary stability lots.

Relevant parameters were selected to study the stability of the finished product. The analytical methods were appropriately validated.

The data from primary stability studies support a shelf life of 36 months for the finished product when stored at the labelled storage condition of 5°C ± 3°C in the specified container closure system.

Adventitious agents

The information regarding the acceptability of animal-derived raw materials with respect to transmissible spongiform encephalopathy (TSEs) provided by the Applicant are deemed satisfactory as includes information of the source of animals with respect to geography, age, and

nature of the animal tissue. The relevant certification has been provided. Compliance with the TSE Guideline (EMA/410/01 – rev. 3) has been sufficiently demonstrated.

The manufacturing steps considered for virus validation studies are acceptable. The virus validation studies were performed in specialized laboratories in compliance with GLP Regulations.

The selected model viruses are appropriate, as enveloped and non-enveloped viruses are included.

Overall reduction factors are satisfactory and demonstrate the efficacy of the manufacturing process to remove/inactivate possible viral contaminants. The adventitious safety evaluation is overall acceptable. The approach used to assess residual retrovirus transmission risk can be considered appropriate and demonstrate a negligible risk for retrovirus-like particles (RLVPs).

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

The control of the manufacturing process was extensively discussed during the course of the procedure.

The proposed approach to control the manufacturing process was subject to a Major Objection.

It was proposed that the applicant resolve these deficiencies either by re-writing the operating parameters in line with the data from the full scale batch validation, or by including a sufficient number of batches in order to increase the reliability of the estimate of intervals. Moreover, the applicant was requested to add a number of additional in-process control limits for fermentation steps and to revise the control strategy.

To address the Major Objection, the operating parameters were tightened to reflect the manufacturing batches. The operating conditions were extensively revised.

The Applicant has responded satisfactorily to all of the other quality concerns and questions identified during the course of procedure.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the manufacture and control of the Vedolizumab Active Substance and the Finished Product are considered acceptable.

The Quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in satisfactory way.

Safety concerning adventitious agents including viruses and TSE has been sufficiently assured.

2.3 Non-clinical aspects

2.3.1 Introduction

Vedolizumab is a humanized immunoglobulin (Ig)G1 mAb that binds exclusively to the $\alpha 4\beta 7$ integrin. It does not bind to the $\alpha 4\beta 1$ integrin or the $\alpha E\beta 7$ integrin, and is therefore designed to be highly selective.

Immunosurveillance is characterised by the preferential migration of lymphocyte subsets through specific tissues. It has been demonstrated that the $\alpha 4 \beta 1$ integrin mediates memory T lymphocyte migration into the CNS, bone marrow, and skin, via firm adhesion to VCAM-1 (vascular cell adhesion molecule 1). However, memory T lymphocytes expressing the $\alpha 4 \beta 7$ integrin preferentially migrate into the gastrointestinal (GI) tract, via firm adhesion to MAdCAM-1 (mucosal addressin cell adhesion molecule 1). These mechanisms of lymphocyte migration also mediate inflammation.

The primary pharmacologic target of Vedolizumab is a subpopulation of leukocytes that expresses high levels of the $\alpha 4 \beta 7$ integrin. This subpopulation of cells is a pivotal mediator of gut inflammation.

Vedolizumab is composed of 2 light chains of the kappa subclass and 2 IgG1 heavy chains. Vedolizumab was generated via grafting of the murine Act-1 mAb complementarity-determining regions (CDRs) into human IgG1 heavy and light chains. Vedolizumab and Act-1 share the same antigen recognition motifs (or CDRs) in the variable region of both the heavy and light chains.

Pivotal non-clinical studies on safety pharmacology and general toxicity, including reproduction toxicity studies, were conducted in accordance with GLP principles. Toxicokinetic and some pharmacokinetic studies were also conducted according to GLP, while some other studies were not strictly GLP. These studies appeared to conform to adequate scientific standards of quality.

2.3.2 Pharmacology

Primary pharmacodynamic studies

The Applicant presented 21 in vitro and 1 in vivo pharmacology studies for assessment of primary PD.

Table 1 *In vitro* pharmacology studies

Study Type	Test Article	GLP
Binding specificity	MLN0002 (Process B)	No
Expression pattern of $\alpha 4 \beta 7$ integrin	Act-1 and MLN0002 (Process B)	No
T lymphocyte activation and cytokine production	MLN0002 (Process B)	No
T lymphocyte proliferation	MLN0002 (Process C)	No
CDC	MLN0002 (Process B)	No
ADCC	MLN0002 (Process B)	No
Selectivity of antagonism of $\alpha 4 \beta 7$ integrin-ligand interactions	MLN0002 (Process B)	No
Tissue cross-reactivity (assay condition optimization)	MLN0002 (Process A)	No
Tissue cross-reactivity (monkeys)	MLN0002 (Process B)	Yes
Tissue cross-reactivity (humans)	Act-1 MLN0002 (Process A) MLN0002 (Process B)	Yes

Binding to Th17 and Treg cells	Act-1 and MLN0002 (Process B)	No
Effects on activity of Treg cells	MLN0002 (Process C)	No
Restoration of $\alpha 4 \beta 7$ integrin function <i>in vitro</i>	MLN0002 (Process B)	No
Affinity for leukocytes from different species	<u>Act-1 and MLN0002 (Process A and B)</u>	<u>No</u>

Binding specificity

The specificity of vedolizumab for binding to human $\alpha 4 \beta 7$ integrin versus human $\alpha 4 \beta 1$ or $\alpha E \beta 7$ integrins was demonstrated with cell lines selectively expressing only one of these integrins. Using antibodies specific for the integrin subunits $\alpha 4$, αE , $\beta 1$, and $\beta 7$, it was shown that: a) RPMI8866 cells (a human B cell lymphoma-derived cell line) express $\alpha 4$ and $\beta 7$ but not $\beta 1$ or αE ; b) RAMOS cells (a human B cell lymphoma-derived cell line) express $\alpha 4$ and $\beta 1$ but not $\beta 7$ or αE and c) $\alpha E \beta 7$ -L1.2 (murine pre-B cell lymphoma) cell transfectants express αE and $\beta 7$ but not $\alpha 4$ or $\beta 1$. Vedolizumab bound to RPMI8866 cells but not to RAMOS or $\alpha E \beta 7$ L1.2 cell transfectants, indicating binding to $\alpha 4 \beta 7$ but not $\alpha 4 \beta 1$ or $\alpha E \beta 7$.

Human Leukocytes Bound by vedolizumab

The expression profile of the $\alpha 4 \beta 7$ integrin in human whole blood from healthy subjects was investigated to identify specific leukocyte subtypes whose function could be potentially inhibited by vedolizumab and conversely, leukocytes whose function could not be directly inhibited by vedolizumab. It was shown that discrete subpopulations of human leukocytes, expressing either the $\alpha 4 \beta 1$ or the $\alpha 4 \beta 7$ integrin, exist *in vivo*. Vedolizumab targets a smaller population of leukocytes than that targeted by dual $\alpha 4 \beta 1$ and $\alpha 4 \beta 7$ integrin-specific antagonists. These limited targeted cells are likely a primary determinant of the gut-selective pharmacologic profile of vedolizumab.

Selectivity of vedolizumab for Inhibition of $\alpha 4 \beta 7$ Mediated Cell Adhesion Interactions

Selectivity and potency of vedolizumab for blocking the adhesive interactions between the integrins $\alpha 4 \beta 1$ or $\alpha 4 \beta 7$ and the cell adhesion molecules MAdCAM-1, VCAM-1, and fibronectin were determined with cell lines selectively expressing only one of these adhesion molecules. These data showed that: a) $\alpha 4 \beta 7$ binds to MAdCAM-1, VCAM-1 and fibronectin, while $\alpha 4 \beta 1$ binds to VCAM-1 and fibronectin but not to MAdCAM-1; b) vedolizumab is a sub-nanomolar inhibitor of *in vitro* cellular adhesion mediated by interactions between $\alpha 4 \beta 7$ and MAdCAM-1 or fibronectin and c) vedolizumab does not inhibit $\alpha 4 \beta 7$ -VCAM-1, $\alpha 4 \beta 1$ -VCAM-1, or $\alpha 4 \beta 1$ -fibronectin-mediated adhesive interactions. The selectivity of vedolizumab was maintained at 400 $\mu\text{g/ml}$, a concentration that is above mean C_{max} in humans (115 $\mu\text{g/ml}$) after a single 30-minute IV infusion at 300 mg.

Binding affinities

A comparison of the relative potencies of multiple lots (process A and B material only) of vedolizumab and Act-1 (a murine homologue of vedolizumab) was carried out in competition binding assays in human whole blood lymphocytes from healthy subjects. Mean IC₅₀ values for the inhibition of either vedolizumab- or Act-1-biotin binding to B and memory CD4 T lymphocytes by vedolizumab were within a range of 0.045 to 0.060 µg/ml (0.3 to 0.4 nM) and for Act-1, mean IC₅₀ values were in the range 0.059 to 0.078 µg/ml (0.39 to 0.52 nM). The binding affinities of several lots of vedolizumab (including CHO and NS0-derived material) and Act-1 for the α4β7 integrin on human whole blood B and memory CD4-T lymphocytes were similar (process A and B material only).

Binding affinity of vedolizumab was very similar for α4β7 integrins in cynomolgus monkey and human whole blood lymphocytes from healthy subjects. The IC₅₀ values for the inhibition of vedolizumab binding to either B or memory CD4 T lymphocytes by vedolizumab were 0.059 µg/ml (0.39 nM) and 0.060 µg/ml (0.40 nM) for monkey and human B cells, respectively and 0.057 µg/ml (0.37 nM) and 0.055 µg/ml (0.38 nM) for monkey and human memory CD4 T lymphocytes, respectively. The binding affinity of vedolizumab was very similar for the α4β7 integrin of rabbit and human whole blood lymphocytes from healthy subjects. The IC₅₀ values for the inhibition of vedolizumab binding to either B or CD4+ T lymphocytes were 0.039 ± 0.009 µg/ml (0.26 nM) and 0.051 µg/ml (0.34 nM) for rabbit and human B cells, respectively and 0.063 µg/ml (0.42 nM) and 0.070 µg/ml (0.47 nM) for rabbit and human CD4+ T lymphocytes, respectively.

The kinetics of reconstitution of α4β7 function in human cd4-positive memory T lymphocytes after removal of vedolizumab

Non-clinical studies have shown that the pharmacodynamic effects of vedolizumab are reversible upon removal of the antibody. The mechanism of reversal was investigated in human purified or whole blood CD4 memory T lymphocytes. This study aimed to observe the mechanism of the vedolizumab receptor pharmacodynamic (PD) effect in terms of whether bound vedolizumab causes α4β7 receptor internalisation and, if it did, the mechanism and kinetics of the restoration of α4β7 function after removal of vedolizumab. These data showed that the pharmacologic activity of cells inhibited by vedolizumab could be partially restored within 24 hours after removal of vedolizumab, with near complete restoration within 4 days.

Species cross-reactivity

The species cross-reactivity of vedolizumab was assessed using mouse, rat, guinea pig, New Zealand white rabbit, cynomolgus monkey, rhesus monkey, and human whole blood stained with vedolizumab and Act-1. Binding of vedolizumab and Act-1 to α4β7 was measured by saturation binding and in competition binding experiments and quantified by flow cytometry. It was shown that vedolizumab and Act-1 bind with similar subnanomolar affinity to α4β7 in rabbit, cynomolgus monkey, rhesus monkey and human blood. Neither vedolizumab nor Act-1 bound to the α4β7 integrin expressed in mouse, rat, or guinea pig blood. Rabbits and rhesus and cynomolgus monkeys were therefore shown to be pharmacologically appropriate species to use when testing vedolizumab.

Comparative studies Binding affinity of vedolizumab process A and B

The relative potencies of multiple lots of Process A and CHO-derived vedolizumab (process B) for binding to the $\alpha 4\beta 7$ integrin on peripheral blood lymphocytes in human whole blood were determined. Data indicated that the binding affinities of Process A material and CHO derived vedolizumab were nearly identical.

Tissue Cross-reactivity studies

GLP-compliant tissue cross-reactivity studies were conducted on monkey and normal human tissues. Binding was restricted to leukocytes in lymphoid tissues, within the lumens of blood vessels, or as low-grade inflammatory infiltrates in various non-lymphoid tissues.

Cotton-top Tamarin

In vivo, colitic cotton-top tamarins (these develop a type of colitis spontaneously) were used to determine the functional relevance of $\alpha 4\beta 7$ in the pathogenesis of chronic inflammatory disease. Animals were given 2.0 mg/kg Act-1, the murine vedolizumab precursor, for 8 days. There was improvement in stool quality throughout the study, starting on Day 3, in animals given Act-1 compared to controls. Histopathology evaluated on Day 5 revealed a reduction in inflammatory infiltrates with Act-1 treatment compared to the control group, demonstrating anti-inflammatory activity.

Evaluation of humanised monoclonal antibodies against alpha 4 integrins in the rhmog (myelin oligodendrocyte protein) induced experimental autoimmune Encephalomyelitis (EAE) model in Rhesus monkeys

As part of the evaluation of vedolizumab in the context of other integrin antagonists and unwanted effects (such as PML), a study was conducted to determine if specific blockade of the $\alpha 4\beta 7$ integrin with vedolizumab would affect immune surveillance and inflammation of the central nervous system (CNS) in a NHP model of EAE. Animals were given intravenous (IV) doses once a week of vedolizumab, vehicle control or the positive control antibody natalizumab. Exposure was demonstrated. All 7 animals exposed to vedolizumab exhibited trough vedolizumab concentrations that exceeded the EC50 (27.6 ng/ml) for $\alpha 4\beta 7$ saturation in vitro between Day 7 and 21.

Clinical Signs

Fifty percent (4 of 8) of vehicle-dosed animals and 57% (4 of 7) of vedolizumab-dosed animals developed symptoms of EAE, whereas 14% (1 of 7) of natalizumab-exposed animals developed symptoms of EAE. Vehicle and vedolizumab-exposed animals developed EAE with similar kinetics, whereas clinical symptoms of EAE were delayed or prevented in the natalizumab group. Since natalizumab is a dual $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin antagonist, whereas vedolizumab is a selective $\alpha 4\beta 7$ integrin antagonist, the results of this study indicate that antagonism of the $\alpha 4\beta 1$ integrin impairs development of clinical symptoms of EAE.

Infiltration of the CNS as Measured by Leukocyte Count in the CSF

Normal immune surveillance of the CNS was demonstrated by increases in the level of CSF leukocytes in this model. Conversely, impaired CNS immune surveillance is indicated by no increases in the level of CSF leukocytes in this model. An increase in the level of white blood cells (WBCs) in the CSF was observed in animals that developed EAE as compared to their pre-exposure levels. The mean values of WBCs in the CSF of the vehicle control and vedolizumab groups were higher at necropsy than at predose sampling. This CSF infiltrate consisted primarily of total T lymphocytes, helper and cytotoxic T lymphocyte subsets and monocytes, and total B lymphocytes to a far lesser extent. A decrease in the level of NK cells was observed, thought to be a result of an indirect consequence of other subsets increasing. In contrast, the mean level of WBCs in the CSF of the natalizumab group was unchanged from predose sampling. These data are consistent with data from a chronic toxicology study in which vedolizumab did not decrease CSF parameters (WBC counts, red blood cell [RBC] counts, and total protein concentrations) or T lymphocyte populations in healthy NHP. These data are also consistent with clinical data showing that natalizumab decreased the levels of WBCs, helper and cytotoxic T lymphocytes, and B lymphocytes in the CSF of patients with multiple sclerosis or who developed PML (*Literature reference Stuve O, Marra CM, Jerome KR, Cook L, Cravens PD, Cepok S, et al. Immune surveillance in multiple sclerosis patients treated with natalizumab. Ann Neurol. 2006;59(5):743-7*)).

It was concluded that antagonism of the $\alpha 4\beta 1$ integrin is associated with impairment of leukocyte infiltration into the CSF, since increases in levels of CSF leukocytes were observed for the vehicle control and vedolizumab groups, but not with the dual $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin antagonist (natalizumab) group.

Infiltration of the CNS as measured by brain MRI

The clinical symptoms of rhesus EAE result from inflammation and demyelinating lesions in cerebral white matter that are initiated by autoreactive helper T lymphocytes.

The mean values for lesion loads in brain hemispheres from the vehicle or vedolizumab groups were shown to be similar and were higher than the mean value observed for the animals given natalizumab, indicating that less immune surveillance of the CNS occurred in the natalizumab group. It was therefore concluded that antagonism of the $\alpha 4\beta 1$ integrin impairs the development of white matter lesions, since natalizumab, the dual $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin antagonist, delayed or prevented the development of EAE compared to vedolizumab.

Infiltration of the CNS as measured by brain tissue histopathology

Qualitatively comparable demyelination was observed in the white matter of vehicle controls and in animals given vedolizumab. Qualitatively comparable inflammation was observed in the white matter of control animals and in animals given vedolizumab. These findings were not seen in animals given natalizumab.

Leukocytosis in the Vasculature

Vascular leukocytosis results from impaired migration of leukocytes out of the vessels and into peripheral tissue of organs, such as the CNS. Levels of total leukocytes and various leukocyte subsets in the vasculature were monitored as an inverse indicator of immune surveillance of peripheral tissue. Animals given natalizumab showed a significant ($p < 0.05$) vascular leukocytosis and lymphocytosis compared to controls. The leukocytosis consisted of significant ($p < 0.05$) elevations in monocytes, lymphocytes, basophils, and eosinophils, but not neutrophils. The lymphocytosis consisted of significant ($p < 0.05$) elevations in total T lymphocytes, total and memory helper T lymphocytes, total and memory cytotoxic T lymphocytes, and total B lymphocytes, but not NK cells. No differences in leukocyte count, erythrocyte count, reticulocyte count, platelet count, and differential counts of neutrophils (segmented), lymphocytes, monocytes, eosinophils, and basophils were observed in animals given vedolizumab compared to controls. There were no differences between animals given vedolizumab and controls (observed by flow cytometry analysis) of lymphocyte subpopulations, most notably total B lymphocytes, total T lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes, memory helper T lymphocytes, memory cytotoxic T lymphocytes, and NK cells. It was therefore concluded that dual $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin antagonist natalizumab induces a broad-spectrum, vascular leukocytosis in contrast to the selective $\alpha 4\beta 7$ integrin antagonist vedolizumab, which does not induce leukocytosis. This leukocytosis results from inhibiting migration of leukocytes from the vasculature, which, in turn, impairs immune surveillance of peripheral tissue.

Migration of leukocytes into the CNS

The frequency of mononuclear leukocytes that recognized MOG in each animal was assessed to determine if vedolizumab and natalizumab affected the induction of these autoreactive cells. The aim of this study was to gain mechanistic insight into any potential effects on EAE. The presence of recombinant human MOG (rhMOG)-reactive leukocytes (i.e., pathogenic cells) was determined in ex vivo proliferation assays of peripheral blood mononuclear cells and splenocytes from animals given vehicle, natalizumab, or vedolizumab. These data indicate that 21 of 22 animals contained a quantity of autoreactive cells that was sufficient to induce EAE, thus showing that the inhibition of EAE by natalizumab did not result from failure to induce autoreactive cells. It was concluded that the inhibitory effect of the dual $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin antagonist natalizumab on the development of EAE in rhesus monkeys may result from impaired migration of autoreactive leukocytes from the vasculature into the CNS, thereby preventing recognition of endogenous MOG expressed by oligodendrocytes (i.e., immune surveillance of the CNS) and the development of EAE.

Secondary pharmacodynamic studies

Cytokine release or T lymphocyte activation

The potential of vedolizumab to mediate cytokine release or T lymphocyte activation was examined by incubating 400 $\mu\text{g/ml}$ of antibody in diluted whole blood at 37°C for up to 24 hours and evaluating activation by measuring cytokine release into the processed plasma and the expression of T lymphocyte activation cell surface markers. Vedolizumab did not elicit increases in concentration of the cytokines IFN γ , TNF α , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-12 (P70), IL-12

(P40), IL-17, and IL-23. In addition, no effect was observed on the expression of the T lymphocyte activation markers CD25 and CD69.

Human regulatory T cell function

The potential effects of vedolizumab, the anti- α 4 mAb natalizumab, and the anti- β 7 mAb FIB504 on the suppressive activity of the total regulatory T (Treg) cell population, and more specifically of the gut-homing subset of this population, were investigated *in vitro* in peripheral blood from healthy human volunteers (study RPT-01954). There were no consistent effects of vedolizumab (anti- α 4 β 7), natalizumab (anti- α 4), or FIB504 (anti- β 7) on the suppressive activity of the total and gut-homing subset of Treg cells, as compared to vehicle control or an isotype control antibody. These results suggest that the *in vivo* activity of vedolizumab does not affect Treg function.

Complement-Dependent Cytotoxicity (CDC) of Human Peripheral Blood Mononuclear Cells (PBMCs) Fc-mediated cytotoxic

The potential CDC activity of vedolizumab was compared in human peripheral blood mononuclear cells (PBMCs) to that of OKT3 (muromonab-CD3 – known Fc-mediated cytotoxicity). The assay measured lactate dehydrogenase (LDH) release from PBMCs incubated with rabbit complement in the presence of vedolizumab (test article), OKT3 (positive control), or human IgG1/kappa (MLN1202, the isotype control for MLN0002) at various concentrations. Vedolizumab did not cause CDC *in vitro* in mononuclear cells isolated from human peripheral blood.

Antibody-dependent cell-mediated cytotoxicity (ADCC) of a α 4 β 7 -expressing RPMI 8866 cells

Cytotoxicity was measured using CytoTox 96 Non-Radioactive Cytotoxicity Assay kit. ADCC was not induced by either vedolizumab or Act-1 at concentrations as high as 10 μ g/ml, a concentration approximately 100- to 200-fold over what is needed for saturation binding of vedolizumab to RPMI 8866 cells.

Safety pharmacology programme

Telemetered Cynomolgus monkeys were given the control article by a 1-hour IV infusion on Day 1. Four animals per dose (10 and 100 mg/kg) were given a 1 hour IV infusion of vedolizumab on Day 6. Vedolizumab was well tolerated and there were no test article-related changes in clinical signs or effects on heart rate, mean arterial pressure, and ECG parameters (qualitative and quantitative) up to 100 mg/kg. From approximately 1 hour after the end of infusion (120-minute time point) through the end of the recording period, the mean arterial pressure (MAP) was approximately 5 to 15 mmHg less at 10 and 100 mg/kg vedolizumab compared to controls. On review of the procedure during the collection of the MAP measurements, it was noted that the primate jackets and ambulatory infusion pumps were removed after the administration of the 10 and 100 mg/kg vedolizumab were completed on Day 6. In contrast, the primate jackets remained on the animals following administration of the control dose on Day 1 in preparation for dosing on Day 6. The Applicant stated that it was subsequently learned that animals wearing a jacket similar to the one used in this study results in an increase in the MAP which returns to pre-jacketed values upon its removal (Soloviev, MV et. al., Safety Pharmacology Society

meeting, San Diego, California, September 2006). Therefore, the difference in MAP between control and vedolizumab groups was considered to be due to the effect of the jackets during the control group recordings. The 100-mg/kg dose is associated with a mean C_{max} (5260 µg/ml) approximately 46 times the geometric mean C_{max} (115 µg/ml) in humans after a single 300-mg 30-minute IV infusion.

Pharmacodynamic drug interactions

The Applicant stated that no studies of pharmacodynamic drug interactions have been conducted as vedolizumab is a humanized antibody and does not modulate production of cytokines, which can affect drug metabolism. This was considered acceptable to the CHMP.

2.3.3 Pharmacokinetics

Pharmacokinetic studies

The PK and TK profile of vedolizumab was investigated in numerous *in vivo* studies in New Zealand white rabbits and NHP. These two species have been shown to be pharmacologically responsive to *vedolizumab*.

Table 11: Test articles used in pharmacokinetics studies

Study Type	Test Article	GLP
Single-Dose		
TK, PD, and rabbit antihuman antibodies (RAHA) support for an embryo-fetal toxicity study in New Zealand white rabbits	Process B	See note a below
PK in cynomolgus monkeys	Process A	See note b below
PK, PD, and PAHA in cynomolgus Monkeys	Process B	No
TK, PD, and PAHA support for a single-dose toxicology study in cynomolgus monkeys	Process B and C	Yes
Repeat-Dose		
TK, PD, and RAHA support for a 3-month toxicology study in New Zealand white rabbits	Process B	Yes
TK, PD, and PAHA support for a 14-day repeat-dose toxicology study in cynomolgus monkeys	Process A	See note b below
PK and PD in cynomolgus monkeys (2-week study)	Process A and B	No
TK, PD, and PAHA support for a 13-week toxicology study in cynomolgus monkeys	Process B	See note c below
TK, PD, and PAHA support for a 26-week toxicology study in cynomolgus monkeys	Process B	Yes
TK, PD, and PAHA support for a prenatal and postnatal toxicity study in cynomolgus monkeys	Process B	Yes
TK, PD, and PAHA support for an immunotoxicity study in cynomolgus monkey	Process B	Yes
a The range-finding study was non-GLP-compliant, while the definitive study was GLP-compliant.		
b The TK, PD, and PAHA analyses for these studies were non-GLP-compliant.		

c The TK, PD, and PAHA analyses for the initial 13-week study were non-GLP-compliant, while the definitive 13-week study was GLP-compliant.

Methods of analysis

In the early GLP compliant studies of vedolizumab (Process A), non-GLP-compliant methods were used to measure vedolizumab concentrations, primate anti-human antibody (PAHA) levels, and levels of free $\alpha\beta 7$ sites and bound vedolizumab. Suitable validation data have been provided. The methods used for analysis were acceptable to the CHMP.

Process change

To support process changes in manufacturing vedolizumab, a GLP-compliant single-dose toxicology study was conducted with intravenous doses of 0, 10 and 30 mg/kg. The study showed similar serum C_{max}, AUC_{0-168hr} and TK profiles in NHP/monkeys

Absorption

The intended route of administration is IV therefore there are no absorption data. The lack of absorption data was accepted to the CHMP given the biological nature of the product.

Distribution

Dedicated studies of tissue distribution or protein binding and red blood cell distribution were not conducted with vedolizumab. The lack of specific distribution data was accepted to the CHMP given the biological nature of the product.

Metabolism

Metabolism studies were not conducted with vedolizumab, in accordance with International Conference on Harmonisation (ICH) Guideline S6(R1), which states that classical biotransformation studies are not required for biotechnology-derived pharmaceuticals, as the expected consequence of their metabolism is degradation to small peptides and individual amino acids, and the metabolic pathways are therefore generally understood.

Excretion

Dedicated excretion studies were not conducted with vedolizumab, in accordance with ICH Guideline S6(R1), which states that routine studies that attempt to assess mass balance are not useful. This was agreed by the CHMP.

Pharmacokinetic drug interactions

No studies of PK drug interactions have been conducted as vedolizumab is a humanized antibody and does not modulate production of cytokines, which can affect drug metabolism. The lack of specific PK drug interaction data was accepted by the CHMP given the biological nature of the product.

Overall pharmacokinetic characteristics

The PK of vedolizumab was characterized by low CL (0.180 to 0.266 ml/hr/kg), low apparent Vss (80.7 to 88.3 ml/kg), and long terminal elimination t_{1/2} (336 to 362 hr). Vedolizumab was immunogenic in animals, with lower immunogenic titers at higher doses. The PD of vedolizumab was independent of cell type (CD20+, CD4+, CD8+, and CD45^{+/+}). In the toxicology studies, saturation of $\alpha 4\beta 7$ (as measured by the bound vedolizumab assay) was rapid and, in all NHPs and most New Zealand white rabbits, was maintained throughout the dosing interval and the duration of the dosing phase of the studies at the highest dose (100 mg/kg).

The exposure at the NOAEL of 100 mg/kg in monkeys is approximately 46 and 18 times higher than the geometric mean clinical C_{max} and AUC, respectively, after a single 300-mg 30-minute intravenous (IV) infusion. The results of the PK/TK studies demonstrate that there was adequate exposure and a demonstrable PD effect in the toxicology studies.

Immunogenicity

The immunogenicity of vedolizumab was assessed by measuring rabbit and primate antihuman antibodies (RAHA and PAHA) to determine whether antihuman antibodies affected exposure to vedolizumab in animals. As expected with a humanized mAb, vedolizumab is immunogenic in animals, with lower titers at higher doses. Overall, the incidence of RAHA and PAHA was variable across single- and repeat-dose studies and across doses. RAHA/PAHA had a neutralising effect on the PK and PD of vedolizumab in some of the animals at the low and mid doses (10 and 30 mg/kg), but continuous $\alpha 4\beta 7$ saturation was achieved in animals that did not develop a neutralising RAHA/PAHA effect. At the highest dose (100 mg/kg), RAHA/PAHA had little effect on the PK or PD of vedolizumab. At this dose (NOAEL), continuous saturation of the target, $\alpha 4\beta 7$, was maintained throughout the dosing and recovery phases of the study in nearly all of the animals in the GLP-compliant repeat-dose toxicology studies.

2.3.4 Toxicology

Non-clinical Toxicology Program for vedolizumab – all dosing was IV unless otherwise stated.

Table 18: Test articles used in toxicology studies

Study Type	Species	Duration of Dosing	Test Article	GLP
Single-dose	Cynomolgus monkey	Singe dose	Process A	No
	Cynomolgus monkey	Singe dose	Process C & B	Yes
Repeat-dose	New Zealand white rabbit	3 months	Process B	Yes
	Cynomolgus monkey	2 weeks	Process A	Yes
	Cynomolgus monkey	2 weeks	Process A & B	No
	Cynomolgus monkey	3 months	Process A	Yes
	Cynomolgus monkey	3 months	Process B	Yes
	Cynomolgus monkey	6 months	Process B	Yes
<i>In vitro</i> carcinogenicity	Human tumour tissue	N/A	Act-1	No
	Human tumour cell line	N/A	Process C	No
Embryo-fetal	New Zealand white rabbit	Single dose	Process B	No

development				
	New Zealand white rabbit	Single dose	Process B	Yes
Prenatal and postnatal development	Cynomolgus monkey	4 months	Process B	Yes
Local tolerance (SC and IM)	New Zealand white rabbit	Single dose	Process C	Yes
Immunogenicity ^a	Cynomolgus monkey and New Zealand white rabbit	Up to 6 months	Process A, B and C	Yes and no
Immunotoxicity	Cynomolgus monkey	13 weeks ^b	Process B	Yes
	Cynomolgus monkey	3 weeks	Process C	Yes
	Rhesus monkey	Single dose	Act-1	No

a Immunogenicity was assessed as part of the general toxicology studies.

b Part of the 13-week repeat-dose toxicology study

Three manufacturing processes of vedolizumab (processes A, B and C) were used. A comparative GLP-compliant single-dose intravenous infusion toxicology study with process B and process C material was conducted in male and female cynomolgus monkeys. Process B and C material showed similar serum C_{max}, AUC_{0-168hr}, and TK profiles at 10 and 30 mg/kg vedolizumab.

A comparative GLP-compliant 2 week IV repeat dose study was conducted with Process A and B material. One animal given process A vomited on Day 1 approximately 4 minutes after the start of infusion and had mild to moderate swelling of the left eye. One animal given process B material vomited approximately 2 minutes postdose on Day 4. The signs resolved without treatment. Transient increases in aminotransferase (ALT) and aspartate aminotransferase (AST) were noted in most animals at 1 or more time points after dosing. These occurred with similar frequency with Process A or B material. TK parameters (AUC and C_{max}) were generally not comparable in this study. However the mean T_{max} for process A was biased by the data from one animal where the T_{max} was 48 hours. In the other 3 animals in this dose group the T_{max} occurred at 0.5 hours postdose (the earliest sampling time point). The exposure to vedolizumab (as measured by either C_{max} or AUC) was slightly higher for process A after both the first and last dose. The pharmacodynamics of both materials were broadly similar for both CD4⁺ and CD8⁺ cells.

Single dose toxicity

A comparative GLP-compliant single-dose intravenous infusion toxicology study with process B and process C material was conducted in male and female Cynomolgus monkeys. Animals were given IV doses of 10 or 30 mg/kg of either process B or C material. Controls were given 50-mM histidine, 125-mM arginine, 100-mg/ml sucrose, and 0.6-mg/ml polysorbate 80. Animals were observed for 7 days after dosing. Both process and B material were well tolerated with no in-life clinical signs noted or effects on food consumption, body weight, serum chemistry or haematology parameters. Process B and Process C material showed similar serum C_{max}, AUC from 0 to 168 hours (AUC_{0-168hr}). There were no marked differences in the extent of binding to the target $\alpha 4\beta 7$ sites between process B and process C material. Pronounced PAHA was not observed (all titers were ≤ 100).

Repeat dose toxicity

Non-human primate

2 weeks

Male cynomolgus monkeys were given a 30-minute infusion (Day 1) and slow bolus (approximately 1-minute) IV injection (Days 4, 8, 11, and 15) of process A or B vedolizumab at 10 mg/kg. One animal given process A material vomited on Day 1 approximately 4 minutes after the start of infusion and had mild to moderate swelling of the left eye. One animal given process B material vomited approximately 2 minutes postdose on Day 4. The signs resolved without treatment. There were no effects on body weight or test article-related effects on haematology parameters. Transient increases in aminotransferase (ALT) and aspartate aminotransferase (AST) were noted in most animals at 1 or more time points after dosing. These occurred with similar frequency with Process A or B material. These elevations were of unknown significance and were not observed in subsequent studies.

13 weeks

Male and female cynomolgus monkeys were given I.V doses of vedolizumab (process B) at 10, 30, or 100 mg/kg once every 2 weeks (Days 1, 15, 29, 43, 57, 71, and 85) by slow intravenous infusion. No changes in clinical signs, body weight, food consumption, ophthalmology, ECG, clinical pathology, urinalysis, immunological assessments, organ weights, and macroscopic data were observed. An increased number of *Balantidium* protozoa were noted in the cecum and colon of 1 of 12 animals dosed at 30 mg/kg and 2 of 12 animals dosed at 100 mg/kg, respectively. This was not associated with adverse effects. *Balantidium* protozoa were not observed in recovery animals. Because predose *Balantidium* levels in the cecum and colon were unknown, the significance of this finding was uncertain. The Applicant stated that the possibility of a test article-related effect upon intestinal flora cannot be ruled out. The NOAEL was considered to be 100 mg/kg.

Vedolizumab was immunogenic in most animals. In general, the PAHA had an effect on the TK and PD of vedolizumab, with the effect being most pronounced at 10 mg/kg. The $\alpha\beta 7$ sites on peripheral lymphocytes were shown to be saturated with vedolizumab for the duration of this study.

A bound site assay was used in this study to monitor levels of the gut-homing subset ($\alpha\beta 7^{\text{high}}$) of memory (CD45RA⁺) helper (CD4⁺) T lymphocytes in the vasculature of monkeys. At predose, this gut-homing subset represented 19% to 28% of the overall memory helper T lymphocyte population in the vasculature. After administration of vedolizumab, these percentages increased to highs of 61% by Day 29. This elevation persisted for the duration of the investigation at 30 and 100 mg/kg, but was reduced by Day 29 at 10 mg/kg, indicating that the response was lost in some at this dose. These data indicate that the relative proportion of the gut-homing subset within the overall memory helper T lymphocyte population in the vasculature increased 3- to 4-fold, possibly because egress into the gut submucosa was blocked by vedolizumab. No changes were observed in any other leukocyte subset examined, including the overall memory helper T lymphocyte population, indicating, according to the Applicant, that the relative increase in the

percentage of gut-homing memory helper T lymphocytes is caused by an increase in the absolute number of cells expressing $\alpha 4\beta 7$ in the vasculature.

NK cells are a constituent of innate immunity that expresses the $\alpha 4\beta 7$ integrin. Potential effects of vedolizumab on NK cell cytolytic activity were assessed *ex vivo* from samples taken at predose and postdose. No significant effect of vedolizumab was observed on NK cell cytolytic activity.

T cell-dependent antigen response (TDAR) was also examined. Primary TDAR was induced during the third month of exposure to vedolizumab by immunising monkeys SC with keyhole limpet hemocyanin (KLH). Animals at all doses mounted primary IgM and IgG TDARs to KLH that were comparable to controls and there were no significant differences in group mean anti-KLH IgM or IgG TDARs, compared to mean control values. Exposure to vedolizumab does not decrease systemic TDAR in the NHP.

26 weeks

Male and female cynomolgus monkeys were given I.V doses of vedolizumab (process B) at 10, 30, or 100 mg/kg once on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169 with by IV infusion. A 12 week recovery period was included on this study. There were no in-life behavioural effects and there were no test article-related changes on food consumption, electrocardiology, ophthalmology, clinical pathology, cerebrospinal fluid evaluations, organ weights or macroscopic data evaluated through to Day 183 (26 weeks).

Microscopic findings consisted of minimal to mild lymphoid depletion in the Peyer's patches of the GI tract in males at all doses and increased epithelial regeneration in stomachs of both sexes, with lymphoplasmacytic gastritis at all doses. An effect on Peyer's patches is consistent with the role of $\alpha 4\beta 7$ in mediating lymphocyte trafficking into this secondary lymphoid organ. After an approximately 12-week dose-free period, lymphoid depletion in the Peyer's patches of the GI tract was only noted in 1/4 animals at 100 mg/kg (a female); microscopic changes in the stomach did not differ between animals given vedolizumab and controls. The NOAEL was considered to be > 100 mg/kg.

Vedolizumab was immunogenic in most animals. In general, PAHA had an effect on the TK and PD, with the effect being most pronounced at 10 mg/kg. PAHA had no effect on TK and PD at 100 mg/kg.

At predose, free $\alpha 4\beta 7$ integrin was detected on 32% to 36% of this population. Free $\alpha 4\beta 7$ integrin could not be detected on this population within 30 minutes after the initial infusion and at predicted trough exposure levels (i.e., pre-infusion) for the remainder of the study, in contrast to controls. These data demonstrate that the target was saturated by vedolizumab throughout this study.

A bound site assay was used to monitor levels of the gut-homing subset ($\alpha 4\beta 7^{\text{high}}$) of memory (CD45RA⁺) helper (CD4⁺) T lymphocytes in the vasculature. At predose, the gut-homing subset of memory helper T lymphocytes represented 15% to 22% of the overall population of lymphocytes in the vasculature of these animals. After dosing, these percentages increased to highs of 64% to 73%. This elevation persisted for the duration of the study at all doses. These data indicate that the relative proportion of the gut-homing subset within the overall memory helper T lymphocyte population in the vasculature increased 3- to 4-fold, as egress into the gut

submucosa was blocked by vedolizumab. No changes were observed in any other leukocyte subset, including the overall memory helper T lymphocyte population, indicating that the relative increase in the percentage of gut-homing memory helper T lymphocytes is caused by an increase in the absolute number of cells expressing $\alpha 4\beta 7$ in the vasculature.

Vedolizumab also induced a reduction in the frequency of leukocytes expressing $\beta 7$ integrins in the GI tract of these monkeys, consistent with the pharmacologic inhibition of $\alpha 4\beta 7$ – MAdCAM-1 binding by Vedolizumab. Therefore, it can be postulated that the Vedolizumab associated increase in gut-homing memory helper T lymphocytes in the vasculature was a consequence of impaired lymphocyte migration into the tissue.

Rabbits

12 weeks

Male and female New Zealand white rabbits were given I.V doses of 30 or 100 mg/kg vedolizumab once every 2 weeks (Days 0, 14, 28, 42, 56, 70, and 84). A 4 week recovery period was included in this study.

Two of the 20 animals exposed to vedolizumab were found dead. The cause of death for these animals was not determined from the microscopic examination. Clinical pathology changes consisted of increased urea nitrogen (BUN) and AST and decreased lower red cells, haemoglobin, haematocrit, and mean corpuscular haemoglobin concentration (MCHC), and higher mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) compared to values at predose in these animals. Similar clinical pathology changes were not seen in animals that survived until the end of the in-life phase. The female that died also had higher mean absolute and percent lymphocytes; these changes were considered test article-related, as similar changes were observed in surviving animals at the scheduled primary necropsy on Day 98. The cause of these deaths was unknown. These deaths are not believed to be test article-related as similar effects were not seen in the GLP-compliant embryo-fetal developmental toxicity study in rabbits and 13-week repeat-dose toxicity study in NHPs.

In those animals that were euthanized at the end of the in-life phase, haematologic and histologic effects were consistent with the mechanism of action of vedolizumab (inhibition of $\alpha 4\beta 7$, resulting in retention of $\alpha 4\beta 7^+$ leukocytes within the vasculature). Higher spleen weights were correlated with lymphoid hyperplasia and increased amyloidosis of the periarteriolar lymphoid sheaths (PALS) of the spleen. Similar observations have been made in other species, such as mice, with elevated serum amyloid protein A, which is the precursor of secondary amyloid protein. Infusion of non-human species with a humanized mAb results in recognition of the non-self-protein by the animal's immune system. The lymphoid hyperplasia was attributed to this immunogenicity. The splenic effects were attributed to this immunogenicity, and not to antagonism of the $\alpha 4\beta 7$ integrin, and were therefore not considered adverse.

The applicant defined the NOAEL as 100 mg/kg for this study.

There were no pronounced sex-related differences in serum concentrations or derived TK parameters. Vedolizumab was immunogenic in most animals. RAHA affected the TK and PD, with the effect being most pronounced at 30 mg/kg. At 100 mg/kg, vedolizumab was detected up to 14 days after the last dose (Day 84) in 8 of 9 animals and up to 42 days after administration of

the last dose in 4 of 4 animals. At 30 mg/kg, vedolizumab was detected up to 14 days after the last dose in 4 of 9 animals. After the last dose, exposure to vedolizumab (as measured by either Cmax or AUC) increased as the dose increased. This increase was greater than dose-proportional due to the presence of neutralising RAHA.

At 100 mg/kg, saturation of $\alpha 4\beta 7$ (as measured by the bound vedolizumab assay) was maintained throughout the dosing interval and for the duration of the dosing phase of the study in the majority of animals. At 30 mg/kg, the effect of neutralizing RAHA on the PK and PD was pronounced, with approximately 60% of the animals having reduced exposure to vedolizumab and a reduced PD response.

Findings common across both species

Minimal to mild small lymphoid follicles (a decrease in the size) in the submucosal lymphoid nodules (Peyer's patches) of the sacculus rotundus was seen in the 3 month rabbit study at 30 and 100 mg/kg. In the 6 month monkey study, minimal to mild lymphoid depletion in the Peyer's patches of the gastrointestinal tract was seen in males at all doses (10, 30, and 100 mg/kg). After a 12-week dose free period, lymphoid depletion in the Peyer's patches of the gastrointestinal tract was noted in one animal at 100 mg/kg dosed animals (a female). It should be noted that although animals were dosed for 6 months (as an IV infusion every 2 weeks), the presence of complete saturation of $\alpha 4\beta 7$ sites on peripheral lymphocytes in all animals during the 12-week dose-free period demonstrated that animals were exposed to pharmacological concentrations of vedolizumab for 9 months. These lymphoid effects were considered to be due to pharmacology (decreased trafficking of peripheral lymphocytes to the gut). It is agreed that this is probably the case.

Systemic exposure comparisons

Table 1 shows the comparative systemic exposure to vedolizumab after intravenous administration to rabbits, monkeys, and humans at the NOAEL values.

Table 1

Species	Dose	Dose Association	Vedolizumab Systemic (Serum) Exposure ^a		
			Cmax (µg/ml)	AUC (day*µg/ml)	Exposure Margin (AUC)
Rabbit - 3 month study	100 mg/kg	NOAEL	9890	51,250 ^{bg}	25.6
Monkey - 26 week study	100 mg/kg	NOAEL	5260	36,500 ^{ch}	18.3
Human	300 mg	Proposed dose	115 ^e	2000 ^{e,f}	N/A

AUC = area under the concentration-versus-time curve; Cmax = maximum concentration; N/A = not applicable; NOAEL = no observed adverse effect level.

a Observed Cmax and AUC data are presented for Days 85 and 169, respectively, of the 3-month repeat-dose toxicity study in rabbits (n = 9) Subreport RPT-01060) and the 26-week repeat-dose toxicity study in monkeys (n = 12:), and after a single 30-minute intravenous (IV) infusion in patients (n = 10 for Cmax and 8 for AUC; Clinical Study Report [CSR] C13009).

b AUC from 0 to 337 hours (AUC0-337hr).

c AUC from 0 to 336 hours (AUC0-336hr).

d Approximately equivalent to 4 mg/kg.

e Geometric mean.

f AUC from 0 to infinity (AUC0-∞).

g AUC report = 1,230,000 hr*ug/ml, AUC MAA = 51,250 day*ug/ml, Unit Conversion: 1,230,000 hr*ug/ml x 1 day/24 hours = 51,250 day*ug/ml
h AUC report = 876,000 hr *ug/ml , AUC MAA = 36,500 day * ug/ml, Unit Conversion: 876,000 hr*ug/ml x 1 day/24 hours = 36,500 day*ug/ml

Table 2 shows the comparative systemic exposure to Vedolizumab after intravenous administration to rabbits, monkeys, and humans at the lowest dose used.

Table 2

Species	Dose	Vedolizumab Systemic (Serum) Exposure ^a		
		Cmax (µg/ml)	AUC (day*µg/ml)	Exposure Margin (AUC)
Rabbit 3 month study	30 mg/kg	645	3454 ^{bg}	1.7
Monkey 26 week study	10 mg/kg	503	3437 ^{ch}	1.7
Human	300 mg/kg	115 ^e	2000 ^{e,f}	N/A

AUC = area under the concentration-versus-time curve; Cmax = maximum concentration;

N/A = not applicable; NOAEL = no observed adverse effect level.

a Observed Cmax and AUC data are presented for Days 85 and 169, respectively, of the 3-month repeat-dose toxicity study in rabbits (n = 9) and the 26-week repeat-dose toxicity study in monkeys (n = 12;), and after a single 30-minute intravenous (IV) infusion in patients (n = 10 for Cmax and 8 for AUC; Clinical Study Report [CSR] C13009).

b AUC from 0 to 337 hours (AUC0-337hr).

c AUC from 0 to 336 hours (AUC0-336hr).

d Approximately equivalent to 4 mg/kg.

e Geometric mean.

f AUC from 0 to infinity (AUC0-∞)

g AUC report = 82,900 hr*ug/ml, AUC MAA = 3454 day*ug/ml, Unit Conversion: 82,900 hr*ug/ml x 1 day/24 hours = 3454day*ug/ml

h AUC report = 82,500 hr*ug/ml, AUC MAA = 3437 day*ug/ml, Unit Conversion: 82,900 hr*ug/ml x 1 day/24 hours = 3437day*ug/ml

Immunogenicity seemed lower at higher doses in animals which was suggested to reflect induction of immune tolerance.

The primary goal of a further study was to compare PK and pharmacodynamic profiles between Processes B and C, additionally immunogenicity was tested at 7 days post dose. TK and PD non-clinical data, together with quality evaluation, support the comparability between Vedolizumab Processes B and C.

Genotoxicity

Genotoxicity studies were not conducted as vedolizumab is a humanized monoclonal antibody and so are not required in-line with ICH Guideline S6(R1). Given the biologic nature of vedolizumab the lack of genotoxicity studies was accepted by the CHMP.

Carcinogenicity

Conventional carcinogenicity risk assessment studies (ie, rodent bioassays) have not been conducted with vedolizumab as rodents are not pharmacologically responsive to this mAb. This is consistent with ICH Guideline S6(R1).

Effect of Act-1 Antibody on the Growth of the α4β7 Expressing RPMI 8866 Human B-Cell Lymphoma Cell Line (non-GLP).

A study was carried out to investigate the effect of Act-1 on the growth rate of a human chronic myeloid B cell line that expresses the α4β7 integrin targeted by Vedolizumab. The effect of the Act-1 antibody was assessed during a 4-day period during which the cells proliferated

approximately 6 times. Cells were plated into 96-well plates at 30,000 cells per well and treated either with the IgG1 control or the Act-1 antibodies at concentrations ranging from 0.039 to 20 µg/ml. The first cell growth assay was performed 24 hours after antibodies were added to the cells, then once every consecutive day for a total of 4 measurements. Both the control and Act-1 antibodies had a minimal inhibitory effect on cell growth. Statistical analysis of the data showed that both antibodies inhibited cell growth, although the degree of cell growth inhibition in the Act-1 groups was lower than in the corresponding IgG1 groups, a difference that was most visible at Days 3 and 4. Over all it was shown that binding of Act-1 to a hematopoietic tumour cell line that expresses the $\alpha 4\beta 7$ integrin did not enhance cell proliferation in vitro.

Binding Specificity of Act-1 in malignant human tumours (non-GLP)

A study was conducted to characterise immunohistochemical staining of Act-1 with malignant human tumour tissues. Act-1 was tested at 2 and 20 µg/ml on 10 samples of human colon malignant adenocarcinoma. All 10 samples demonstrated Act-1- specific staining of cytoplasmic granules and membranes of mononuclear cells (representing the resident or infiltrating lymphocyte population, with a lack of staining in surrounding neoplastic tissue). This pattern of staining is consistent with the expression pattern of $\alpha 4\beta 7$ integrin, which is expressed on the surface of lymphocytes.

Reproduction Toxicity

No studies of fertility and early embryonic development have been conducted.

A GLP-compliant study was conducted in rabbits to evaluate potential for embryofetal toxicity (Study WIL-416044 Amendment 1). The NOAEL for maternal toxicity and embryofetal developmental was considered to be 100 mg/kg.

The vehicle control or vedolizumab (10, 30 or 100 mg/kg) was administered as an intravenous infusion to 4 groups of 25 time-mated female New Zealand White rabbits on Gestation Day 7. For the TK, RAHA and PD evaluations, an additional 3 rabbits/group were administered the vehicle or test article on a comparable regimen as main study rabbits. The exposure to vedolizumab showed trends towards increasing in a greater than dose-proportional manner. At 100 mg/kg (the highest dose examined), saturation of binding to $\alpha 4\beta 7$ sites was achieved throughout the study period. Immunogenicity in the 10 mg/kg group was greater than those in the higher dose groups and the PD effects appeared to be broadly similar at doses with no immunogenic response.

All females survived to the scheduled laparohysterectomy. There were no test article-related clinical findings at any dose level. Slightly lower mean maternal body weight gains and food consumption were noted in the 100 mg/kg group immediately following infusion (Gestation Day 7 to 8) and when the entire period of major organogenesis (Gestation Days 7 to 20) was evaluated. However, a slight compensatory increase in mean body weight gain was noted in this group during Gestation Days 20 to 29, when test article exposure would have been minimal at best (previous toxicokinetic data indicates test article exposure is maintained for at least 2 weeks). There were no test article-related effects on maternal net body weight, net body weight gain, or gravid uterine weight, and intrauterine growth and survival were unaffected at all dose levels.

Based on the lack of maternal and embryo/fetal effects and no significant effects on mean maternal body weight gain and food consumption during the period of major organogenesis, 100 mg/kg was considered to be at least the NOAEL for maternal toxicity and embryo/fetal developmental toxicity.

Prenatal and postnatal development, including maternal function

Pregnant female cynomolgus monkeys were given a 20- to 30-minute IV infusion every 2 weeks from Days 20 to 140 of gestation at 10 or 100 mg/kg vedolizumab (process B material). All surviving dams and infants were euthanized on Day 181 postpartum. Vaginal smears were examined daily from Day 20 postcoitum until delivery. In infants, external abnormalities, morphologic measurements, neurobehavioral test battery, grip strength, and anatomic pathology were examined. Organ weights and macroscopic and microscopic findings were also assessed.

Two of 12 dams at 100 mg/kg were euthanized due to poor clinical condition secondary to diarrhoea, weight loss and dehydration. This was not considered test article-related as microscopic evaluation revealed crypt microabscesses throughout the large intestine that were consistent with bacterial infections common in cynomolgus monkeys. These infections were considered to have caused the moribundity. Stress during gestation and a generally weak condition after birth may have increased the susceptibility of these dams to infection. None of the other 10 high dose animal (100 mg/kg) showed comparable symptoms, nor the 12 low dose (10 mg/kg) animals. .

In other animals there was no increase the incidence of prenatal loss or death, or stillbirth. No effects were seen in clinical signs, body weight, or food consumption and there was no macroscopic evidence of organ toxicity in dams. There were no test article-related effects on the number of infants born, clinical signs, and infant development. At the end of the study (Day 181 postpartum), the survival rate of the infants was similar across all groups. There were no test article-related effects on infant clinical pathology and organ weights, and there was no macroscopic or microscopic test article-related organ toxicity.

The NOAEL both maternally and for off-spring was considered to be \geq 100 mg/kg.

In all infants born to dams dosed at 100 mg/kg, vedolizumab was detected in the serum at concentrations of approximately 10-100 µg/ml on Day 28.

Vedolizumab was detected at low levels on Day 28 postpartum in the breast milk in 3 /11 animals at 100 mg/kg. Vedolizumab was not detected in the breast milk at 10 mg/kg. Vedolizumab was present at low levels in the serum of infants at both doses. On Day 28 postpartum, vedolizumab was detected in 3/7 infants at 10 mg/kg and all infants at 100 mg/kg. On Day 120 postpartum, vedolizumab was detected at a low concentration in 1 infant at 100 mg/kg. Amniotic fluid was not sampled; the presence of vedolizumab in infant serum is attributed to placental transfer, rather than as a result of ingestion of breast milk.

Vedolizumab was immunogenic in some dams. In general, the PAHA had an effect on the TK and PD of vedolizumab, with the effect being most pronounced at 10 mg/kg. Pharmacodynamic results showed a high percentage of cells staining positive for bound Vedolizumab, and a low percentage of cells staining positive for free $\alpha 4\beta 7$ sites through to Gestation Day 277.

A PAHA response existed in some infants at both doses. Positive titers were seen in 2/7 infants at 10 mg/kg and in 1/9 infants at 100 mg/kg. A PAHA response existed in the mother of these infants and it could not be determined whether the PAHA detected in infants was derived from the infant and/or mother. The PD response in infants whose mothers were dosed with vedolizumab tracked closely with the PD response in the mothers. On Day 28 postpartum, target saturation was noted in all infants at 100 mg/kg. On Day 120 postpartum, target saturation was noted in 3/9 infants at 100 mg/kg. On Day 181 postpartum, no target saturation was noted in any of the infants at 100 mg/kg.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Toxicology studies in juvenile animals have not been conducted. The Applicant argued that $\alpha 4\beta 7$ integrin does not play a role in mammalian growth and development (literature references have been provided) and that the developmental effects of inhibiting the $\alpha 4\beta 7$ integrin can be studied sufficiently in mice with genetic ablation of the $\beta 7$ integrin gene (*Itgb7*) as vedolizumab binds to the $\alpha 4\beta 7$ integrin, but not to the $\alpha 4\beta 1$ integrin. Homozygous null mice (mice with no functional $\alpha 4\beta 7$ integrin protein) are healthy and have a normal life span, thus confirming that $\alpha 4\beta 7$ is not necessary for growth and development in the mouse.

In addition vedolizumab did not affect prenatal and postnatal development in cynomolgus monkeys. In the 13-week study, all males (4/4) at 100 mg/kg were sexually immature at the termination of the study, while in the 26-week study, 3/4 males at 100 mg/kg were sexually immature at the end of the study. In both these repeat-dose toxicology studies, all females were sexually mature. The NOAEL was considered to be 100 mg/kg in both studies.

Local Tolerance

A GLP study was conducted to determine the local irritancy potential of Process C material when administered by subcutaneous or intramuscular injection to male New Zealand white rabbits. The incidence and severity of the macroscopic and microscopic observations were similar in animals given vedolizumab compared to controls.

Immunotoxicity

A repeat-dose study in cynomolgus monkeys was conducted to compare the potential immunotoxicity, TK, and PD of natalizumab (Lot 090324A) and vedolizumab (process C material) when given by IV infusion once weekly for 3 weeks. Vedolizumab elevated the level of gut-homing memory T cells ($\alpha 4\beta 7^{\text{hi}}/\text{CD}4^{+}/\text{CD}45\text{RA}^{-}$) in peripheral blood approximately 3-fold which was consistent with results from the 13 and 26 week toxicology studies. Natalizumab was immunogenic in all animals. Vedolizumab elicited a more selective pharmacodynamic effect. It did not affect levels of these relatively large leukocyte subpopulations in peripheral blood, but specifically elevated levels of gut-homing memory helper ($\text{CD}4^{+}/\text{CD}45\text{RA}^{-}/\alpha 4\beta 7^{+}$) T lymphocytes. The data also demonstrated that natalizumab and vedolizumab did not inhibit the recall adaptive immune response to tetanus toxoid (TT) by recall IgM and IgG TDAR, 10 to 20 days after challenge with TT.

To determine if $\alpha 4\beta 7$ blockade would interfere with T cell responses at sites other than the gastrointestinal tract, rhesus monkeys given Act-1 were challenged intradermally with TT in a model of cutaneous delayed type hyper-sensitivity. Compared to controls those animals given Act-1 had no significant difference in $\text{CD}3^{+}$ T cell or HAM-56⁺ monocyte/macrophage cell density

within the inflammatory foci. Anti-TT antibody titres were measured by enzyme-linked immunosorbent assay (ELISA) for 29 days after challenge. Compared to controls, Act-1 did not inhibit systemic humoral immunity, as both groups mounted comparable antitetanus antibody titres. It was therefore concluded that blocking the $\alpha 4 \beta 7$ integrin did not affect the ability to mount adaptive immune responses in the skin.

Other toxicity studies

Microscopic examination of the injections sites were carried out as part of the GLP-repeat-dose toxicology studies in rabbits and monkeys. No test article related effects at the injection sites were observed. Process B material was used in these studies. Vedolizumab was well tolerated in patients with UC or CD when administered as a 30-minute IV infusion at weeks 0, 2, and 6, and then every 4 or 8 weeks at a dose of 300 mg.

2.3.5 Ecotoxicity/environmental risk assessment

Vedolizumab is a sequence of amino acids and a protein and in accordance with the CHMP guideline on the environmental risk assessment (EMA/CHMP/SWP/4447/00) is exempted from testing because of the chemical structure.

2.3.6 Discussion on non-clinical aspects

Pharmacology

The only pharmacology studies that used process C material (the proposed clinical material) were the studies that investigated effects on activity of Treg cells and T lymphocyte proliferation. No other studies (binding specificity or selectivity) were conducted with process C material. However, a GLP-compliant single dose study in monkeys was conducted using material from both processes B and C and this showed similar pharmacodynamics and toxicokinetic profiles; in addition, a 3 week immunotoxicity study has been conducted in monkeys with process C material and there are clinical data with process C material. The Applicant was asked to provide more information on the comparability of vedolizumab made by processes B and C (used in clinical trials). The applicant did not provide any in vitro pharmacodynamics characterisation in support of the comparability but relied on a claim that material from each process was tested in humans and were shown to be equivalent (clinical trial C13009 in healthy subjects). This was accepted by the CHMP.

The Applicant demonstrated that vedolizumab selectively binds to the $\alpha 4 \beta 7$ integrin and that the functional activity of the $\alpha 4 \beta 7$ integrin occurs by inhibition of adhesion to MAdCAM-1 and fibronectin. The Applicant discussed the functions of MAdCAM-1 and fibronectin and the implications of blocking interactions between these molecules and $\alpha 4 \beta 7$. Some studies show that the expression of MAdCAM-1 is necessary but not sufficient for mediating physiological effects within a tissue (i.e. the brain in the EAE model). However, some non-clinical and clinical evidence accounts for a localised activity of vedolizumab in inhibiting the immune response in the gastrointestinal tract. Moreover, $\alpha 4 \beta 7$ seems not to be required for mediating fibronectin physiological function (i.e. biological redundancy of integrins and widespread distribution of

fibronectin). Thus, these data are in support of the selective action of vedolizumab on the gastrointestinal tract. However, no information is available on whether this pattern remains unchanged under conditions in the disease state.

In support of the claimed binding specificity of vedolizumab to gut homing $\alpha 4\beta 7^{\text{high}}$ helper T lymphocytes, the Applicant referred to data on eosinophils expressing low levels of $\alpha 4\beta 7$ in the peripheral blood of CD patients (study C13007) as well as in the placebo group showing that mean values remained unchanged from baseline and following vedolizumab treatment.

The issue on the potential effect of vedolizumab on Treg in patients was considered important in light of the role of Treg cells in the inflamed lamina propria in patients where they are expected to be higher than in the peripheral blood, as well as in healthy subjects. The only available results on vedolizumab binding to Treg cells and their function are in healthy subjects showing that vedolizumab bound to about 10% of these cells and did not affect the suppressive activity of $\alpha 4\beta 7$ -expressing Treg cells. From this evidence, it could be inferred that Treg function in patients' gut mucosa is not affected.

When bound to $\alpha 4\beta 7$, vedolizumab is internalised by a mechanism consistent with antibody-mediated capping. Human memory T lymphocytes remain viable upon removing vedolizumab. The Applicant's discussion of the modifications of $\alpha 4\beta 7$ integrin following binding of vedolizumab is adequate.

In cross-reactivity studies rabbits and rhesus and cynomolgus monkeys were shown to be pharmacologically appropriate species to use when testing vedolizumab. No unanticipated cross-reactivity or off-target staining was noted in each of monkey and human tissues. Binding of vedolizumab in these studies was consistent with the expected patterns of $\alpha 4\beta 7$ integrin expression.

As part of the evaluation of vedolizumab in the context of other integrin antagonists and unwanted effects (such as progressive multifocal leukoencephalopathy, PML), a study was conducted to determine if specific blockade of the $\alpha 4\beta 7$ integrin with vedolizumab would affect immune surveillance and inflammation of the central nervous system in monkeys with experimentally induced autoimmune encephalomyelitis, in comparison with the effect of the dual $\alpha 4\beta 1/\alpha 4\beta 7$ antagonist natalizumab. Monkeys were given IV weekly doses of 30 mg/kg vedolizumab, which did not inhibit clinical symptoms, leukocytic infiltration of cerebrospinal fluid, cerebral inflammation or demyelination, or affect levels of leukocytes, lymphocytes, and monocytes. These results showed that vedolizumab had no effect on immune surveillance in this experimental system.

The Applicant was asked to discuss further the risk of inducing PML by use of vedolizumab, with consideration for the possibility that an immunocompromised status in patients with inflammatory bowel disease could contribute to PML. The Applicant further discussed results from the publication provided with the initial MAA (Haanstra et al. 2013) and provided a comprehensive discussion of the known mechanisms involved in PML occurrence. Results reported by the Applicant suggested that vedolizumab did not block migration of leukocytes into the brain. As to whether this risk is different in patients with inflammatory bowel disease, the Applicant cited in support, data from clinical studies in which no sign of inhibition of CNS immune surveillance or of PML were associated to vedolizumab in patients with inflammatory bowel disease. On the basis of the limited safety data collected so far, although the risk of PML

associated with vedolizumab cannot be completely ruled out, from a mechanistic point of view it is suggested that vedolizumab could have a lower risk than natalizumab for developing PML. Of note, PML risk is considered a potential risk as described in the RMP and will be monitored in the post marketing setting.

The data provided by the applicant showed that the action of vedolizumab does not involve CDC.

The potential for vedolizumab to induce antibody-dependent cytotoxicity (ADCC) of RPMI8866 cells that express $\alpha 4\beta 7$ was examined in vitro. The CHMP concluded that the action of vedolizumab does not involve ADCC.

Vedolizumab did not activate leukocytes in vitro. Incubation of human whole blood with vedolizumab at 400 $\mu\text{g/ml}$ did not induce release of cytokines or affect expression of cell surface markers of T lymphocyte activation. In contrast, positive controls did induce cytokine release and increase expression of cell activation markers on T lymphocytes. Vedolizumab appears to lack agonist activity.

The effects of vedolizumab on the gastrointestinal, urinary, pulmonary and central nervous systems were evaluated for functional and structural changes in GLP-compliant repeat-dose toxicology studies of up to 26 weeks in pharmacologically responsive species. This is acceptable to the CHMP. Vedolizumab did not cause adverse functional or structural effects in the gastrointestinal, urinary, pulmonary or central nervous systems at 100 mg/kg in monkeys, a dose associated with a mean Cmax of 5260 $\mu\text{g/ml}$, ~46-fold the mean human Cmax (115 $\mu\text{g/ml}$) after a single 300 mg 30 minute IV infusion.

Pharmacokinetics

Vedolizumab had low serum clearance and serum apparent volume of distribution at steady-state was moderately greater than the serum volume. Therefore distribution is expected to be limited. The terminal $t_{1/2}$ was long (336 to 362 hours) and vedolizumab exhibited a generally linear PK over the dose range of 10 to 100 mg/kg in rabbits and monkeys. These data are in-line with other antibodies.

The immunogenicity of vedolizumab was assessed by measuring rabbit and primate antihuman antibodies (RAHA and PAHA). RAHA/PAHA had a neutralising effect on the PK and PD of vedolizumab in some of the animals at the low and mid doses (10 and 30 mg/kg), but continuous $\alpha 4\beta 7$ saturation was achieved in animals that did not develop a neutralising RAHA/PAHA effect. At the highest dose (100 mg/kg), RAHA/PAHA had little effect on the pharmacokinetics or pharmacodynamics. At this dose (the no observed adverse effect level (NOAEL)), continuous saturation of the target, $\alpha 4\beta 7$, was maintained throughout the dosing and recovery phases in nearly all of the animals in the repeat-dose toxicology studies.

Vedolizumab was excreted at low levels for 28 days postpartum in the breast milk of cynomolgus monkeys given 100 mg/kg vedolizumab during gestation. Vedolizumab was found to be present at low levels in the serum of infants whose mothers were dosed with vedolizumab during the gestation period. However, the presence of vedolizumab in infant serum is mainly attributed to placental transfer, rather than as a result of ingestion of breast milk.

Processes B and C showed similar serum Cmax, AUC0-168hr, and TK profiles after a 10 and 30 mg/kg intravenous infusion of vedolizumab was given to cynomolgus monkeys.

Toxicology

13 and 26 week studies were conducted in which cynomolgus monkeys were given i.v. doses of 10, 30 or 100 mg/kg vedolizumab every 2 weeks. In the 13 week study there were no in-life behavioural effects or effects on body weight, food consumption, ophthalmology, ECG, clinical pathology, urinalysis, immunological assessments, organ weights, and microscopic data. An increased number of *Balantidium* protozoa were noted in the cecum and colon of 1 and 2 females at 30 and 100 mg/kg, respectively. As predose *Balantidium* levels in the cecum and colon were unknown, the significance of this finding was uncertain. The Applicant stated that the possibility of a test article-related effect upon intestinal flora cannot be ruled out. It is likely that this was not test article-related; however given that vedolizumab is targeting the gut, a test article-related effect upon intestinal flora cannot be ruled out.

Vedolizumab modulates intestinal immunity by inhibiting lymphocyte trafficking into the gastrointestinal tract. Potential effects on gastrointestinal immune response and the risk of enteric infections associated with vedolizumab administration were evaluated in the clinical development program. Opportunistic infections are a potential risk as described in the risk management plan.

In the 26 week study there were no in-life behavioural effects and there were no test article-related changes on food consumption, electrocardiology, ophthalmology, clinical pathology, cerebrospinal fluid evaluations, organ weights or macroscopic findings. Microscopic findings consisted of minimal to mild lymphoid depletion in the Peyer's patches of the gastrointestinal tract in males at all doses and increased epithelial regeneration in stomachs of both sexes, with lymphoplasmacytic gastritis at all doses. The Applicant stated that an effect on Peyer's patches is consistent with the role of $\alpha 4\beta 7$ in mediating lymphocyte trafficking into this secondary lymphoid organ. After an approximately 12-week dose-free period, lymphoid depletion in the Peyer's patches of the gastrointestinal tract was only noted in 1/4 animals at 100 mg/kg (a female). Once again vedolizumab was immunogenic in most animals. In general, PAHA had an effect on the TK and PD which was most pronounced at 10 mg/kg. The NOAEL was considered to be ≤ 100 mg/kg.

A 13 week rabbits study was conducted in which animals were given 30 or 100 mg/kg vedolizumab once every 2 weeks.

Two of the 20 animals exposed to vedolizumab were found dead at 30 and 100 mg/kg. The cause of death for these animals was not determined from the microscopic examination. Clinical pathology changes consisted of increased urea nitrogen (BUN) and AST and decreased lower red cells, haemoglobin, haematocrit, and mean corpuscular haemoglobin concentration (MCHC), and higher mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) compared to values at predose in these animals. Similar clinical pathology changes were not seen in animals that survived until the end of the in-life phase.

These effects were also not seen in the embryofetal developmental toxicity study in rabbits. Those animals that were killed at the end of the scheduled in-life period showed increased globulin and total protein, reduced albumin-to-globulin (A:G) ratio; increased mean absolute and percent lymphocytes, resulting in increased mean total white cell counts.

Small lymphoid follicles (a decrease in the size) of the submucosal lymphoid nodules (Peyer's patches) of the sacculus rotundus and increased mean absolute and relative spleen weights that correlated with lymphoid hyperplasia and increased amyloidosis of the periarteriolar lymphoid sheaths (PALS) of the spleen were noted at 30 and 100 mg/kg.

The effect of small lymphoid follicles was reversible (still observed in 1 male at 100mg/kg male). The increased globulin, decreased A:G ratio, increased mean absolute and relative spleen weights, and splenic lymphoid hyperplasia (M&F), and increased amyloidosis in males were seen at the end of the recovery period at 100 mg/kg.

The Applicant stated that in those animals that were euthanized at the end of the in-life phase, haematological and histological effects were consistent with the mechanism of action of vedolizumab (inhibition of $\alpha 4\beta 7$, resulting in retention of $\alpha 4\beta 7^+$ leukocytes within the vasculature). Higher spleen weights were correlated with lymphoid hyperplasia and increased amyloidosis of the periarteriolar lymphoid sheaths (PALS) of the spleen. Similar observations have been made in other species, such as mice, with elevated serum amyloid protein A. Infusion of non-human species with a humanised antibody results in recognition of non-self protein by the animal's immune system. Lymphoid hyperplasia was attributed to this immunogenicity. The splenic effects were also attributed to this immunogenicity and not to antagonism of the $\alpha 4\beta 7$ integrin, and were therefore not considered adverse by the Applicant. This was accepted by the CHMP.

The Applicant stated that the minimal to mild lymphoid depletion in Peyer's patches and an analogous decrease in leukocytes expressing the $\beta 7$ integrin in crypt epithelium noted represented a pharmacological effect of vedolizumab (decreased trafficking of peripheral lymphocytes to the gut); however, there was no evidence of systemic immunosuppression, consistent with pharmacological antagonism of the $\alpha 4\beta 7$ /MAdCAM-1 pathway.

Vedolizumab was immunogenic in most animals. RAHA affected the TK and PD, with the effect being most pronounced at 30 mg/kg. Vedolizumab was still detected in each animal at the end of this recovery period. The Applicant therefore defined the NOAEL as 100 mg/kg for this study.

Reproductive toxicology

No specific studies of fertility and early embryonic development have been conducted. A GLP-compliant study was conducted in rabbits to evaluate potential for embryofetal toxicity.

The vehicle control (sterile saline, USP) or vedolizumab (10, 30 or 100 mg/mL) was administered as an intravenous infusion to 4 groups of 25 time-mated female New Zealand White rabbits on Gestation Day 7. For the TK, RAHA and PD evaluations, an additional 3 rabbits/group were administered the vehicle or test article on a comparable regimen as main study rabbits. The exposure to vedolizumab showed trends towards increasing in a greater than dose-proportional manner. At 100 mg/kg (the highest dose examined), saturation of binding to $\alpha 4\beta 7$ sites was achieved throughout the study period. Immunogenicity in the 10 mg/kg group was greater than those in the higher dose groups and the PD effects appeared to be broadly similar at doses with no immunogenic response.

All females survived to the scheduled laparohysterectomy. There were no test article-related clinical findings at any dose level. Slightly lower mean maternal body weight gains and food

consumption were noted in the 100 mg/kg group immediately following infusion (Gestation Day 7 to 8) and when the entire period of major organogenesis (Gestation Days 7 to 20) was evaluated. However, a slight compensatory increase in mean body weight gain was noted in this group during Gestation Days 20 to 29, when test article exposure would have been minimal at best (previous toxicokinetic data indicates test article exposure is maintained for at least 2 weeks). There were no test article-related effects on maternal net body weight, net body weight gain, or gravid uterine weight, and intrauterine growth and survival were unaffected at all dose levels.

Based on the lack of maternal and embryo/fetal effects and no significant effects on mean maternal body weight gain and food consumption during the period of major organogenesis, the NOAEL for maternal toxicity and embryofetal developmental was considered to be greater than or equal to 100 mg/kg, the highest dose investigated.

In this study there were a number of findings that were not discussed in the final summary reports. 1) Malaligned sternbrae were observed in 3 fetuses at 100 mg/kg and in 1 fetus at 30 mg/kg (not seen in controls). The mean litter proportion of malaligned sternbrae at 100 mg/kg (1.9% per litter) was outside the range of the historical control data (0.0% to 1.1% per litter). The Applicant noted that slightly malaligned sternbrae without other indications of developmental toxicity is not a test article-related effect. 2) 13th full rib. A dose related increase in 13th full rib variation was also seen. 3) Spherical enlargement of the rib was noted at 30 and 100 mg/kg (none in control). Taken together, these effects could be indicative of an effect on the axial skeleton. In response, the Applicant summarised evidence to the effect that the frequency observed is not higher than historical controls and that consequently, there is no indication that these effects were caused by vedolizumab on sternbrae. This was accepted by the CHMP.

Prenatal and postnatal development, including maternal function was examined in pregnant female cynomolgus monkeys. Two (2) of 12 dams at 100 mg/kg were euthanized due to poor clinical condition that was consistent with bacterial infections common in cynomolgus monkeys throughout the large intestine that were consistent with bacterial infections. No other high dose animal (100 mg/kg) showed comparable symptoms. Despite the final summary's stating that both animals delivered healthy infants, the final study report states that the infant of one of the dams that was euthanized early was also euthanized due to poor clinical condition along with its mother on Day 34 post-partum. The poor clinical condition of the infant was considered related to poor condition of the mother and was not considered test article-related. Histopathological evaluation of this male infant showed mucosal atrophy in parts of the intestine; in the ileum it was accompanied by lymphoid atrophy of the Peyer's patches and villous atrophy. Additional findings were moderate atrophy in the bone marrow of the sternum, spleen, and thymus. The tail had an area of marked necrosis and a severe ulceration. The atrophy of the lymphatic system was considered due to the poor condition of the infant secondary to insufficient nutrition and was not considered test article-related. While it can be accepted that most of the findings noted in this infant were not test article-related and probably due to insufficient nutrition and the poor condition of the dam, mucosal atrophy in parts of the intestine that was accompanied in the ileum by lymphoid atrophy of the Peyer's patches was noted. Based on the data provided by the applicant, the CHMP concluded that due to the excessive pathology present in this animal, the evidence was too weak to associate causally with vedolizumab. This was also the conclusion for a finding that lymphoid depletion was observed not to be completely reversed in animals allowed a

12 week recovery period. As these monkeys did not show any signs of infection, this issue was considered by the CHMP as not to be of clinical relevance.

Concerning fertility, the 26 week general toxicity study in monkeys given vedolizumab is judged insufficient to conclude an absence of an effect, although an effect on male fertility is unlikely. However as no definitive conclusion can be drawn on the male reproductive organs in the cynomolgus monkey repeat dose general toxicity study the following wording has been included in the SmPC: “No specific fertility studies in animals have been performed with vedolizumab. No definitive conclusion can be drawn on the male reproductive organs in the cynomolgus monkey repeat dose general toxicity study, but given the lack of binding of vedolizumab to male reproductive tissues from monkeys and humans and the intact male fertility in $\beta 7$ integrin-knockout mice, it is not expected that vedolizumab will affect male fertility”.

In relation to the risk of cancer, there were instances where monkeys showed lymphoplasmacytic gastritis and epithelial regeneration. The data provided by the applicant showed that these are common findings in control monkeys and such findings are not seen in $\beta 7$ knockout mice indicating that their occurrence is unlikely to be linked to vedolizumab. This was accepted by the CHMP. The incidence of certain malignancies, in particular lymphoma and colorectal cancer, may, in theory, increase in patients on long-term immunosuppressive therapies, particularly those which target cell-mediated immunity. Patients with prior exposure to immunosuppressants or immunomodulators (e.g., TNF α antagonists, natalizumab) may be at a greater risk for developing certain malignancies. This potential risk is addressed in the product information and the RMP.

2.3.7 Conclusion on the non-clinical aspects

The Applicant demonstrated that vedolizumab selectively binds to the $\alpha 4\beta 7$ integrin and that the functional activity of the $\alpha 4\beta 7$ integrin occurs by inhibition of adhesion to MAdCAM-1 and fibronectin. Although vedolizumab pharmacodynamics characterisation was only performed in human peripheral blood from healthy subjects, its gut selective action is sufficiently supported by efficacy and safety clinical results in the target population.

The murine precursor of vedolizumab proved to alleviate gastrointestinal inflammation in a non-human primate model of ulcerative colitis (colitic cotton top tamarins).

Reassuring data on non-human primates with experimentally induced autoimmune encephalomyelitis (but not suffering from inflammatory bowel disease) showed that vedolizumab does not compromise the central nervous system immunosurveillance. However this does not allow to completely ruling out a risk of progressive multifocal leukoencephalopathy (PML) associated to vedolizumab. The PML risk is considered a potential risk as described in the RMP and will be monitored in the post marketing setting.

Pharmacokinetic data were consistent with expectations for a humanised monoclonal antibody given to animals. The general toxicity studies were acceptable to support registration of the product.

No specific fertility studies in animals have been performed with vedolizumab. No definitive conclusion can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity study, but given the lack of binding of vedolizumab to male reproductive tissue in

monkey and human, and the intact male fertility observed in $\beta 7$ integrin-knockout mice, it is not expected that vedolizumab will affect male fertility.

Vedolizumab did not cause developmental toxicity in pregnant animals.

2.4 Clinical aspects

2.4.1 Introduction

The clinical programme of Vedolizumab (VDZ) is composed of a total of 19 clinical studies: 7 were phase 1 studies conducted in healthy subjects, 8 were phase 1b/2 studies conducted in patients with UC or CD, and 4 were phase 3 studies conducted in patients with UC or CD.

GCP

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

The applicant 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.

Tabular overview of clinical studies

Clinical Studies With Vedolizumab in Healthy Subjects and Patients With UC and CD

Study Identifier	Design/Population	Dosing Regimen, Process	Subjects Enrolled/ Subject with PK	Key PK/PD Objectives
Phase 1 Studies in Healthy Subjects				
L297-007	Phase 1, randomized, double-blind, placebo-controlled, ascending single-dose study. Healthy male subjects (aged 18-50 years)	Single dose, Process A 0.15 mg/kg IV (n = 3) 0.15 mg/kg SC (n = 3) 0.5 mg/kg IV (n = 3) 1.5 mg/kg IV (n = 3) 2.5 mg/kg IV (n = 2) Placebo SC or IV (n = 5)	Total = 19 Vedolizumab = 14 Placebo = 5 PK=14	Characterize single-dose PK following IV and SC administration. Assess immunogenicity. Determine the effect of vedolizumab on cytokine levels. Quantify saturation of $\alpha 4\beta 7$.
C13001	Phase 1, double-blind, single ascending dose, randomized, placebo-controlled study. Healthy subjects (aged 18-65 years)	Single dose, Process B 0.2 mg/kg IV (n = 8) 0.5 mg/kg IV (n = 7) 2.0 mg/kg IV (n = 8) 6.0 mg/kg IV (n = 8) 10.0 mg/kg IV (n = 8) Placebo IV (n = 10)	Total = 49 Vedolizumab = 39 Placebo = 10 PK=32	Evaluated single-dose PK over a range of IV doses. Describe the extent and duration of binding to $\alpha 4\beta 7$ on peripheral blood lymphocytes. Characterize relationship between PK and PD.
C13005	Phase 1, open-label, single 6-mg/kg dose in subjects with low and high body weights. Healthy subjects (aged 18-65 years)	Single dose, Process B 6 mg/kg IV	Total = 26 Vedolizumab = 26 PK=23	Determine the PK following single dose in males and females with low and high body weight.
C13009	Phase 1, single-dose study evaluating PK, PD, safety and tolerability of Process C vedolizumab. Part 1, open-label, Part 2, double-blind. Healthy subjects (aged 18-60 years)	Single dose, Process B & C 300 mg IV, Process C 600 mg IV, Process C 600 mg IV, Process B Placebo	Total = 87 Vedolizumab = 62 Placebo = 25 PK=55	Determine PK and PD of single dose IV Process C. Determine PK and PD of 600 mg single dose Process C relative to Process B. Evaluate the effect of vedolizumab on cardiac repolarization.
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, Process C 180 mg SC (n = 14) 180 mg IM (n = 14) 180 mg IV (n = 14)	Total = 42 Vedolizumab = 42 PK=42	Determine vedolizumab bioavailability when administered SC and IM (relative to IV administration).
Study Identifier	Design/Population	Dosing Regimen, Process	Subjects Enrolled/ Subject with PK	Key PK/PD Objectives
C13012	Phase 1, open-label, single-arm study to evaluate the effects of vedolizumab on CD4 ⁺ CD8 ⁺ lymphocyte ratio in the cerebrospinal fluid. Healthy subjects (aged 18-45 years)	Single dose, Process C 450 mg IV	Total = 14 Vedolizumab = 14 PK=14	Determine if reversal of the normal CSF CD4 ⁺ CD8 ⁺ lymphocyte ratio to < 1 occurs after 450 mg IV single dose.
C13013	Phase 1, randomized, double-blind, placebo-controlled study to determine the immune response to systemic and mucosal antigenic challenge in the presence of vedolizumab. Healthy subjects (aged 18-39 years)	Single dose, Process C 750 mg IV	Total = 127 Vedolizumab = 64 Placebo = 63 PK=63	Determine rates of seroconversion to a hepatitis B vaccine series after single dose administration. Determine the rates of seroconversion to an oral cholera vaccine series. Assess change in hepatitis B surface antibody after a single dose.
Phase 1 or 2 studies in patients with UC or CD				
L297-005*	Phase 1b/2a, randomized, double-blind, placebo-controlled, multiple ascending dose, multicenter study. Hospitalized patients with severe UC (aged ≥ 18 years)	2 doses (Days 1 and 15), Process A 0.15 mg/kg SC (n = 5) 0.5 mg/kg IV (n = 4) 2.0 mg/kg IV (n = 0) Placebo IV (n = 5)	Total = 14 Vedolizumab = 9 Placebo = 5 PK=9	Characterize PK. Determine saturation and $\alpha 4\beta 7$ binding on peripheral blood lymphocytes. Evaluate the effectiveness in reducing inflammation as measured by clinical immune histochemistry.
L297-006	Phase 1b/2a, randomized, double-blind, placebo-controlled, multiple ascending dose, single rising dose, multicenter study. Patients with moderately severe UC (aged ≥ 18 years). Prior steroid use was limited (≤ 20 mg/day). Use of 5-ASAs was allowed.	Single dose, Process A 0.15 mg/kg SC (n = 5) 0.15 mg/kg IV (n = 5) 0.5 mg/kg IV (n = 5) 2.0 mg/kg IV (n = 6) Placebo SC or IV (n = 8)	Total = 29 Vedolizumab = 21 Placebo = 8 PK=21	Characterize PK. Determine saturation and $\alpha 4\beta 7$ binding on peripheral blood lymphocytes. Evaluate the effectiveness in reducing inflammation as measured by clinical immune histochemistry.
L299-016	Phase 2, randomized, double-blind, placebo-controlled, parallel-group study. Patients with active CD involving the colon and/or ileum (aged 18-80 years).	2 doses (Days 1 and 29), Process A 0.5 mg/kg IV (n = 62) 2.0 mg/kg IV (n = 65) Placebo IV (n = 58)	Total = 185 Vedolizumab = 127 Placebo = 58 PK=21	Characterize PK. Determine saturation and $\alpha 4\beta 7$ binding on peripheral blood lymphocytes. Investigate relationship of serum concentrations to $\alpha 4\beta 7$ saturation on memory T cells.

Study Identifier	Design/Population	Dosing Regimen, Process	Subjects Enrolled/ Subject with PK	Key PK/PD Objectives
M200-021	Phase 1/2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Patients with active UC not receiving corticosteroids or immunosuppressive agents (aged 18-80 years).	2 doses (Days 1 and 29), Process A 0.5 mg/kg IV (n = 12) 2.0 mg/kg IV (n = 12) Placebo IV (n = 6)	Total = 30 Vedolizumab = 24 Placebo = 6 PK=24	Characterize PK in patients not receiving corticosteroids or immunosuppressive agents.
M200-022	Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Patients with active UC not receiving corticosteroids or immunosuppressive agents (aged 18-80 years).	2 doses (Days 1 and 29), Process A 0.5 mg/kg IV (n = 58) 2.0 mg/kg IV (n = 60) Placebo IV (n = 63)	Total = 181 Vedolizumab = 118 Placebo = 63 PK=22	Characterize PK in patients not receiving corticosteroids or immunosuppressive agents.
C13002	Phase 2, randomized, double-blind, placebo-controlled, PK/PD, multiple-dose, multicenter study. Patients with mild to moderately severe UC (aged 18-70 years).	4 doses, Process B 2.0 mg/kg IV (n = 13) 6.0 mg/kg IV (n = 14) 10.0 mg/kg IV (n = 11) Placebo IV (n = 9)	Total = 47 Vedolizumab = 38 ^b Placebo = 9 PK=35	Characterize PK. Determine extent and duration of $\alpha_4\beta_7$ binding on peripheral blood lymphocytes. Investigate relationship of serum concentrations to $\alpha_4\beta_7$ binding. Explore relationship between disease activity and therapeutic response to UC biomarkers.
CPH-001	Phase 1, open-label, multiple-dose study in Japanese patients with UC (aged 18-70 years)	3 doses (Days 1, 15 and 43) Process C 150 mg IV (n=3) 300 mg IV (n=6)	Total = 9 Vedolizumab = 9 PK=9	Investigate the PK, safety and tolerability of vedolizumab in Japanese patients with UC after multiple IV infusions of vedolizumab. Investigate the PD and efficacy of vedolizumab in Japanese patients with UC after multiple infusions.
C13004	Phase 2, open-label, multiple-dose, multicenter, long-term safety study. Patients with mild to moderately severe UC or CD (aged 18-75 years); study population included treatment-naïve UC and CD patients, as well as UC rollover patients from C13002.	12 doses, Process B 2 mg/kg IV Q8W 6 mg/kg IV Q8W	Total = 72 ^c Vedolizumab = 72 ^c (No placebo) PK= 46	Provide additional PK and $\alpha_4\beta_7$ binding information for use in population PK and PD analyses.

Study Identifier	Design/Population	Dosing Regimen, Process	Subjects Enrolled/ Subject with PK	Key PK/PD Objectives
Phase 3 studies in patients with UC or CD				
C13006	Phase 3, randomized, placebo-controlled, blinded, multicenter study of induction and maintenance. Patients with moderately or severely active UC and inadequate response to, loss of response to, or intolerance of 1 of more immunomodulators or TNFa antagonists (aged 18-80 years). Percentage of patients with previous TNFa antagonist exposure was limited to 50%.	Multiple dose, Process C Induction (Weeks 0-2): 300 mg IV Placebo Maintenance (for 44 weeks): 300 mg IV Q4W 300 mg IV Q8W Placebo	ITT: Vedolizumab = 225 Placebo = 149 Non-ITT: Vedolizumab = 521 ITT: Vedolizumab Q4W = 125 Vedolizumab Q8W = 122 Placebo = 126 Non-ITT: Vedolizumab Q4W = 373 Placebo = 149 PK=654	Develop a population PK model that describes the PK of vedolizumab in patients with moderately to severely active UC. Assess the overall PK and PD characteristics of vedolizumab in patients with moderately to severely active UC. Evaluate the relationship between PK and PD and explore the relationship between PK parameters with the safety and efficacy of vedolizumab in these patients. Determine the effect of vedolizumab treatment on fecal calprotectin.

Study Identifier	Design/Population	Dosing Regimen, Process	Subjects Enrolled/ Subject with PK	Key PK/PD Objectives
C13007	Phase 3, randomized, placebo-controlled, blinded, multicenter study of induction and maintenance. Patients with moderately or severely active CD and demonstrated inadequate response to, loss of response to, or intolerance of 1 of more immunomodulators or TNFa antagonists (aged 18-80 years). Percentage of patients with previous TNFa antagonist exposure was limited to 50%.	Multiple dose, Process C Induction (Weeks 0-2): 300 mg IV Placebo Maintenance (for 44 weeks): 300 mg IV Q4W 300 mg IV Q8W Placebo	ITT: Vedolizumab = 220 Placebo = 148 Non-ITT: Vedolizumab = 747 ITT: Vedolizumab Q4W = 154 Vedolizumab Q8W = 154 Placebo = 153 Non-ITT: Vedolizumab Q4W = 506 Placebo = 148 PK=827	Develop a population PK model that describes the PK of vedolizumab in patients with moderately to severely active CD. Assess the overall PK and PD characteristics of vedolizumab in patients with moderately to severely active CD. Evaluate the relationship between PK and PD and explore the relationship between PK parameters with the safety and efficacy of vedolizumab in these patients. Determine the effect of vedolizumab treatment on serum CRP levels in patients with elevated CRP levels at baseline.
C13008	Phase 3, open-label, long-term safety and efficacy study. Patients (aged 18-80 years) with UC or CD who participated in a prior vedolizumab study.	Multiple dose, Process C 2 years of open-label dosing 300 mg every 4 weeks.	Vedolizumab = 704 UC Vedolizumab = 1118 CD	N/A.

Study Identifier	Design/Population	Dosing Regimen, Process	Subjects Enrolled/ Subject with PK	Key PK/PD Objectives
C13011	Phase 3, randomized, placebo-controlled, blinded, multicenter study of induction. Patients with moderate to severe CD who have failed TNFa antagonist therapy (aged 18-80 years).	Multiple dose, Process C Induction (Weeks 0, 2 & 6) 300 mg IV	ITT: Vedolizumab = 209 Placebo = 207 TNF antagonist Failure: Vedolizumab = 158 Placebo = 157	Develop a population PK model that describes the PK of vedolizumab in patients with moderate to severe CD. Assess the overall PK characteristics of vedolizumab in patients with moderate to severe CD. Evaluate the relationship between PK and safety and efficacy of vedolizumab in these patients. Determine effect of vedolizumab on clinical remission in patients with baseline CRP levels ≥ 5 mg/L. Determine the effect of vedolizumab on clinical remission in patients with baseline fecal calprotectin ≥ 250 μ g/g.

Abbreviations: 5-ASA = 5-aminosalicylic acid; CD = Crohn's disease; CRP = C-reactive protein; CSF = cerebrospinal fluid; IM = intramuscular; ITT = Intent-to-Treat; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; TNFa = tumor necrosis factor alpha; UC = ulcerative colitis.

a Study discontinued by sponsor due to slow enrollment.

b One patient in the vedolizumab group was determined to be ineligible after randomization and was never dosed; a total of 37 patients received vedolizumab in this study.

c 72 patients in Study C13004 includes 38 patients who rolled over from Study C13002; of these 38 patients, 7 had received placebo.

2.4.2 Pharmacokinetics

Absorption

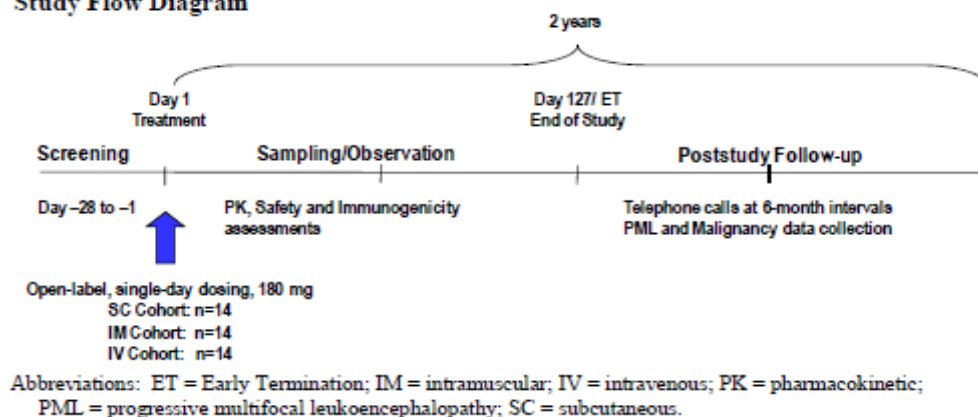
Bioavailability

VDZ is administered intravenously.

During clinical development, a phase 1 study (Study C13010) was performed to determine vedolizumab bioavailability when administered SC and IM, relative to IV administration. The study was composed of 3 dosing cohort. Subjects received a single dose of 180 mg vedolizumab (~ 4 mg/kg) as an SC injection, IM injection, or IV infusion (over 30 minutes).

Forty-two subjects were planned for the study, and a total of 42 subjects were enrolled (14 per dosing cohort).

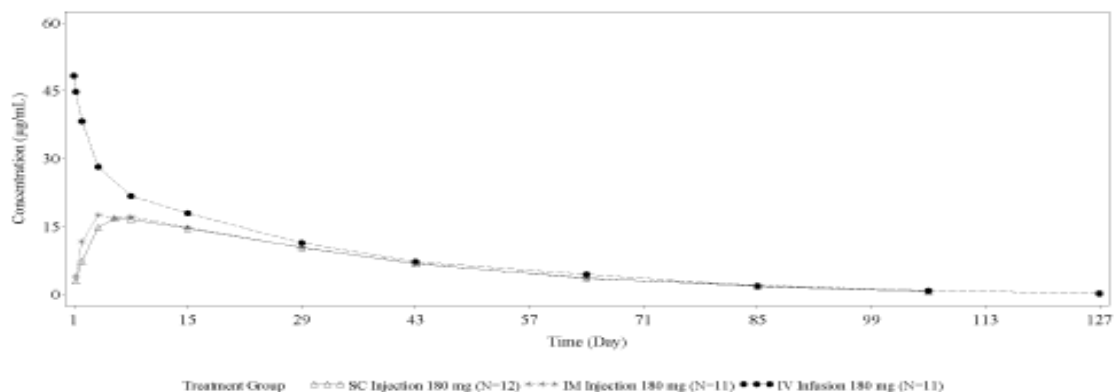
Study Flow Diagram



Blood specimens for the determination of serum vedolizumab concentrations were obtained as follows: 5 minutes after then end of infusion (IV group only), and 6, 24, 72, 120 (except for the IV group), 168, 336, 672, 1008, 1512, 2016, 2520, and 3024 hours after start of infusion/injection

Following IM and SC administration, vedolizumab, achieves maximum concentration at 5-7 days post injection. The C_{max} following IM and SC injection was approximately 1/3 of the C_{max} following 30-minute IV infusion. There was no difference in the terminal elimination profile of IM and SC cohorts compared to the IV cohort, indicating that the elimination of vedolizumab is not absorption rate-limited.

Linear Plot of Mean Vedolizumab Serum Concentrations Over Time by Treatment Group (PK Analysis Set)



Source: Figure 14.2.2.1A.

Abbreviations: PK = pharmacokinetic; SC = subcutaneous; IM = intramuscular; IV = intravenous.

Dosing: Vedolizumab administered by 30-minute IV infusion, IM Injection or SC Injection on Day 1.

The absolute bioavailability of vedolizumab, calculated as the geometric mean ratio of AUC_{0-inf} of test to reference (e.g., SC vs. IV infusion and IM vs. IV infusion) and the associated 80% CI are presented in the table reported below.

Absolute Bioavailability Results

	SC Injection 180 mg (N = 12)	IM Injection 180 mg (N = 11)
AUC_{0-inf}		
Ratio	0.746	0.799
80% Confidence Intervals	(0.666, 0.836)	(0.721, 0.885)

Source: Table 14.2.1.1.

Abbreviations: N = number of subjects; SC = subcutaneous; IM = intramuscular; AUC_{0-inf} = area under the drug concentration-time curve, extrapolated to infinity.

Bioequivalence

Study C13009 was conducted to evaluate the PK, PD, safety, and tolerability of Process C vedolizumab. This study also evaluated the relative bioavailability of Process C vedolizumab compared to Process B vedolizumab. An overview of the study design is presented in Table 16.

Table 16 Summary of Biopharmaceutic Studies With Vedolizumab

Study	Objectives	Study Design
C13009	<p>To determine the PK and PD of a single IV 300 mg dose of Process C vedolizumab</p> <p>To determine the PK and PD of a single IV 600 mg dose of Process C vedolizumab relative to single IV 600 mg Process B vedolizumab</p> <p>To assess the safety and tolerability of a single IV dose of a process C drug product of vedolizumab</p> <p>To evaluate the effect of vedolizumab on cardiac repolarization</p>	<p>Study comprises 2 parts:</p> <p>Part 1: Open-label study to evaluate the single dose PK, PD, safety, and tolerability of 300 mg IV Process C vedolizumab</p> <p>Part 2: Randomized, placebo-controlled, double-blind, parallel group study to evaluate the PK, PD, safety, and tolerability of a single dose of 600 mg IV Process C vedolizumab relative to 600 mg IV Process B vedolizumab</p>

Abbreviations: IV = intravenous; PD = pharmacodynamics, PK = pharmacokinetics.

A summary of the vedolizumab PK parameters is provided in Table 17.

Table 17 Summary of Vedolizumab Pharmacokinetic Parameters (C13009)

Parameter	Vedolizumab Intravenous Dose/Process		
	300 mg Process C ^a	600 mg Process C ^b	600 mg Process B ^c
C _{max} (µg/mL)	115 (31.1)	206 (23.7)	205 (12.6)
AUC _{0-last} (µg*day/mL)	1990 (13.5)	3750 (22.9)	3980 (17.1)
AUC _{0-inf} (µg*day/mL)	2000 (13.2)	3890 (20.7)	4040 (16.1)
t _{1/2} (days)	18.3 (22.1)	21.0 (20.9)	19.4 (21.1)
CL (L/day)	0.150 (12.2)	0.154 (19.7)	0.148 (13.9)
V _z (L)	3.87 (18.9)	4.57 (27.8)	4.06 (17.0)
V _{ss} (L)	4.49 (14.3)	4.95 (20.9)	4.69 (13.1)

Source: [Study C13009, Table 14.2.1.1.](#)

Abbreviations: AUC_{0-inf} = area under the drug concentration-time curve, extrapolated to infinity; AUC_{0-last} = area under the drug concentration-time curve from time 0 to time of last non-zero concentration; CL = clearance; C_{max} = maximum observed drug concentration; CV = coefficient of variation; t_{1/2} = terminal disposition half-life; V_{ss} = volume of distribution at steady state; V_z = volume of distribution during the terminal phase.

Values are presented as geometric mean (%CV) for all parameters except t_{1/2}, which is presented as arithmetic mean (%CV).

n = number of subjects in the pharmacokinetic analysis set.

a n = 10 for C_{max} and 8 for all other parameters.

b n = 24 for C_{max} and 22 for all other parameters.

c n = 21 for C_{max} and 19 for all other parameters.

A summary of the statistical analysis of maximum observed drug concentration (C_{max}) and a under the drug concentration-time curve (AUC) parameters is presented in Table 18.

Table 18 Summary of Statistical Analysis of Vedolizumab Pharmacokinetic Parameters (C13009)

Parameter	Geometric Mean Ratio = Process B/Process C (600 mg)	90% Confidence Interval	
		Lower Bound	Upper Bound
C _{max}	0.995	0.908	1.091
AUC _{0-inf}	1.037	0.944	1.140

Source: [Study C13009, Table 14.2.1.2A.](#)

Abbreviations: AUC_{0-inf} = area under the drug concentration-time curve, extrapolated to infinity;

C_{max} = maximum observed drug concentration.

A summary of the pharmacodynamic parameters is presented in Table 18.

Table 19 Summary of Vedolizumab Pharmacodynamic Parameters (C13009)

Parameter	Vedolizumab Intravenous Dose/Process		
	300 mg Process C (n = 9)	600 mg Process C (n = 24)	600 mg Process B (n = 18) ^a
ACT-I ⁺ [CD4 ⁺ CD45RO ^{high}]			
E _{max} (% Inhibition)	99.8 (0.285)	99.7 (0.378)	99.7 (0.268)
AUEC (% Inhibition*day)	11800 (34.3)	11600 (41.1)	15700 (20.1)
MAAdCAM ⁺ [CD4 ⁺ CD45RO ^{high}]			
E _{max} (% Inhibition)	99.2 (0.567)	98.0 (2.18)	98.3 (0.945)
AUEC (% Inhibition*day)	11300 (32.3)	11400 (38.6)	15300 (19.1)

Source: [Study C13009, Table 14.2.1.4.](#)

Abbreviations: AUEC = area under the drug effect-time curve; E_{max} = maximum drug effect;

CV = coefficient of variation.

Values are presented as geometric mean (%CV).

n = number of subjects in the PD analysis set.

a n = 17 for MAAdCAM.

Distribution

Study C13001: Single Ascending Intravenous Dose Study (Process B).

Table 20 Summary of Vedolizumab Pharmacokinetic Parameters Following Intravenous Infusions (C13001)

Parameter	Vedolizumab dose (IV infusion)				
	0.2 mg/kg (n = 4)	0.5 mg/kg (n = 4)	2.0 mg/kg (n = 7)	6.0 mg/kg (n = 6)	10.0 mg/kg (n = 7)
C _{max} (µg/mL)	5.62 (11.1)	10.4 (19.7)	58.4 (19.6)	150 (12.6)	243 (9.07)
AUC _{0-∞} (µg·day/mL)	31.3 (15.8)	119 (37.9)	955 (15.2)	3020 (24.2)	4840 (12.8)
AUC _{0-inf} (µg·day/mL)	39.1 (14.7)	127 (36.5)	969 (14.9)	3030 (24.2)	4850 (13.0)
V _z (L)	4.02 (3.76)	4.89 (3.76)	3.28 (19.9)	2.92 (21.6)	2.73 (35.2)
CL (L/day)	0.412 (10.1)	0.297 (34.3)	0.164 (10.7)	0.136 (22.0)	0.139 (16.9)
t _{1/2} (day)	6.79 (0.736)	11.7 (2.83)	14.1 (2.67)	15.1 (3.15)	14.8 (7.38)

Source: Study C13001, Table 14.2.2.1.

Abbreviations: C_{max} = maximum observed drug concentration; AUC_{0-inf} = area under the drug concentration-time curve, extrapolated to infinity; AUC_{0-last} = area under the drug concentration-time curve from time 0 to time of last non-zero concentration; CL = clearance; t_{1/2} = terminal disposition half-life; V_z = volume of distribution during the terminal phase; CV = coefficient of variation.

Values are presented as geometric mean (%CV) for all parameters except t_{1/2} which is presented as arithmetic mean (%CV).

n = number of subjects in the PK analysis set.

Elimination

Metabolism

Vedolizumab is a humanized monoclonal antibody and the primary routes of elimination are likely to be proteolytic degradation, similar to that of physiological immunoglobulins, and receptor-mediated clearance.

Dose proportionality and time dependencies

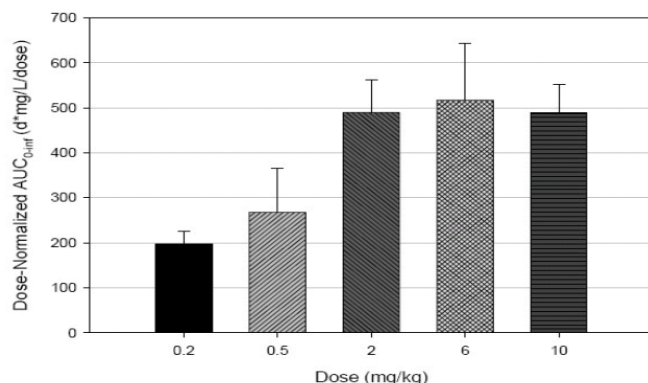
Dose proportionality

Single-dose PK data following IV administration are available over a dose range of 0.2 to 10 mg/kg and 180 to 750 mg vedolizumab. Maximum vedolizumab serum concentrations were achieved at or near the end of infusion and declined in a bi-exponential manner. Concentration-time profiles showed some evidence of nonlinearity once concentrations reached approximately 1 to 10 µg/mL, suggesting clearance may increase at low concentrations.

Dose proportionality was evaluated in C13001 as dose-normalized AUC_{0-inf} versus dose.

The dose normalized AUC_{0-inf} increased with increasing dose until 2.0 mg/kg, as shown in Figure 5, indicating non-proportionality in PK over the lower dose range (0.2-2.0 mg/kg). From 2.0 to 10.0 mg/kg, however, no further increases in dose-normalized AUC_{0-inf} were observed

Figure 5 Mean (\pm Standard Deviation) Dose-Normalized AUC_{0-inf} by Dose Cohort (Study C13001)



Source: Study C13001, Figure 11-3.

Similarly, estimates of clearance, volume of distribution, and terminal half-life were dose dependent over the dose range 0.2 to 2.0 mg/kg. As dose increased, clearance was reduced, distribution volume increased, and consequently, the terminal half-life was prolonged. From 2.0 to 10.0 mg/kg, however, there was no apparent change in these parameters, which suggests a saturation of a rapid elimination process for vedolizumab at low concentrations. Slower linear elimination processes likely account for a large fraction of clearance of vedolizumab at higher doses.

The only study to investigate more than 1 fixed dose of vedolizumab was Study C13009, which included 300 mg and 600 mg vedolizumab. In this study, C_{max} and AUC_{0-inf} increased proportionally to dose (Table 21), while clearance and volume parameters appeared to be dose independent over this dose range.

Table 21 Summary of Single-Dose Pharmacokinetic Parameters Across the 180- to 750-mg Vedolizumab Dose Range ()

Parameter	Vedolizumab (Process C) IV single dose (Study)				
	180 mg (C13010)	300 mg (C13009)	450 mg (C13012)	600 mg (C13009)	750 mg (C13013)
N	N = 11	N = 10 ^a	N = 13	N = 24 ^b	N = 63
C _{max} (µg/mL)	48.2 (13.0)	115 (31.1)	188 (12.6)	206 (23.7)	243
AUC _{0-last} (µg*day/mL)	884 (19.0)	1990 (13.5)	NC	3750 (22.9)	5929
AUC _{0-inf} (µg*day/mL)	899 (18.0)	2000 (13.2)	NC	3890 (20.7)	NC
t _{1/2} (days)	14.3 (20.0)	18.3 (22.1)	NC	21.0 (20.9)	26
CL (L/day)	0.200 (25.5)	0.150 (12.2)	NC	0.154 (19.7)	NC
V _z (L)	4.05 (33.1)	3.87 (18.9)	NC	4.57 (27.8)	NC
V _{ss} (L)	5.72 (14.8)	4.49 (14.3)	NC	4.95 (20.9)	NC

Source: Study C13010, Table 14.2.1.3, Study C13009, Table 14.2.1.1, Study C13012, Table 14.2.1.2A, and Study C13013, Table 14.2.1.1C.

Abbreviations: C_{max} = maximum observed drug concentration; AUC_{0-inf} = area under the drug concentration-time curve, extrapolated to infinity; AUC_{0-last} = area under the drug concentration-time curve from time 0 to time of last non-zero concentration; CL = clearance; t_{1/2} = terminal disposition half-life; V_z = volume of distribution during the terminal phase; V_{ss} = volume of distribution at steady state; CV = coefficient of variation.

Values are presented as geometric mean (%CV) for all parameters except t_{1/2} which is presented as arithmetic mean (%CV).

Sampling schedules differed between studies. All studies had a postdose sample 5-10 minutes after the end of the infusion. Study C13009 had further samples at 1, 2, 12 and 24 hours postdose, and then 8 samples at intervals from Days 8 to Day 197. Study C13010 had samples at 6 and 24 hours postdose and then 10 samples at intervals from Days 4 to Day 127. Study C13012 had samples on Days 5 and 16. Study C13013 had 5 samples at intervals from Days 18 to 127.

a N = 8 for all parameters except C_{max}.

b N = 22 for all parameters except C_{max}.

Study C13010 investigated 180 mg vedolizumab, and the clearance and volume parameters were similar to those in C13009 at 300 and 600 mg. This apparent linear PK at doses of 180 mg

(equivalent to 2.4 mg/kg in a 75-kg person) and above is consistent with the data from the studies with mg/kg dosing.

Time dependency

Repeat-dose PK data following IV administration are available over a dose range of 0.5 to 10.0 mg/kg from studies in patients with UC and CD, including Studies C13002, M200-021, M200-022, and L299-016.

Study C13002 was a Phase 2, Randomized, Placebo-Controlled, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MLN0002 Following Multiple Intravenous Doses in Patients with Ulcerative Colitis. **Process B** vedolizumab was used in the study.

Among the main objectives this study was also designed to define the multiple-dose PK of MLN0002 for a range of IV doses in subjects with UC.

Approximately 45 subjects were to be enrolled in 1 of 3 cohorts (2.0, 6.0, and 10.0 mg/kg) and randomized in a 4:1 ratio of MLN0002 to placebo. Subjects were to receive 4 doses of study drug on Days 1, 15, 29, and 85 and were to be followed until Day 253.

PK samples (Standard PK Sampling Schedule) were collected on Day 1 (prior to and 2 and 12 hours after dosing) and on Day 2 (24 hours after dosing), Day 3 (48 hours after dosing), Day 4 (72 hours after dosing), Day 8 (at any time), Days 15 and 29 (prior to and 2 hours after dosing), Days 43, 57, 71 (at any time), Day 85 (prior to and 2 and 12 hours after dosing), Day 86 (24 hours after dosing), Day 87 (48 hours after dosing), Day 89 (96 hours after dosing), and at any time on Days 92, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, and 253.

Pharmacokinetics results

The PK parameters of vedolizumab following a 30-minute IV infusion of 2.0 to 10.0 mg/kg MLN0002 by dose cohort are summarized in the following Table:

Overview of MLN0002 PK by Dose Cohort (PK Analysis Set)

Parameter	MLN0002 Dose	N	Mean	SD	Geometric Mean	%CV	Median	Min	Max
C_{max}, Day 1 (µg/mL)	2.0 mg/kg	10	54.0	8.9	53.4	16.4	53.8	37.7	69.5
	6.0 mg/kg	14	154.3	41.5	149.2	26.9	149.0	99.3	231.0
	10.0 mg/kg	11	279.0	167.9	243.1	60.2	255.0	69.9	742.0
C_{min}, Day 85 (µg/mL)	2.0 mg/kg	9	7.25	2.41	6.84	33.20	8.06	3.71	10.10
	6.0 mg/kg	14	29.33	13.36	26.24	45.56	28.20	6.97	57.70
	10.0 mg/kg	11	44.74	19.80	40.58	44.26	38.90	13.40	88.50
C_{max}, Day 85 (µg/mL)	2.0 mg/kg	9	60.4	12.5	59.2	20.7	58.3	38.8	76.7
	6.0 mg/kg	14	191.9	42.6	187.9	22.2	184.5	131.0	303.0
	10.0 mg/kg	11	291.9	95.0	273.5	32.6	294.0	94.3	422.0
AUC_(Day 0-14) (day·µg/mL)	2.0 mg/kg	10	375	59	370	16	378	268	471
	6.0 mg/kg	14	1058	270	1026	26	1061	701	1529
	10.0 mg/kg	11	1765	822	1622	47	1671	667	3948
AUC_(Day 85-99) (day·µg/mL)	2.0 mg/kg	9	473	92	465	19	476	312	601
	6.0 mg/kg	14	1532	227	1514	15	1556	1001	1940
	10.0 mg/kg	11	2608	795	2463	31	2631	927	3774
AUC_(Day 85-141) (day·µg/mL)	2.0 mg/kg	9	1082	243	1056	22	1139	662	1490
	6.0 mg/kg	14	3318	698	3248	21	3264	2252	4533
	10.0 mg/kg	11	5633	1927	5305	34	5310	2112	9705
t_{1/2} (day)	2.0 mg/kg	9	15.1	2.0	14.9	13.4	15.6	10.4	17.1
	6.0 mg/kg	14	22.0	6.7	21.0	30.3	22.2	9.5	34.9
	10.0 mg/kg	11	20.6	7.2	19.5	35.0	19.4	11.4	31.9

Source: Section 14.2, Table 14.2.2.1.

Abbreviations: C_{max}, Day 1 = maximum concentration on Day 1; C_{min}, Day 85 = minimum concentration on Day 85; C_{max}, Day 85 = maximum concentration on Day 85; AUC_(Day 0-14) = area under the drug concentration-time curve from Day 0 to Day 14; AUC_(Day 85-99) = area under the drug concentration-time curve from Day 85 to Day 99; AUC_(Day 85-141) = area under the drug concentration-time curve from Day 85 to Day 141; t_{1/2} = terminal elimination half-life

Dosing: MLN0002 administered by 30 minute IV infusion on Days 1, 15, 29 and 85

Pharmacokinetic parameters were generally consistent for Day 1 and Day 85.

C_{max} increased with increasing dose in a linear manner on both Day 1 and Day 85.

The C_{max} on Day 85 was approximately 1.0-fold to 1.2-fold higher than the Day 1 C_{max} across all dose cohorts.

AUC (following first dose and the fourth dose) increased with increasing dose in a linear manner. Comparing between Day 1 and Day 85, the AUC for the 14-day post dose interval (AUC_{Day0-14} and AUC_{Day85-99}) was approximately 1.3-fold to 1.5-fold higher across all dose cohorts, indicating that the 8-week interval between the Day 29 dose and the Day 85 dose was sufficiently long to allow for almost complete elimination of vedolizumab from the serum prior to the dosing on Day 85.

MLN0002 concentrations achieved following dosing on Day 85 were similar to those following dosing on Day 1. The mean elimination half-life was approximately 15 to 20 days across the dose range tested.

Two subjects developed persistent HAHA positivity in this study. In 1 of these subjects, a faster clearance of vedolizumab and loss of α4β7 receptor saturation was observed as compared to the HAHA-negative subjects in the respective dose level.

Special populations

Impaired hepatic function

There were no specific PK studies performed in those with hepatic disease and the pivotal trials excluded those with AST ALT or alkaline phosphatase levels that were >3 x ULN.

Weight

Body weight-adjusted dosing was used in a total of 10 clinical studies, primarily during early clinical development (L297-005, L297-006, L297-007, L299-016, M200-021, M200-022, C13001, C13002, C13004, and C13005). Single and multiple doses ranging from 0.15 to 10.0 mg/kg were investigated

The change from body weight-adjusted dosing to fixed dosing of vedolizumab was made following Study C13005, which investigated the PK of vedolizumab administered at a dose of 6 mg/kg in healthy subjects across predefined ranges of low and high body weights. In addition, population PK analyses were conducted to assess the importance of weight as a predictor of vedolizumab PK. Fixed doses of vedolizumab were used in all subsequent studies including 4 phase 1 studies (C13009, C13010, C13012, and C13013) and all 4 phase 3 studies (C13006, C13007, C13008, and C13011).

Study C13005: Single Intravenous Dose in Subjects With Low and High Body Weight (Process B)

Table 23 Summary of Vedolizumab Pharmacokinetic Parameters Following Intravenous Infusion

Parameter	Vedolizumab 6.0 mg/kg	
	Low body weight (n = 10)	High body weight (n = 13)
C _{max} (µg/mL)	109 (21.2)	170 (17.2)
AUC _{0-∞} (µg·day/mL)	2320 (27.8)	3180 (16.6)
AUC _{0-inf} (µg·day/mL)	2340 (27.4)	3210 (16.1)
V _z (L)	3.56 (33.8)	5.74 (19.6)
CL (L/day)	0.149 (51.7)	0.219 (24.1)
t _{1/2} (day)	17.0 (23.0)	18.6 (21.9)

Source: Study C13005, Table 14.2.2.1.

Abbreviations: C_{max} = maximum observed drug concentration; AUC_{0-∞} = area under the drug concentration-time curve, extrapolated to infinity; AUC_{0-last} = area under the drug concentration-time curve from time 0 to time of last non-zero concentration; CL = clearance; t_{1/2} = terminal disposition half-life; V_z = volume of distribution during the terminal phase; CV = coefficient of variation.

Values are presented as geometric mean (%CV) for all parameters except t_{1/2} which is presented as arithmetic mean (%CV).

n = number of subjects in the PK analysis set.

Weight-adjusted dosing of vedolizumab resulted in a higher mean C_{max} and mean AUC_{0-inf} in heavier subjects compared to subjects with low body weight. Both weight-normalized CL and V_z were lower in the high body weight cohort than in the low body weight cohort. After normalization by body surface area (BSA), both CL and V_z were similar between the 2 cohorts; hence, there was no notable difference in BSA-normalized exposure (AUC_{0-inf}/BSA) by body weight.

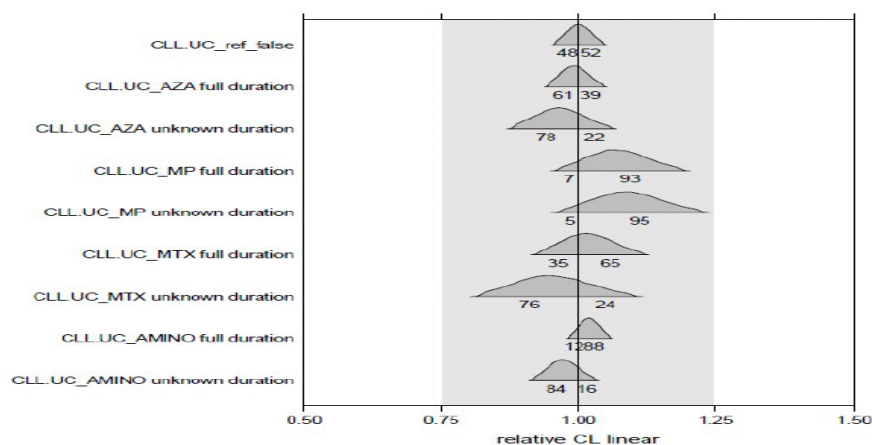
The PK findings suggest that weight-adjusted dosing does not provide similar exposure of vedolizumab to subjects of varying body size.

Exposure relevant for safety evaluation

Finally, once data from phase 3 studies were available, a population PK model was developed from pooled data from phase 1, 2, and 3 studies to assess the effects of patient demographic characteristics and other covariates on vedolizumab PK and to characterize the PK-PD relationships.

No dedicated clinical studies were conducted to evaluate the effect of immunomodulators that can affect or be affected by vedolizumab during co-administration. Concomitant immunomodulator therapies were tested using a population PK approach. The effect of concomitant therapy on vedolizumab Clearance (CLL) was not considered to be clinically meaningful based on covariate effect sizes of less than $\pm 25\%$ from the typical reference population value when evaluated across a representative range of covariate values and categories in the dataset. The effects of the concomitant administration of immunomodulators on CLL are illustrated in Figure 6.

Figure 6 Effect of Concomitant Immunomodulator Therapies on Vedolizumab Clearance in Patients



Source: Population Pharmacodynamic and Pharmacodynamic Modeling of Vedolizumab in Subjects with Crohn's Disease and Ulcerative Colitis for Studies C13002, C13006, C13007, C13009, and C13011. Metrum Research Group.

Abbreviations: CLL = linear clearance; UC = ulcerative colitis; AZA = azathioprine; MP = 6-mercaptopurine; MTX = methotrexate; AMINO = aminosalicylates.

Legend: The filled polygons represent density smooths of values within the 95% central range ($0.025 < p < 0.975$) of 60000 samples from Markov Chain Monte Carlo (MCMC) posterior distributions of the PK parameter. Thus polygon width is proportional to uncertainty. All Bayesian MCMC samples were normalized by dividing by the named PK parameter's point estimate from the final population PK model. Therefore a value 1 represents unity or a null covariate effect. A vertical line is drawn at the reference value, and the shaded region is $\pm 25\%$ of the reference value chosen to represent an uncertainty range of minimal concern. The numbers at the bottom of the polygons indicate the percent of the posterior probability distribution relative to the reference region (ie, unshaded and shaded regions on both sides of the parameter reference value).

2.4.3 Pharmacodynamics

Mechanism of action

The $\alpha 4 \beta 7$ integrin is expressed on the surface of a discrete subset of T lymphocytes that preferentially migrate into the GI tract and cause inflammation that is characteristic of UC and CD. Vedolizumab is a humanized IgG1 monoclonal antibody that binds exclusively to the $\alpha 4 \beta 7$ integrin and inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not vascular cell adhesion molecule-1 (VCAM-1). Disruption of this interaction prevents transmigration of T lymphocytes across the endothelium into inflamed parenchymal tissue. Vedolizumab also blocks $\alpha 4 \beta 7$ -mediated cell binding to an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1) in vitro, which is a component of extracellular matrix. Vedolizumab does not bind to, nor inhibit function of, the $\alpha 4 \beta 1$ and $\alpha E \beta 7$ integrins. Specifically inhibiting the $\alpha 4 \beta 7$ /MAdCAM-pathway alleviates GI inflammation, without impairing immune surveillance of the central nervous system (CNS), nor inhibition of systemic immune responses.

Primary and Secondary pharmacology

Primary pharmacology

Integrins are obligate heterodimers consisting of 2 distinct chains, designated the α and β subunits, of which 24 distinct types have been identified to date. This large variety of heterodimers reflects the distinct functional roles of various integrins in cellular physiology.

T cells express several integrin family members that are involved in activation, trafficking, and retention in tissue

The $\alpha 4\beta 7$ integrin is expressed by discrete subpopulations of memory T lymphocytes. $\alpha 4\beta 7$ mediates the migration of these cells selectively into the GI tract by binding to MAdCAM-1 on the vascular lumen.

Human Tissues and Cells Targeted by MLN0002

Tissue cross-reactivity studies of Act-1 and MLN0002 were consistent with the known pattern of $\alpha 4\beta 7$ expression. The data demonstrated that the primary pharmacologic target of MLN0002 is subpopulations of leukocytes.

Human Leukocytes Bound by MLN0002

The expression profile of the $\alpha 4\beta 7$ integrin in human whole blood was investigated to identify specific leukocyte subtypes whose function could be potentially inhibited by MLN0002 and conversely, leukocytes whose function could not be directly inhibited by MLN0002. The expression pattern of $\alpha 4\beta 7$ was found to be more restricted than the expression pattern of $\alpha 4\beta 1$ in human whole blood. For example, substantially lower percentages of monocytes and lymphocytes expressed $\alpha 4\beta 7$ than $\alpha 4\beta 1$ (Table 24).

Table 24 Percentages of Various Cell Types Expressing Alpha 4 Beta 1 and Alpha 4 Beta 7

Cell Type	Percentage of Integrin Expression on Cells Expressing the Indicated Integrin	
	$\alpha 4\beta 1$	$\alpha 4\beta 7$
Neutrophils	4.6%	2.9%
Eosinophils	100.0%	89.0%
Monocytes	99.5%	15.5%
Lymphocytes	92.9%	60.2%

Source: Report [RPT-01099](#).

Consequently, there are large subpopulations of lymphocytes within human whole blood that express the $\alpha 4\beta 1$ integrin but not $\alpha 4\beta 7$ (Table 25).

Table 25 Percentages of Various Lymphocyte Subpopulations Expressing Alpha 4 Beta 1 and Alpha 4 Beta 7

Cell Type	Percentage of Population Expressing $\alpha_4\beta_1$	Percentage of $\alpha_4\beta_1^+$ Population Expressing $\alpha_4\beta_7$
Natural killer cells	99.6%	64.0%
B lymphocytes	100.0%	88.2%
Helper T lymphocytes	89.8%	56.2%
Helper naïve T lymphocytes	90.9%	72.3%
Helper memory T lymphocytes (CD4 ⁺)	79.1%	35.9%
Cytotoxic T lymphocytes (CD8 ⁺)	98.7%	64.0%

Source: Report [RPT-01099](#).

The converse is also true, particularly for memory T lymphocytes. The $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins are expressed in a reciprocal manner by memory T lymphocytes. The $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins were not co-expressed by subpopulations of human memory helper and cytotoxic T lymphocytes, indicating that discrete populations exist in vivo. The expression pattern of the $\alpha_4\beta_7$ integrin in these subpopulations was inversely related to β_1 expression levels (Table 26).

Table 26 Percentages of Subpopulations of Helper and Cytotoxic T Lymphocytes Expressing Alpha 4 Beta 1 and Alpha 4 Beta 7

$\alpha_4\beta_1$ Profile	Percentage of $\alpha_4\beta_7$ Expression on CD4 ⁺ $\alpha_4\beta_1^+$ Subpopulations	Percentage of $\alpha_4\beta_7$ Expression on CD8 ⁺ $\alpha_4\beta_1^+$ Subpopulations
$\alpha_4^{\text{high}}\beta_1^{\text{high}}$	21.2%	35.4%
$\alpha_4^{\text{high}}\beta_1^{\text{low}}$	96.3%	82.1%
$\alpha_4^{\text{low}}\beta_1^{\text{high}}$	5.3%	25.6%
$\alpha_4^{\text{low}}\beta_1^{\text{low}}$	69.9%	80.1%

Source: Report [RPT-01099](#).

The data illustrate that discrete subpopulations of human leukocytes, expressing either the $\alpha_4\beta_1$ or the $\alpha_4\beta_7$ integrin, exist in vivo. The implications of these data are that the $\alpha_4\beta_7$ integrin-specific antagonist MLN0002 targets a smaller population of leukocytes than the population targeted by dual $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin-specific antagonists. This limited scope of targeted cells is likely a primary determinant of the gut-selective pharmacologic profile of MLN0002.

Study C13012 was a phase 1, single-arm study to evaluate the effects of vedolizumab on the CD4⁺:CD8⁺ lymphocyte ratio in the CSF of healthy subjects.

The primary objective was:

- to evaluate the change in CSF CD4⁺:CD8⁺ lymphocyte ratio before and after a single 450-mg intravenous (IV) dose of vedolizumab.
- The secondary objectives were:
- To determine if reversal of the normal CSF CD4⁺:CD8⁺ lymphocyte ratio to < 1 occurs after a single 450-mg IV dose of vedolizumab
- To assess the safety and tolerability of a single 450-mg IV dose of vedolizumab

All subjects received a single dose of 450 mg vedolizumab as an IV infusion over 30 minutes.

CSF was obtained by lumbar puncture (LP) before and 5 weeks after dosing. Peripheral blood samples for serum vedolizumab concentrations and PD markers were obtained to confirm vedolizumab exposure and $\alpha 4\beta 7$ binding saturation, respectively. Vedolizumab concentration was also analyzed in the post-dose CSF sample. Peripheral blood CD4+ and CD8+ lymphocytes were measured in parallel with CSF samples before and after dosing to determine if changes in peripheral blood may have affected lymphocyte counts in the CSF. Testing for HAHA to vedolizumab was also conducted.

Effect on CD4+:CD8+ Ratio in Cerebrospinal Fluid

Results for the 2 key study endpoints in the CD4+:CD8+ evaluable population are presented in the table reported below.

For the primary endpoint, change from baseline in the CSF CD4+:CD8+ ratio, the results showed essentially no change in the mean CD4+:CD8+ lymphocyte ratio before and after vedolizumab dosing (mean of 3.59 and 3.61, respectively). The mean of the difference in ratios before and after vedolizumab dosing was 0.013 (90% confidence intervals [CI]: -0.337, 0.363).

For the secondary endpoint, the p-value ($p < 0.001$, 1-sided, 1-sample t-test) was highly significant, showing that the CD4+:CD8+ ratio after vedolizumab dosing is not less than 1.

Summary of Treatment Effect on CSF CD4⁺:CD8⁺ Ratio (C13012 CD4⁺:CD8⁺ Evaluable Population)

	N = 13	P-value ^a
Baseline CD4 ⁺ : CD8 ⁺ ratio		
Mean (SD)	3.592 (0.9852)	
Week 5 CD4 ⁺ : CD8 ⁺ ratio		
Mean (SD)	3.605 (0.9560)	< 0.0001
(90% 2-sided CI for ratio)	(3.132, 4.077)	
CD4 ⁺ : CD8 ⁺ ratio difference ^b		
Mean (SD)	0.013 (0.7087)	
(90% 2-sided CI for difference)	(-0.337, 0.363)	

Source: Study C13012, Table 14.3.1.2.

Abbreviations: CI = confidence interval; SD = standard deviation.

^a P-value was from 1-sided, 1- sample t-test for the secondary endpoint, $H_0: \mu < 1$ versus $H_1: \mu \geq 1$.

^b Difference is defined as Week-5 ratio minus baseline ratio.

^c To test the primary endpoint, the lower bound of the 90% 2-sided confidence interval was used. H_0 was rejected if the lower bound value was ≥ -1.67 .

Similar results were observed in the CD4+:CD8+ evaluable population with Week-16 assessments and in the safety population.

Effect on CD4+ and CD8+ Cells in Cerebrospinal Fluid

There were no significant mean or mean percentage changes from baseline in either absolute cell counts or percentage of cells for CSF CD4+ and CD8+ lymphocytes in the CD4+:CD8+ evaluable population (see Table below). The 95% CI for the differences between baseline and Week 5 included zero for both cell populations. The mean change in percentage of CD4+ and CD8+ cells in the CSF after a single dose of vedolizumab was <1%.

Baseline changes for percentage of CD4+ and CD8+ lymphocytes at both baseline and Week 5 are consistent with published data from studies of healthy subjects.

Summary of Treatment Effect on CSF CD4⁺ and CD8⁺ Lymphocytes (C13012 CD4⁺:CD8⁺ Evaluable Population, N = 13)

	Baseline		Week 5		Change from Baseline			
	Mean	SD	Mean	SD	Mean	SD	Median	95% CI
CD4 ⁺ (cells/ μ L)	108.2	94.93	122.5	90.20	14.4	57.72	5.0	-20.493, 49.263
CD4 ⁺ /lymphocytes (%)	75.16	7.383	74.22	6.373	-0.94	4.037	-0.07	-3.384, 1.495
CD8 ⁺ (cells/ μ L)	35.3	35.72	37.1	25.85	1.8	19.59	3.0	-10.070, 13.609
CD8 ⁺ /lymphocytes (%)	22.27	5.432	22.01	6.162	-0.27	2.911	-0.87	-2.024, 1.494

Source: Study C13012, Table 14.3.1.1.

Abbreviations: CI = confidence interval; SD = standard deviation.

% corresponds to % of T lymphocytes.

Baseline is defined as the value collected at the time closest to, but prior to, the start of study drug administration.

The baseline mean (\pm SD) at each visit includes only those baseline results for which there is a corresponding result at that on-study (Week 5) visit.

Similar results were observed for the CD4+:CD8+ evaluable population with Week-16 assessments and the safety population.

Secondary pharmacology

MLN0002 was engineered to contain 2 amino acid changes (Leu239 and Gly241 to Ala) in the FcR binding region of the heavy chain in order to eliminate competent binding mechanism chain. The potential CDC activity of MLN0002 was compared in vitro in human peripheral blood mononuclear cells (PBMCs) to that of OKT3. No cytotoxicity was observed in the presence of MLN0002 or IgG1 isotype control at concentrations as high as 10 μ g/mL, a concentration that was approximately 20-fold greater than that needed to achieve saturation binding of MLN0002 to human whole blood cells. In contrast, OKT3 induced CDC in PBMCs in a dose-dependent manner. These results suggest that the in vivo activity of MLN0002 does not involve CDC.

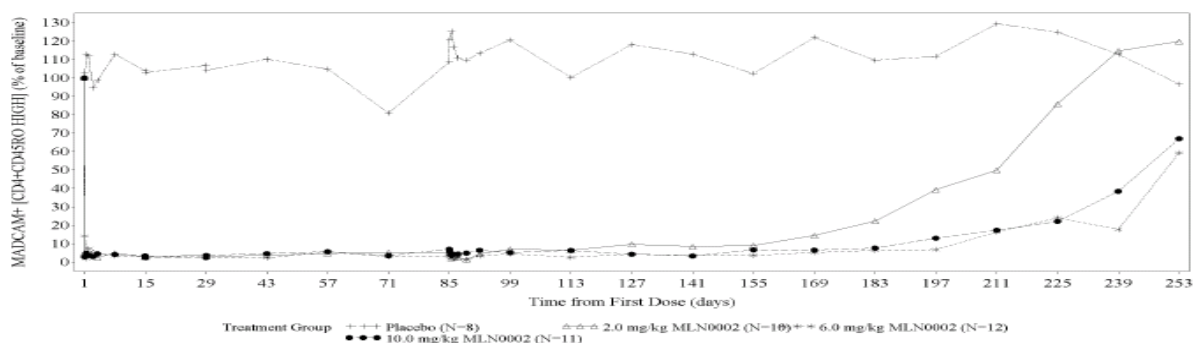
Antibody-dependent cell-mediated cytotoxicity (ADCC) is another common Fc-mediated cytotoxic mechanism of action for therapeutic mAbs, such as the anti-CD20 mAb rituximab, in vivo. The Fc portion of MLN0002 was also engineered to eliminate binding to FcRs. The potential ADCC activity of MLN0002 in vitro in RPMI8866 cells, which express high levels of the α 4 β 7 integrin and CD20, was compared to that of rituximab in vitro. No ADCC was observed in the presence of MLN0002 or IgG1 isotype control at concentrations as high as 10 μ g/mL, a concentration which was approximately 100-fold greater than that needed to achieve saturation binding of MLN0002 to RPMI8866. In contrast, rituximab induced ADCC in RPMI8866 cells in a dose-dependent manner. These results suggest that the in vivo activity of MLN0002 does not involve ADCC.

Binding of vedolizumab to leukocytes in human whole blood in vitro did not elicit cytokine production, including γ -interferon, tumour necrosis factor (TNF) α , interleukin (IL)-1 β , IL-2, IL-4, IL-6, IL-8, IL-12 (P70), IL-17, IL-12 (P40), and IL-23 proteins. Complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) are common Fc-mediated cytotoxic mechanisms for mAbs in vivo. No CDC or ADCC was observed in vitro with vedolizumab at concentrations as high as 10 μ g/mL. The effect of vedolizumab on human regulatory T (Treg)-cells has also been studied in human peripheral blood in vitro, and the data suggest that vedolizumab does not inhibit the suppressive effects of Treg cells.

Relationship between plasma concentration and effect

The relationship between vedolizumab serum concentration and extent of $\alpha 4 \beta 7$ binding saturation by vedolizumab was investigated during the clinical development program. In Study C13001, maximum $\alpha 4 \beta 7$ binding saturation was rapidly achieved following vedolizumab administration (0.2-10.0 mg/kg); hence, it was not possible to draw a clear relationship between vedolizumab dose or concentration with $\alpha 4 \beta 7$ binding inhibition.

Figure 8 Mean Percentage of Baseline Percentage of MAdCAM-1-Fc+ Over Time by Dose Cohorts (Study C13002)



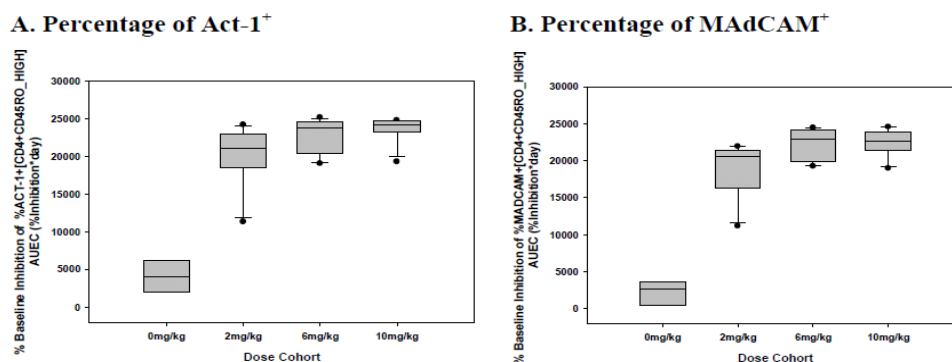
Source: Study C13002, Figure 14.2.4C.

Dosing: Vedolizumab administered by 30-minute IV infusion on Days 1, 15, 29, and 85.

Based on graphical evaluation from study C13002, the loss of near maximal inhibition (> 10% of baseline) of Act-1 began by Days 183, 225, and 211 in the 2.0, 6.0, and 10.0 mg/kg cohorts, respectively, and loss of near maximal inhibition of MAdCAM-1-Fc began by Days 169, 211, and 197 in the 2.0, 6.0, and 10.0 mg/kg cohorts, respectively (Figure 8). Inhibition of both Act-1 and MAdCAM-1-Fc was much lower in patients receiving placebo, and the data were highly variable. A slight dose related trend in AUEC0-tlast was detectable between 2.0 and 6.0 mg/kg vedolizumab, although the values were similar following 6.0 and 10.0 mg/kg vedolizumab (Figure 9). Faster clearance of vedolizumab and loss of $\alpha 4 \beta 7$ binding saturation was observed in 1 of the 2 patients with persistent HABA-positivity compared to HABA-negative patients.

The relationship between Act-1 and vedolizumab serum concentrations was modeled using an Emax model, and the concentration at half maximum effect (IC50) values were low (ranging from 0.093-0.611 ug/mL dependent on inclusion of phase 1 or 2 data and MLN0002 [Process A] or vedolizumab [Process B] material), indicating that saturation is achieved at low vedolizumab concentrations.

Figure 9 Percentage of Baseline Inhibition of Percentage of Act-1 + and Percentage of MadCAM+ AUEC(0-tlast) Versus Dose Cohort (C13002)



Source: Study C13002 PK PD Report, Figure 37 and Figure 39.

The lower and upper edges of the box indicate the 25th and 75th percentiles, the lower and upper whiskers are the 10th and 90th percentiles, and the horizontal line within the box is the median. Solid circles are subjects outside the 10th/90th percentiles.

Vedolizumab led to near-complete saturation of the $\alpha 4\beta 7$ integrin at all dose levels used in the clinical program; consequently, inhibition of $\alpha 4\beta 7$ binding to Act-1 or MAdCAM-1 was found to be an insensitive predictor of clinical response.

Pharmacodynamic interactions with other medicinal products or substances

Study C13013 was conducted to assess the effect of a single dose of 750mg VDZ on the immune response to systemic and mucosal antigenic challenge.

The primary objective was to determine the rates of seroconversion to a hepatitis B vaccine series after a single 750-mg intravenous (IV) dose of vedolizumab or placebo.

The secondary objectives were:

- To determine the rates of seroconversion to an oral cholera vaccine (Dukoral) series after a single 750-mg IV dose of vedolizumab or placebo
- To assess the mean (geometric) change in hepatitis B surface antibody (anti-HBs), after a single 750-mg IV dose of vedolizumab or placebo

Based on the results of this study, the following conclusions can be made:

- Treatment with vedolizumab prior to vaccination with the intramuscular hepatitis B vaccine series did not affect seroconversion rates
- The overall quantitative response to hepatitis B vaccination (as expressed by geometric mean anti-HBs) was not affected by serum vedolizumab concentrations similar to the therapeutic range
- The percentage of subjects who responded to an oral killed cholera vaccine was reduced by pretreatment with vedolizumab

2.4.4 Discussion on clinical pharmacology

Vedolizumab is administered by intravenous (IV) infusion, therefore absorption is not relevant and the bioavailability is expected to be 100%. A phase 1 study (Study C13010) was performed to determine VDZ bioavailability of subcutaneously (SC) and intramuscular (IM) administration. Following IM and SC administration, vedolizumab achieves maximum concentration at 5-7 days post injection. The C_{max} following IM and SC injection was approximately 1/3 of the C_{max} reached after 30 minutes post IV infusion. There was no difference in the terminal elimination profile of IM and SC cohorts compared to the IV cohort, indicating that the elimination of VDZ is not limited to the absorption rate.

Three processes of MLN0002, have been used in nonclinical evaluations and in clinical development program and are identified as Process A, Process B, and Process C. These processes show differences in the manufacturing and/or drug substance/drug product formulation.

The relative bioavailability of Process C and Process B was assessed in study C13009. All PK parameters obtained from these processes were very similar as confirmed by statistical analysis of the bioequivalence, thus indicating that Process B and Process C are bioequivalent (geometric mean ratio of Process B/Process C for C_{max} and AUC are close to 1)

Data from phase 1 studies showed a V_z value of vedolizumab of approximately 0.04 L/kg and PK analyses performed in the population PK study indicated that the distribution volume of VDZ is approximately 5 litres.

The volume of distribution of VDZ clearly indicates that the drug is essentially confined in the systemic circulation, as expected for a protein with a high molecular weight (approximately 146,000 Da).

Vedolizumab is a therapeutic monoclonal antibody and is not expected to bind to plasma proteins, for this reason, plasma protein binding of vedolizumab has not been evaluated, which is acceptable to the CHMP. Since the expected consequence of metabolism of vedolizumab is degradation to small peptides and single amino acid, no studies were performed to assess the route of excretion of vedolizumab; this is in line with ICH S6(R1) guideline and accepted by the CHMP. Moreover, vedolizumab is a high molecular weight protein and the contribution of renal clearance is negligible.

Population PK analyses indicated that vedolizumab has a total body clearance of approximately 0.157 L/day and a plasma half-life of 25 days. The half-life value is consistent with those of therapeutic antibodies (typically 3-4 weeks), which is also similar to that of endogenous IgGs. This relatively long half-life is probably due to binding to neonatal Fc receptor (FcRn), which protects the antibody from proteolysis.

Low doses (≤ 2 mg/kg) of vedolizumab are linked to a decrease of CL, whereas doses higher than 2 mg/kg that lead to a dose-proportional increase of exposure are not associated to a corresponding increase of the CL. This is probably due to a saturable clearance mechanism that is predominating at low concentrations (probably mediated by binding to the cell surface target), while at higher concentrations this mechanism is saturated and the drug is eliminated through a general mechanism of IGgs elimination. This mechanism was also observed with other therapeutic antibodies.

PK parameters were generally consistent for Day 1 and Day 85. C_{max} of VDZ increased dose dependently on both Day 1 and Day 85. The C_{max} on Day 85 was approximately 1.0-fold to 1.2-fold higher than Day 1 across all dose cohorts. Consistently, AUC (following first dose and the fourth dose) also increased in a dose-dependent manner. Day 1 AUC analysis as compared to Day 85, both analysed for 14 days post dose interval (AUC_{Day0-14} and AUC_{Day85-99}) was approximately 1.3-fold to 1.5-fold higher across all dose cohorts, indicating that the 8-week interval between the Day 29 and the Day 85 was long enough to allow almost complete elimination of VDZ from the serum. The only time-dependent change in PK is due to the formation of HAHA.

The findings of the Population PK analysis showed an influence of body weight on weight-normalized CL and V_z (consistent with data from phase 1 study C13005). Weight was found to influence the clearance and exposure, because higher body weight increases the drug clearance. However, the effect should not have any clinical relevance.

The effect of basal albumin level on the clearance is consistent with the observation that the clearance of other therapeutic antibodies (i.e. infliximab, adalimumab) was higher in patients with lower albumin levels. Importantly, patients with low albumin levels also had lower response rates to infliximab (*Int J Clin Pharmacol Ther.* 2010 May; 48(5):297-308).

An exploratory analysis was performed by the Applicant showing that increasing C_{average} leads to a higher probability of clinical remission, clinical response, and enhanced clinical response at Week 6. However, a possible bias should be taken into account in this exposure-response relationship exploratory analysis considering that there are baseline covariates that are or may be related to both exposure and the probability of clinical response or remission in the placebo group.

An exposure-response models for clinical remission and clinical response adjusted for four covariates: baseline ALB, baseline FeCP, baseline CRP, and prior anti-TNF_α use for CD and baseline ALB, baseline FeCP, and prior anti-TNF_α use for UC was developed. The exposure-response relationships estimated in the adjusted models provide some evidence that the exploratory, unadjusted models do not adequately characterize the effect of exposure in this patient population.

In conclusion, the adjusted models for clinical response and clinical remission make an assumption that the exposure-response relationship does not depend on baseline ALB, baseline FeCP, baseline CRP, or prior TNF_α use for UC and CD.

Population PK analysis failed to find a clinically significant effect of HAHA status on the clearance. However, findings of phase 1 and 2 studies clearly showed that in HAHA positive subjects, clearance of the drug and loss of binding saturation to α4β7 sites were faster than in non-positive subjects. PK data after a single dose indicate that PK of VDZ is essentially the same in both HS and patients.

Data from phase 1b/2 studies show that: 1) HAHA formation increase the clearance of the drug and decreases its PD effects; 2) Process A is highly immunogenic; 3) immunogenicity of the drug produced by CHO (Process B and C) is lower than Process A.

Trough concentration data from phase 3 studies are remarkably similar across studies, thus indicating a low variability of the clearance of the drug. Steady-state is reached by week 22, which is consistent with the half-life value found in phase 1 studies.

There was no evidence for a direct interaction with transporters or metabolising enzymes. However, monoclonal antibodies that are cytokine modulators may modify the metabolism of drugs that are substrates for P450 enzymes through their effects on the regulation pathways of P450 enzymes. The effect of vedolizumab on cytokines has been evaluated *in vitro* in human leukocytes isolated from peripheral blood and in clinical studies. Binding of VDZ to leukocytes in human whole blood did not elicit cytokine production, including γ -interferon, TNF α , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-12 (P70), IL-17, IL-12 (P40), and IL-23 proteins, thus suggesting that VDZ is not a cytokine-modulator.

To evaluate the effect of other drugs on vedolizumab PK, concomitant immunomodulator therapies were tested using a population PK approach. The immunomodulator drugs were tested individually in the model: azathioprine, methotrexate, mercaptopurine, and aminosaliclates and the effects of the concomitant administration of immunomodulators on CL_L were not considered clinically relevant.

Pharmacodynamics

Two PD assays (Act-1 and MAdCAM-1-Fc) have been used during the development program. Although termed PD assay by the applicant these assays were designed to assess the lack of Act-1 and MAdCAM-1-Fc binding to the cells of interest; namely memory CD4 and CD8 cells expressing the $\alpha 4 \beta 7$ integrin. It is noted that as cells in peripheral blood express the $\alpha 4 \beta 7$ integrin and this integrin has been shown to bind to MAdCAM-1 on mucosal epithelium, but epithelia such as respiratory and urogenital have also been described to express MAdCAM. However it is understood that the knowledge of $\alpha 4 \beta 7$ positive cell trafficking into mucosa other than GI has not been fully elucidated. The increased incidence of URTIs is highlighted in the SmPC and described in the RMP.

In the phase 3 program (Studies C13006, C13007, C13008, and C13011), positive samples were confirmed for specificity, titered, and examined for the ability to neutralize vedolizumab activity.

The immunogenicity assays used for the phase 3 trials overall are considered adequate by the CHMP.

In view of the potential risk of PML, the lack of blockade of binding of $\alpha 4 \beta 7$ to VCAM by vedolizumab and the lack of mobilisation of stem cells by vedolizumab, together with the non-clinical studies all support the applicant's proposal that the risk of PML is not considered high. In addition assessment of lymphocyte trafficking into the CSF was assessed. Study C13012 was conducted to evaluate the effects of vedolizumab on the CD4⁺:CD8⁺ lymphocyte ratio in the CSF of healthy subjects. These results are consistent with a lack of a vedolizumab effect on lymphocyte numbers within the CSF and support the position that vedolizumab does not inhibit lymphocyte trafficking into the CSF.

2.4.5 Conclusions on clinical pharmacology

Overall the PK and pharmacodynamic effects of VDZ have been extensively studied and there are no major concerns in relation to the PK or pharmacodynamics. PK data and Population PK

analysis showed no accumulation and steady state PK levels with maintenance dosing of 300mg either every 4 or every 8 weeks. PK data also show that concomitant administration of immunomodulators has no significant impact on the PK.

In clinical trials with VDZ at single doses ranging from 0.2 to 10 mg/kg and fixed doses from 180 to 750 mg, binding of Mad-CAM-1-Fc to $\alpha 4 \beta 7$ binding on subsets of circulating lymphocytes was blocked. This PD effect was present when serum VDZ levels were at $\sim 1\mu\text{g/ml}$ and above. A similar PD effect was noted on other cells tested such as B cells.

The range of cells bound by VDZ is broad, but in terms of the lymphocyte subpopulations that express $\alpha 4 \beta 7$ it has been shown that this is a smaller population than the cells expressing $\alpha 4 \beta 1$ which are bound by natalizumab. As VDZ is specific for $\alpha 4 \beta 7$ and the known function of $\alpha 4 \beta 7$ is binding to Mad-CAM in the gut, VDZ will block this interaction. Mad-Cam is expressed in other mucosal surfaces and the effect of blocking cellular trafficking to other mucosal sites is not clear.

As a result of two amino acid changes in the Fc region, VDZ does not activate complement nor bind to Fc Receptors and so cannot be implicated in antibody dependent cellular cytotoxicity nor does VDZ stimulate cytokine release from lymphocytes. After treatment with a single 750mg dose of VDZ in healthy controls it was shown that response to a systemic immunisation (Hepatitis B) was non-inferior to the responses seen in the control group. The immune response to an oral vaccine (Cholera) was reduced by VDZ. It is not clear at this point whether chronic VDZ treatment may impact on immune response to systemic immunisation. This lack of data is reflected in the product information and described in the RMP.

Although no cases of PML have been identified within the VDZ clinical programme, there remains a potential risk. This is considered less than for natalizumab in view of the more restricted range of cells bound by VDZ, the absence of an increase in circulating stem cells, the lack of an effect on lymphocyte trafficking into the CSF, and the supportive non-clinical studies. This risk is addressed in the product information and the risk minimization activities adequately described in the RMP.

No effect on systemic immune responses but a decrease in gut immune responses was observed.

Although the range of cell bound by VDZ is broad there is little scientific information on the effect of VDZ binding to non-gut homing cells. It is however noted that increased URTIs were observed in the clinical trials with VDZ. This is addressed in the RMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

Studies C13007, C13011, and L199-016 were randomized, double-blind, placebo-controlled trials in patients 18 years of age and older with active CD. In these studies, induction efficacy was assessed by evaluating the effects of vedolizumab treatment on clinical response, clinical remission, and other measures of disease activity. The rationale for the posology was the same as that for the UC indication (study C13006).

The strategy for dose selection in this phase 3 study was based on the following considerations:

- Clinical efficacy and dose response in phase 2
- Suppression of HAHA formation
- Serum concentration of vedolizumab at the efficacious doses in phase 2 studies (PK considerations)
- Maintenance of $\alpha 4\beta 7$ receptor saturation (PD considerations)

A dose of 300 mg vedolizumab (approximately equivalent to 4 mg/kg vedolizumab for a 75-kg patient) was selected for the Induction Phase dosing (Weeks 0 and 2). This selection was based on the phase 2 findings that 2 mg/kg vedolizumab administered Q4W as induction therapy was an efficacious dose for both CD and UC, but that maximal efficacy may not have been achieved. Evidence from other biologic agents suggested that incorporating a loading regimen may induce an immune tolerance effect. Also, formation of HAHA following vedolizumab treatment is dose dependent. Therefore, doses higher than those that might ordinarily be acceptable short-term in the absence of HAHA are required to sustain remission throughout the dosing intervals. The favourable safety profile of vedolizumab induction doses up to 10 mg/kg supported selection of this dose for induction therapy in this study.

In the Maintenance Phase, dosing regimens of 300 mg vedolizumab administered Q8W and 300 mg vedolizumab administered Q4W were to be evaluated in separate treatment arms.

The regimen of dosing Q8W was based on the phase 2 studies where 2 mg/kg vedolizumab administered Q4W effectively induced clinical remission in UC and CD. Based on modeling and simulations across the dose range (0.5 to 10 mg/kg), it was expected that a dose of 4 mg/kg Q8W would provide a similar total vedolizumab exposure as achieved with the most efficacious dose (2 mg/kg administered Q4W) in the phase 2 studies.

The regimen of dosing Q4W aimed to ensure that minimum vedolizumab concentrations, similar to those observed at the efficacy endpoints in the phase 2 studies, are maintained over the dosing interval in the majority of patients. Vedolizumab treatment was generally well tolerated in 79 healthy subjects and IBD patients that were treated with doses and/or dose regimens resulting in concentrations that exceeded the median predicted steady-state vedolizumab peak and trough concentrations for the proposed dose (300 mg vedolizumab administered Q4W).

Both dosing regimens were expected to suppress immunogenicity during multiple dosing, thereby maintaining sufficient vedolizumab exposure and $\alpha 4\beta 7$ receptor saturation throughout the dosing interval which, in previous efficacy studies, have been shown to result in clinical efficacy.

2.5.2 Main studies

Ulcerative colitis

For ulcerative colitis the main pivotal study was C13006 which was divided into an induction and a maintenance phase.

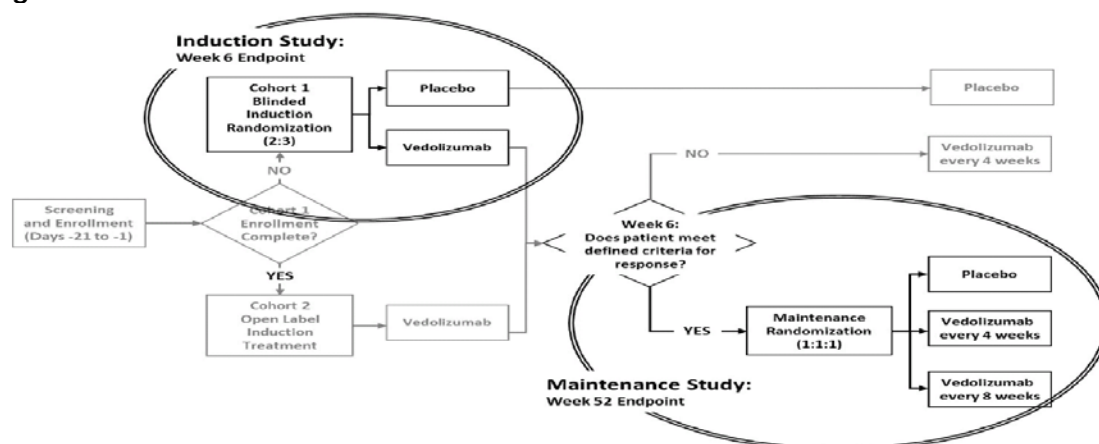
Study C13006 (GEMINI I): A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis.

Methods

Study C13006 was the main pivotal designed to evaluate the efficacy and safety of VDZ as induction and maintenance treatments in patients with moderately to severely active UC who had an inadequate response to, loss of response to, or intolerance to immunomodulators or TNF α antagonists.

Figure 7 shows the overall C13006 trial design, indicating the Induction Phase and the Maintenance Phase treatment periods.

Figure 7 Overview of Induction and Maintenance Studies



Study Participants

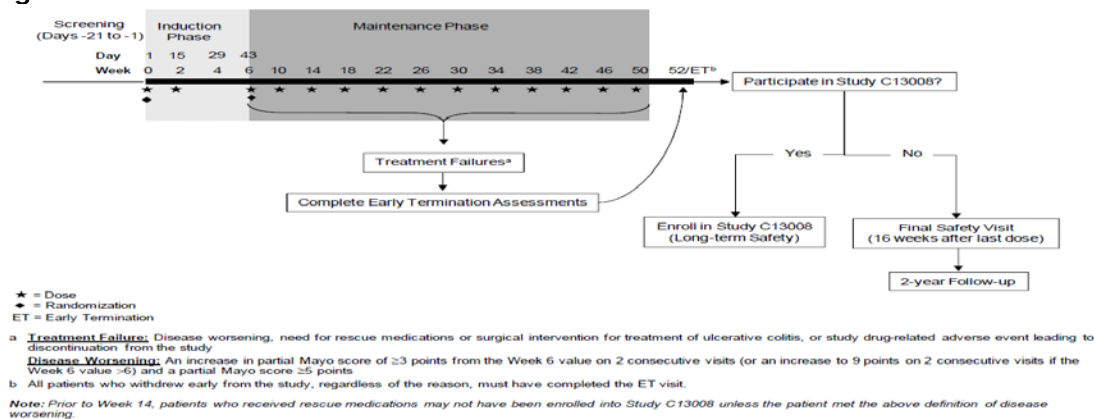
Subjects had to have a diagnosis of UC established at least 6 months and moderately to severely active UC as determined by a Mayo score of 6 to 12 with an endoscopic subscore ≥ 2 within 7 days prior to the first dose of study drug.

They also were required to have evidence of UC extending proximal to the rectum (≥ 15 cm of involved colon) and an inadequate response to, loss of response to, or intolerance of at least 1 of the following: azathioprine (≥ 1.5 mg/kg) 6-mercaptopurine (≥ 0.75 mg/kg) or TNF α antagonists (infliximab).

Treatments

Randomized patients were treated with infusions of double-blind study (VDZ 300mg or saline for placebo arm) drug at Weeks 0 and 2. These patients (Cohort 1) compose the population evaluated for primary efficacy and are referred to as the C13006 Induction Study Intent-to-treat (ITT) population.

Figure 8 Patient Treatment Overview



During the Induction Phase, patients randomized (Cohort 1) or assigned (Cohort 2) to VDZ received an intravenous infusion of VDZ 300 mg at Weeks 0 and 2. VDZ administered to Cohort 1 patients was blinded and VDZ administered to Cohort 2 patients was open label as cohort 2 was enrolled to increase the number of subjects available to enter into the maintenance phase of the study.

During the Maintenance Phase, double-blind VDZ was administered to the 2 VDZ dosing regimen groups in the ITT population (300 mg administered every 4 weeks **or** every 8 weeks). Patients in the VDZ every 4 weeks treatment group received double-blind VDZ infusions every 4 weeks from Week 6 to Week 50, (i.e., Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50). Patients who were randomized to the every 8 weeks dosing regimen received active study drug at Weeks 6, 14, 22, 30, 38, and 46, and, to maintain blinding, placebo saline infusions at Weeks 10, 18, 26, 34, 42, and 50. VDZ-treated patients in the non-ITT population (induction non-responders) received open-label VDZ infusions every 4 weeks from Week 6 through Week 50, i.e., the every 4 week induction dosing regimen was maintained without interruption from the Induction Phase through the duration of the Maintenance Phase.

Objectives

Induction phase

Primary Objective for the Induction Phase

- To determine the effect of vedolizumab induction treatment on clinical response at 6 weeks.

Secondary Objectives for the Induction Phase

- To determine the effect of vedolizumab induction treatment on clinical remission at 6 weeks
- To determine the effect of vedolizumab induction treatment on mucosal healing at 6 weeks
- Safety Objective for the Induction Phase
- To determine the safety profile of vedolizumab induction treatment

Maintenance phase

Primary Objective for the Maintenance Phase

- To determine the effect of vedolizumab maintenance treatment on clinical remission at 52 weeks.

Secondary Objectives for the Maintenance Phase

- To determine the effect of vedolizumab maintenance treatment on durability of clinical response
- To determine the effect of vedolizumab maintenance treatment on mucosal healing at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on durability of clinical remission
- To determine the effect of vedolizumab maintenance treatment on corticosteroid-free remission at 52 weeks
- Safety Objective for the Maintenance Phase
- To determine the safety profile of vedolizumab maintenance treatment

Outcomes/endpoints

Primary and secondary endpoints

Primary Endpoint for the Induction Phase

- Proportion of patients with clinical response at Week 6.

Secondary Endpoints for the Induction Phase

- Proportion of patients in clinical remission at Week 6.
- Proportion of patients with mucosal healing at Week 6.
- Safety Endpoints for the Induction Phase
- Adverse events, SAEs, vital signs, results of standard laboratory tests (clinical chemistry, haematology, coagulation, urinalysis, and HAHA), and results of 12-lead electrocardiograms (ECGs).

Primary Endpoint for the Maintenance Phase

- Proportion of patients in clinical remission at Week 52.

Secondary Endpoints for the Maintenance Phase

- Proportion of patients with durable clinical response.
- Proportion of patients with mucosal healing at Week 52.
- Proportion of patients with durable clinical remission.
- Proportion of patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52. Safety Endpoints for the Maintenance Phase

- Adverse events, SAEs, vital signs, results of standard laboratory tests (clinical chemistry, haematology, coagulation, urinalysis, and HAHA), and results of 12-lead ECGs.

Sample size

A total of 895 patients with moderately to severely active UC were enrolled in Study C13006.

Maintenance phase

The sample size calculation for the Maintenance Study was based on the number of patients who received vedolizumab (in either Cohort 1 or Cohort 2) in the Induction Phase and achieved clinical response at Week 6. Power estimates based on a total sample size of 372 patients (124 per arm) and a two-sided 5% significance level are provided in Table 28.

Table 28 Power Estimates for the Primary and Key Secondary Efficacy Analyses in the Maintenance Study

Objective	Maintenance Period Endpoint at Week 52	Assumed Response Rate	Sample Size per Group ^a	Power
Primary	Remission for vedolizumab vs placebo	Placebo = 30% Vedolizumab = 50%	124	90%
Key secondary	Durable response for vedolizumab vs placebo	Placebo = 14% Vedolizumab = 37%	124	98%
	Mucosal healing for vedolizumab vs placebo	Placebo = 25% Vedolizumab = 50%	124	98%
	Durable remission for vedolizumab vs placebo	Placebo = 7% Vedolizumab = 20%	124	85%
	Corticosteroid-free remission for vedolizumab vs placebo	Placebo = 9% Vedolizumab = 25%	68 ^b	70%

^a Sample sizes included patients from Cohort 1 and Cohort 2. Patients receiving placebo for induction treatment and patients from all treatment arms who were not in clinical response at Week 6 were to be excluded from these analyses.

^b It was expected that 55% of the 124 patients per group would have been on corticosteroids at baseline (ie, at least 68 patients per group would contribute to this endpoint).

Intent-to-Treat Population

For the maintenance efficacy analyses, the ITT population was defined as all randomized patients who received vedolizumab during the Induction Phase and met the protocol definition of clinical response at Week 6, as assessed by the investigator, were randomized, and received any amount of double-blind study drug in the Maintenance Phase. This population was used for the primary efficacy analysis and all proportional-based endpoints, such as remission, response, and corticosteroid-free remission.

Modified Intent-to-Treat Population

Maintenance Study Modified ITT Population

The Modified ITT population for maintenance analyses included all patients randomized as Week 6 responders who received vedolizumab during the Induction Phase, met the protocol definition of clinical response at Week 6, and then received any amount of study drug and had a baseline (Week 0) and at least 1 post Week 6 measurement in the Maintenance Phase for the endpoint under consideration.

This population was used for change from baseline (Week 0) analyses such as analyses of IBDQ, SF-36 and EQ-5D. Patients in this population were analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

Maintenance Study Per-Protocol Population

Patients were to be included in the Maintenance Study Per-Protocol population if they met the following criteria according to the specified hierarchy:

- Confirmed diagnosis of UC of at least 6 months duration and an enrolling Mayo score between 6 and 12 (inclusive) with an endoscopic subscore of ≥ 2
- Received the correct study medication as assigned
- Did not have the treatment assignment unblinded by the investigator
- Met 1 or more of the following criteria for treatment failure prior to week 52:
 - Failed as assessed by the investigator
 - Received any non-study drug due to lack of efficacy
 - Had surgery due to lack of efficacy
 - Had a drug-related AE leading to discontinuation
- Received 80% of doses of study drug, as assigned
- Did not receive concomitant corticosteroids or other potentially effective medications (except as permitted per protocol) for an unrelated comorbid condition (e.g., prednisone for idiopathic thrombocytopenic purpura)
- Had a valid Week 52 or ET assessment for complete Mayo score Analyses using the Per-Protocol population are provided as sensitivity analyses.

Randomisation

Randomization occurred via a central randomization interactive voice response system (IVRS).

The eligibility criteria for both cohorts were identical. In Cohort 1, eligible UC patients were randomized to treatment with double-blind vedolizumab or placebo in a 3:2 ratio. The 3:2 randomization ratio was chosen to increase the number of patients exposed to vedolizumab. The randomization was stratified for 2 factors: 1) concomitant use of oral corticosteroids; and 2) previous exposure to TNF α antagonists and/or concomitant immunomodulators (6-mercaptopurine [6-MP] or azathioprine).

Blinding (masking)

Induction phase C13006

To maintain the blind, all study personnel directly involved with the trial execution, operation, conduct and monitoring, and all study site personnel, except the site investigational pharmacist or designee, were blinded to the patient treatment assignments for the duration of the study.

Statistical methods

Induction Study

The primary endpoint (proportion of patients with clinical response at Week 6) was tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the randomization stratification factors (concomitant use of oral corticosteroids [yes/no] and previous exposure to TNF α antagonists and/or concomitant immunomodulator use [yes/no]). The CMH chi-square p value and the risk difference, along with its 95% two-sided

confidence interval (CI), were provided. The secondary endpoints (proportion of patients in clinical remission at Week 6 and the proportion of patients with mucosal healing at Week 6) were analysed in the same fashion as the primary endpoint. The overall Type I error rate at 5% was controlled through closed sequential methods. The secondary assessments were performed sequentially. The first secondary endpoint was tested only if the primary comparison was significant, and the second secondary endpoint was tested only if the first secondary endpoint was significant for vedolizumab.

For the proportion-based exploratory analyses, the proportions and absolute treatment differences are provided along with their corresponding 95% 2-sided CIs. For continuous variables, the changes from baseline (Week 0) over time were summarized. Changes in HRQOL were assessed by analyses in the IBDQ, SF-36, and EQ-5D scores at Week 6. The mean changes from baseline (Week 0) in IBDQ, SF-36, and EQ-5D scores are presented by treatment arm along with the 95% 2-sided CIs for the differences in mean changes from baseline (Week 0) based on an analysis of covariance (ANCOVA) model.

Maintenance Study

For the 2 dose regimen assessments of the primary endpoint (proportion of patients with clinical remission at Week 52), the CMH chi-square test was used to compare the 2 treatment groups at the 5% level of significance with stratification according to the randomization stratification factors (enrollment in Cohort 1 or 2 in the Induction Phase, concomitant use of oral corticosteroids [yes/no], and previous exposure to TNF alpha antagonists and/or concomitant immunomodulator use [yes/no]). The CMH chi-square p value and the absolute treatment difference along with its 95% 2-sided CI were calculated. The absolute treatment difference was the primary test. In addition, the relative risks were calculated along with the 95% 2-sided CI estimate. For the 2 comparisons of the primary endpoint, the Hochberg method was applied to control the overall Type I error rate at a 5% significance level. Sensitivity Analyses for the primary endpoint were performed considering the Completers (Observe Case) Population and Per-Protocol Population. The secondary efficacy endpoints (proportion of patients with durable clinical response at Week 52, proportion of patients with mucosal healing at Week 52, proportion of patients with durable clinical remission at Week 52, proportion of patients with corticosteroid-free remission at Week 52) were analyzed in the same fashion as the primary endpoint. To maintain the overall Type I error rate at 5% for the 2 dose regimen comparisons for each secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the secondary assessments were also performed sequentially. The first secondary endpoint was tested only if 1 or both of the primary comparisons were significant, and the next secondary endpoint was tested only if the previous secondary endpoint was significant for at least 1 dose. For the proportion-based exploratory analyses, the proportions and absolute treatment differences are provided along with their corresponding 95% 2-sided CI. For continuous variables, the changes from baseline (Week 0) over time were summarized. Changes in HRQOL were assessed by analyses of the IBDQ, SF-36, and EQ-5D questionnaire scores. The mean changes from baseline (Week 0) in IBDQ, SF-36, and EQ-5D scores were tabulated by treatment arm along with 95% 2-sided CIs for the differences in mean changes from baseline (Week 0) based on an ANCOVA model. Time to UC-related hospitalization, time to colectomy, and time to UC-related procedure were analyzed using the Kaplan-Meier method. The 95% CIs around the median were calculated. Time to major UC-related events (defined as the

combination of hospitalizations, colectomies, and UC-related procedures) was assessed using the Marginal Cox Model for multiple Events (Wei, Lin, and Weissfeld Cox-Regression). To apply the Wei, Lin, and Weissfeld method, a separate test statistic (log-rank test) first needed to be computed for each type of event using Cox proportional hazard models adjusting for concomitant medication use at baseline (Week 0), prior exposure to TNFalfa antagonists, geographic region, and Mayo score at baseline (Week 0).

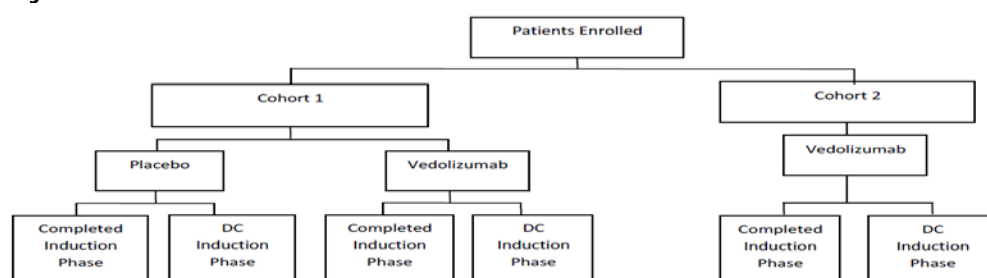
Results

Participant flow

Induction phase C13006

Patient disposition data for the Induction Phase Safety population (i.e., all enrolled patients) are summarized by the ITT treatment group (vedolizumab or placebo; Cohort 1), the non- ITT vedolizumab group (Cohort 2), the combined vedolizumab treatment groups, and by all patients in Figure 14 and in Table 29.

Figure 14 Study Drug Assignment and Disposition of All Patients in Induction Phase – Study C13006



Source: Table 14.1.1.2BP.
Abbreviations: DC = discontinued

A total of 1406 patients were screened for enrollment in the study. Of these, 511 patients failed screening due to the following reasons: did not meet enrollment criteria (394 patients); withdrew consent (36 patients); sponsor's discretion (10 patients); SAE (6 patients); and other or unknown reason (65 patients).

Thus, 895 patients were enrolled in the study and randomized to treatment. Of these, 374 patients were enrolled into Cohort 1 and 521 patients were enrolled into Cohort 2 (including additional patients, per protocol, as recommended by the DSMB based on their monitoring of unblinded response and attrition rates).

Table 29 Patient Disposition – Induction Phase

	Induction Study ITT ^a		Non-ITT		Total N = 895
	PLA N = 149	VDZ Cohort 1 N = 225	VDZ Cohort 2 ^b N = 521	VDZ Combined N = 746	
Randomized/assigned	149	225	521	746	895
Study populations, n (%)					
Safety ^c	149 (100)	225 (100)	521 (100)	746 (100)	895 (100)
Intent-to-treat ^d	149 (100)	225 (100)	—	225 (30)	374 (42)
Per-Protocol ^e	138 (93)	215 (96)	—	215 (29)	353 (39)
Completed Induction Phase, n (%) ^f	135 (91)	218 (97)	485 (93)	703 (94)	838 (94)
Discontinued (reason)	14 (9)	7 (3)	36 (7)	43 (6)	57 (6)
Adverse event	4 (3)	0	7 (1)	7 (< 1)	11 (1)
Protocol violation(s)	1 (< 1)	1 (< 1)	6 (1)	7 (< 1)	8 (< 1)
Lack of efficacy	5 (3)	2 (< 1)	14 (3)	16 (2)	21 (2)
Study terminated by sponsor	0	0	0	0	0
Withdrawal of consent	3 (2)	4 (2)	8 (2)	12 (2)	15 (2)
Lost to follow-up	1 (< 1)	0	1 (< 1)	1 (< 1)	2 (< 1)
Other	0	0	0	0	0

Source: Table 14.1.1.2BP.

Abbreviations: PLA = placebo; VDZ = vedolizumab.

a All patients enrolled in Cohort 1 who were randomized to blinded induction treatment with vedolizumab or placebo.

b All patients enrolled in Cohort 2 who received open-label vedolizumab induction treatment.

c Safety population consists of all patients who received any amount of study drug during the Induction Phase based on what they actually received.

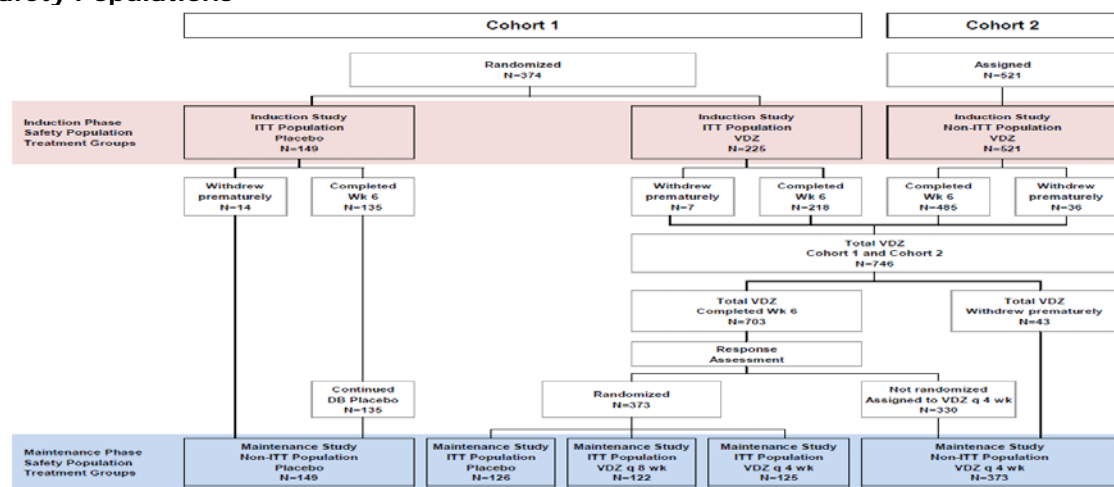
d Intent-to-treat population consists of all randomized patients who received any amount of blinded study drug during the Induction Phase based on what they were randomized to receive.

e Per-Protocol population consists of all patients without any major protocol deviations.

f These patients completed dosing at Weeks 0 and 2 and completed the predose assessments at Week 6.

Maintenance phase C13006

Figure 15 Overview of Treatment Groups in Induction Phase and Maintenance Phase Safety Populations



Non-ITT Population treatment group VDZ q 4 wk (N=373) includes 43 patients who withdrew prematurely from the Induction Phase and were not treated with VDZ q 4 wk during the Maintenance Phase.

In the ITT Population, a greater proportion of placebo-treated patients discontinued treatment than did vedolizumab-treated patients (62% placebo vs. 37% and 33% in the vedolizumab Q8W and Q4W dosing regimens, respectively). The most frequent reason for discontinuation across all of the ITT Population treatment groups was lack of efficacy, which occurred in 48% of the placebo group and less frequently in the vedolizumab groups (25% and 26%, respectively). Discontinuations due to adverse events were twice as frequent in the placebo group (12% vs. 6% and 5% in the two vedolizumab groups, respectively). Most of the patients in the ITT population continued into the long-term Study C13008.

Recruitment

First Patient Enrolled: 19 January 2009

Last Patient Completed: 26 March 2012.

Conduct of the study

Induction phase

Protocol Deviations Leading to Exclusion from the Per-Protocol Population, Induction

A total of 21 patients (11 patients from the placebo group and 10 patients from the ITT vedolizumab group) had at least 1 protocol deviation and are excluded from the Per-Protocol population. For both groups, an invalid Day 43/ET assessment was the most common protocol deviation. An invalid Day 43/ET assessment may have been due to either a clinical assessment outside Days 36 to 56 (inclusive) or a sigmoidoscopy performed outside Days 29 to 56 (inclusive).

Baseline data

Induction phase

Patients were predominantly white (82%), male (59%) with a mean age of 40.3 years (range 18-78 years) and a mean weight of 73.4 kg (range 32-174 kg). Overall, baseline demographics were similar for VDZ and placebo patients in the ITT population. With respect to geographic distribution, 37% were enrolled at sites in North America and 63% were enrolled at sites outside of North America, including 22% in sites located in Asia, Australia, and Africa, 19% in Western/Northern European sites, 13% in Central European sites, and 8% in Eastern European sites.

The mean duration of disease was 6.9 years (median 4.9 years) and the mean baseline disease activity, as assessed by the baseline Mayo score, was 8.6. Fifty percent of patients had a complete Mayo Score of 9 to 12 (inclusive), 64% of patients had baseline fecal calprotectin of > 500 µg/g, and most of the patients had left-sided colitis (38%) or pancolitis (37%). Most of the patients did not have history of extraintestinal manifestations (67%). The ITT population treatment groups were comparable with respect to disease characteristics. The baseline demographic characteristics and baseline disease characteristics of the Cohort 2 patients were similar to those of patients in Cohort 1. Enrollment of patients with prior TNF α antagonist use was limited to no more than 50%; in the entire study population, 52% of patients were TNF α antagonist naive.

Concomitant medications (induction phase)

Most placebo and VDZ patients used at least 1 concomitant medication (UC-related and non-UC related). Of the standard medications used for UC, 5-ASAs were the most common and were used by 74% of patients. There were no notable treatment differences between the groups in the use of concomitant medications for UC.

Maintenance phase C13006

Baseline demographics were similar to the induction phase. Baseline disease characteristics are shown in table 5.

Table 5 Baseline Ulcerative Colitis Disease Characteristics – Maintenance Phase Safety Population

	Maintenance Study ITT ^a (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Non-ITT		Combined	
	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA ^b N = 149	VDZ Q4W ^c (Week 6 nonresponders) N = 373	PLA (from Week 6) N = 275	VDZ N = 620
Baseline fecal calprotectin							
n	122	117	117	139	362	261	596
Mean (std dev)	2055.6 (2935.39)	1686.3 (2609.01)	1782.9 (2918.17)	2369.9 (3258.82)	1700.3 (2439.94)	2223.0 (3109.89)	1713.7 (2569.14)
Median	1070.9	863.7	793.0	1005.5	852.0	1012.4	844.5
Minimum, maximum	23.8, 20000.0	34.9, 18061.8	23.8, 20000.0	23.8, 16443.8	23.8, 20000.0	23.8, 20000.0	23.8, 20000.0
Categorical baseline fecal calprotectin							
≤ 250 µg/g	25 (20)	26 (21)	21 (17)	27 (18)	59 (16)	52 (19)	106 (17)
> 250 to ≤ 500 µg/g	13 (10)	18 (15)	19 (15)	20 (13)	52 (14)	33 (12)	89 (14)
> 500 µg/g	84 (67)	73 (60)	77 (62)	92 (62)	251 (67)	176 (64)	401 (65)
Missing	4	5	8	10	11	14	24
Disease localization, n (%)							
Proctosigmoiditis	9 (7)	18 (15)	14 (11)	22 (15)	53 (14)	31 (11)	85 (14)
Left sided colitis	53 (42)	51 (42)	45 (36)	59 (40)	131 (35)	112 (41)	227 (37)
Extensive colitis	17 (13)	14 (11)	14 (11)	18 (12)	46 (12)	35 (13)	74 (12)
Pancolitis	47 (37)	39 (32)	52 (42)	50 (34)	143 (38)	97 (35)	234 (38)
Smoking status, n (%)							
Current smoker	8 (6)	7 (6)	8 (6)	11 (7)	21 (6)	19 (7)	36 (6)
Nonsmoker	87 (69)	82 (67)	82 (66)	88 (59)	216 (58)	175 (64)	380 (61)
Former smoker	31 (25)	33 (27)	35 (28)	50 (34)	136 (36)	81 (29)	204 (33)
	Maintenance Study ITT ^a (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Non-ITT		Combined	
	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA ^b N = 149	VDZ Q4W ^c (Week 6 nonresponders) N = 373	PLA (from Week 6) N = 275	VDZ N = 620
History of extraintestinal manifestations							
Yes	39 (31)	46 (38)	48 (38)	44 (30)	121 (32)	83 (30)	215 (35)
No	87 (69)	76 (62)	77 (62)	105 (70)	252 (68)	192 (70)	405 (65)

Source: Table 14.1.1.6AM

Baseline refers to Week 0.

Abbreviations: ITT = intent-to-treat; PLA = placebo; std dev = standard deviation; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; VDZ = vedolizumab.

a Patients who were randomized into the ITT population during the Maintenance Phase.

b Patients who received placebo during the Induction Phase and continued to receive placebo during the Maintenance Phase.

c Patients who received vedolizumab in the Induction Phase but did not achieve clinical response at Week 6 and continued to receive vedolizumab every 4 weeks during the Maintenance Phase.

d Duration of Ulcerative Colitis is defined as (1+first dose date – diagnosis date)/ 365.25.

e Baseline disease activity represents the baseline complete Mayo score.

Baseline disease activity, as assessed by mean Mayo score and category of Mayo score, was similar in the 3 groups, as was the category of baseline fecal calprotectin. There were treatment differences in mean baseline fecal calprotectin; however, due to large variability in the values, it is unlikely that these represent actual differences. In general, baseline disease characteristics in the non-ITT treatment groups were similar to those in the ITT treatment groups, with the exception of median UC durations (4.5 years and 4.6 years in the non-ITT placebo and VDZ groups, respectively).

Prior TNFα antagonist use was similar in the ITT population treatment groups (37-42%), as was prior use of other UC treatments. The majority of patients had exposure to systemic corticosteroids and / or immunomodulators: 97% of combined placebo patients and 98% of combined VDZ patients had exposure to corticosteroids; 75% of combined placebo patients and 76% of combined VDZ patients had exposure to immunomodulators.

Concomitant medications (maintenance phase)

Of the standard medications for UC, 5-ASAs were the most common and were used by 70% to 78% of patients.

Numbers analysed

Induction phase

Table 6 summarizes analysis populations within the Induction Study ITT population. The Induction Study ITT population (main analysis population for efficacy) includes the full set of

randomized patients during the Induction Phase. All randomized patients received at least 1 dose of study drug and are included in the Safety population.

Table 6 Summary of Induction Analysis Populations – Cohort

Data Set, Number (%) of Patients	PLA N = 149	VDZ N = 225
Randomized patients	149	225
Safety population ^a	149 (100)	225 (100)
Intent-to-treat population ^b	149 (100)	225 (100)
Modified ITT population ^c	140 (94)	217 (96)
Per-Protocol population ^d	138 (93)	215 (96)
Completers (Observed Case) population ^e	137 (92)	216 (96)

Source: Table 14.1.1.4.

Abbreviations: ITT = intent-to-treat; PLA = placebo; VDZ = vedolizumab.

a Safety population consists of all patients in Cohort 1 who received any amount of study drug during the Induction Phase based on what they actually received.

Maintenance phase

All patients randomized into the Maintenance Study ITT population were treated with VDZ during the Induction Phase and achieved clinical response, as assessed by the investigator. Patients in the Maintenance Study ITT placebo treatment group received their first dose of placebo at Week 6.

Table 7 summarizes the analysis populations within the Maintenance Study ITT population (ie, only patients who received VDZ during the Induction Phase, met the protocol definition of clinical response at Week 6, and then received any amount of study drug in the Maintenance Phase.

Table 7 Summary of Maintenance Analysis Populations – Maintenance Study ITT Population

Data Set	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Randomized patients	126	122	125
Safety population ^a	126 (100)	122 (100)	125 (100)
Intent-to-treat population ^b	126 (100)	122 (100)	125 (100)
Modified ITT population ^c	112 (89)	111 (91)	116 (93)
Per-Protocol population ^d	121 (96)	117 (96)	121 (97)
Completers (Observed Case) population ^e	48 (38)	77 (63)	83 (66)

Source: Table 14.1.1.4M.

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; VDZ = vedolizumab.

- a The Safety population consists of all Maintenance Study ITT patients who received any amount of study drug during the Maintenance Phase based on what they actually received.
- b The ITT population consists of patients designated as responders through IVRS in induction who received any amount of blinded study drug during the Maintenance Phase based on what they were randomized to receive.
- c The Modified ITT population for the Maintenance Phase consists of all Maintenance Study ITT patients who received any amount of blinded study drug and have a baseline (Week 0) and at least 1 measurement post-randomization (Week 6) for complete Mayo score.
- d The Per-Protocol population consists of all Maintenance Study ITT patients without any major protocol deviations.
- e The Completers (Observed Case) population consists of all Maintenance Study ITT patients designated as responders through IVRS in induction who received any amount of blinded study drug during the Maintenance Phase and have a baseline (Week 0) and Week 52 assessment for the endpoint under consideration (complete Mayo score). Percentages are calculated using the number of the "Intent-to-treat population" as the denominator.

Outcomes and estimation

Induction phase results

The primary endpoint for the Induction Study, the proportion of patients with clinical response at Week 6, was met.

Table 8 Clinical Response at Week 6 – Induction Study ITT Population

Clinical Response ^a	PLA N = 149	VDZ N = 225
Number (%) achieving clinical response	38 (25.5)	106 (47.1)
95% CI	(18.5, 32.5)	(40.6, 53.6)
Difference from placebo ^b		21.7
95% CI for difference from placebo		(11.6, 31.7)
P value for difference from placebo ^c		< 0.0001
Relative risk ^d		1.8
95% CI for relative risk		(1.4, 2.5)

Source: [Table 14.3.1.2A](#).

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PLA = placebo; VDZ = vedolizumab.

a Clinical response is defined as reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.

b Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); and 2) previous exposure to TNF α antagonist or concomitant immunomodulator use (yes/no).

d Adjusted relative risk and its 95% CI.

Secondary Efficacy Endpoints, Induction

Clinical Remission at Week 6

Table 9 Clinical Remission at Week 6 – Induction Study ITT Population

Clinical Remission ^a	PLA N = 149	VDZ N = 225
Number (%) achieving clinical remission	8 (5.4)	38 (16.9)
95% CI	(1.7, 9.0)	(12.0, 21.8)
Difference from placebo ^b		11.5
95% CI for difference from placebo		(4.7, 18.3)
P value for difference from placebo ^c		0.0009
Relative risk ^d		3.1
95% CI for relative risk		(1.5, 6.6)

Source: [Table 14.3.1.4A](#).

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PLA = placebo; VDZ = vedolizumab.

a Clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point.

b Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); and 2) previous exposure to TNF α antagonist or concomitant immunomodulator use (yes/no).

d Adjusted relative risk and its 95% CI.

Mucosal Healing at Week 6

Table 10 Mucosal Healing at Week 6 – Induction Study ITT Population

Mucosal Healing ^a	PLA N = 149	VDZ N = 225
Number (%) achieving mucosal healing ^a	37 (24.8)	92 (40.9)
95% CI	(17.9, 31.8)	(34.5, 47.3)
Difference from placebo ^b		16.1
95% CI for difference from placebo		(6.4, 25.9)
P value for difference from placebo ^c		0.0012
Relative risk ^d		1.6
95% CI for relative risk		(1.2, 2.3)

Source: [Table 14.3.1.6A](#).

Abbreviations: CHM = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PLA = placebo; VDZ = vedolizumab.

a Mucosal healing is defined as Mayo endoscopic subscore of ≤ 1 point.

b Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); and 2) previous exposure to TNF α antagonists or concomitant immunomodulator use (yes/no).

d Adjusted relative risk and its 95% CI.

The primary and both secondary endpoints were met with convincing clinical and statistical significance for the induction phase of study C13006.

Maintenance phase results

Primary endpoint

The primary endpoint for the Maintenance Study, the proportion of patients with clinical remission at Week 52, was met. The clinical benefit of VDZ was evident in the significantly higher remission rate for VDZ patients compared to placebo patients ($p < 0.0001$ for both VDZ treatment groups compared to placebo).

Table 11 Clinical Remission at Week 52 – Maintenance Study ITT Population

Clinical Remission ^a	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving clinical remission	20 (15.9)	51 (41.8)	56 (44.8)
95% CI	(9.5, 22.3)	(33.1, 50.6)	(36.1, 53.5)
Difference from placebo ^b		26.1	29.1
95% CI for difference from placebo		(14.9, 37.2)	(17.9, 40.4)
P value for difference from placebo ^c		< 0.0001	< 0.0001
Relative risk ^d		2.7	2.8
95% CI for relative risk		(1.7, 4.2)	(1.8, 4.4)

Source: [Table 14.3.1.2AM](#).

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

a Clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point at Week 52.

b Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with 3 stratification factors: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF α or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

d Adjusted relative risk and its 95% CI.

Secondary endpoints maintenance phase

Durable clinical response, defined as a clinical response at Weeks 6 and 52, was a key secondary endpoint of the Maintenance Study.

Table 12 Durable Clinical Response – Maintenance Study ITT Population

Durable Clinical Response ^a	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving durable clinical response	30 (23.8)	69 (56.6)	65 (52.0)
95% CI	(16.4, 31.2)	(47.8, 65.4)	(43.2, 60.8)
Difference from placebo ^b		32.8	28.5
95% CI for difference from placebo		(20.8, 44.7)	(16.7, 40.3)
P value for difference from placebo ^c		< 0.0001	< 0.0001
Relative risk ^d		2.4	2.2
95% CI for relative risk		(1.7, 3.4)	(1.5, 3.1)

Source: [Table 14.3.1.4AM](#).

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent to treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

a Durable clinical response is defined as reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline (Week 0) 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.

b Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with 3 stratification factors: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF α antagonist or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

d Adjusted relative risk and its 95% CI.

Mucosal Healing at Week 52

The number and proportion of patients with mucosal healing at Week 52 in the Maintenance Study ITT population are summarized by treatment group in Table 13.

Table 13 Mucosal Healing at Week 52 – Maintenance Study ITT Population

Mucosal Healing ^a	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving mucosal healing	25 (19.8)	63 (51.6)	70 (56.0)
95% CI	(12.9, 26.8)	(42.8, 60.5)	(47.3, 64.7)
Difference from placebo ^b		32.0	36.3
95% CI for difference from placebo		(20.3, 43.8)	(24.4, 48.3)
P value for difference from placebo ^c		< 0.0001	< 0.0001
Relative risk ^d		2.6	2.8
95% CI for relative risk		(1.8, 3.9)	(1.9, 4.2)

Source: [Table 14.3.1.6AM](#).

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent to treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

a Mucosal healing is defined as Mayo endoscopic subscore of ≤ 1 .

b Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with 3 stratification factors: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF α antagonists or concomitant immunomodulator use (yes/no); and 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

d Adjusted relative risk and its 95% CI.

Durable Clinical Remission

Table 14 Durable Clinical Remission – Maintenance Study ITT Population

Durable Clinical Remission ^a	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving durable clinical remission	11 (8.7)	25 (20.5)	30 (24.0)
95% CI	(3.8, 13.7)	(13.3, 27.7)	(16.5, 31.5)
Difference from placebo ^b		11.8	15.3
95% CI for difference from placebo		(3.1, 20.5)	(6.2, 24.4)
P value for difference from placebo ^c		0.0079	0.0009

Durable Clinical Remission ^a	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Relative risk ^d		2.4	2.8
95% CI for relative risk		(1.2, 4.6)	(1.4, 5.3)

Source: Table 14.3.1.7AM.

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TNFα = tumor necrosis factor alpha; VDZ = vedolizumab.

a Durable clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point at both Weeks 6 and 52.

b Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with 3 stratification factors: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists or concomitant immunomodulator use (yes/no); and 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

d Adjusted relative risk and its 95% CI.

Corticosteroid-free Remission at Week 52

As specified in the study protocol, all Maintenance Study ITT patients who were on corticosteroids at Week 6 were to begin a corticosteroid tapering regimen; approximately 58% of the ITT population were on corticosteroids at Week 6

Table 15 Corticosteroid-free Remission at Week 52 – Maintenance Study ITT Population, Patients on Corticosteroids at Baseline

Corticosteroid-free Clinical Remission ^a	PLA n = 72	VDZ Q8W n = 70	VDZ Q4W n = 73
Number (%) achieving corticosteroid-free clinical remission	10 (13.9)	22 (31.4)	33 (45.2)
95% CI	(5.9, 21.9)	(20.6, 42.3)	(33.8, 56.6)
Difference from placebo ^b		17.6	31.4
95% CI for difference from placebo		(3.9, 31.3)	(16.6, 46.2)
P value for difference from placebo ^c		0.0120	< 0.0001

Corticosteroid-free Clinical Remission ^a	PLA n = 72	VDZ Q8W n = 70	VDZ Q4W n = 73
Relative risk ^d		2.3	3.3
95% CI for relative risk		(1.2, 4.4)	(1.7, 6.1)

Source: Table 14.3.1.8AM.

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TNFα = tumor necrosis factor alpha; VDZ = vedolizumab.

n represents patients who were on corticosteroids at baseline (Week 0), as entered into IVRS.

a Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.

b Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI.

c P values are based on the CMH chi-square test, with 2 stratification factors: 1) previous exposure to TNFα antagonists or concomitant immunomodulator use (yes/no) 2) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

d Adjusted relative risk and its 95% CI.

Crohn's disease (CD)

Study C13007 (GEMINI II): A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients With Moderate to Severe Crohn's Disease

Methods

Study C13007, was a multinational study conducted at 285 sites. This trial was designed to support the registration of VDZ for induction and maintenance treatment of a broad population of patients who have failed 1 or more standard therapies for CD, including immunomodulators (azathioprine, 6-MP, or methotrexate) and TNF α antagonists. To ensure that the efficacy of VDZ could be evaluated in patients who are naïve to TNF α antagonists, enrollment of patients with previous TNF α antagonist exposure was to be limited to no more than 50% of the overall study population.

Study C13007 was designed to comprise 2 randomized, double-blind, placebo-controlled studies conducted under 1 protocol which, operationally, consisted of 2 phases:

- The Induction Phase, designed to establish the efficacy and safety of VDZ for the induction of clinical response and clinical remission, and
- The Maintenance Phase, designed to establish the efficacy and safety of VDZ for the maintenance of clinical response and clinical remission.
- Patients in the Induction Phase were to continue on into the Maintenance Phase according to protocol-defined criteria. Although conducted under 1 protocol for operational efficiency, the 2 phases described above included 2 separate sequential double-blind, placebo-controlled efficacy studies. Patients who met protocol-specified criteria for clinical response during induction were eligible for randomization into the maintenance efficacy study. Each study has distinct endpoints, randomization schema, defined populations, and analysis plans.

Study Participants

Inclusion criteria were chosen to select for patients with moderately to severely active disease with a CDAI score of 220 to 450 and one of the following:

- CRP level > 2.87 mg/L during the Screening period

OR

- Ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous cm of intestine) consistent with CD, within 4 months prior to randomization

OR

- Fecal calprotectin > 250 mcg/g stool during the Screening period in conjunction with computed tomography (CT) enterography, magnetic resonance (MR) enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing Crohn's ulcerations (aphthae not sufficient), within 4 months prior to screening. (Patients with evidence of fixed stenosis or small bowel stenosis with pre-stenotic dilation should not be included.)

- Patients who were too ill or who could not benefit from medical treatment (such as patients with symptomatic stenoses, patients with severe disease that required surgical treatment, and patients with extensive surgeries) were excluded. Patients with serious comorbidities or who had neurological conditions that could confound the assessments for potential cases of PML were also to be excluded.

Treatments

During the Induction Phase, patients randomized (Cohort 1) or assigned (Cohort 2) to VDZ were to receive an IV infusion of VDZ 300 mg at Weeks 0 and 2. VDZ administered to Cohort 1 patients was to be blinded and VDZ administered to Cohort 2 patients was to be open label. 24 different batches were used in C13007. Patients randomized to placebo were to receive 250 mL of 0.9% sodium chloride IV at Weeks 0 and 2.

During the maintenance phase the active arms received 300mg VDZ as maintenance treatment administered either every 4 weeks (Q4W) **or** every 8 weeks (Q8W).

Objectives

Induction phase:

Primary Objectives for the Induction Phase

- To determine the effect of vedolizumab induction treatment on clinical remission at 6 weeks
- To determine the effect of vedolizumab induction treatment on enhanced clinical response at 6 weeks

Secondary Objective for the Induction Phase

- To determine the effect of vedolizumab induction treatment on serum C-reactive protein (CRP) levels at 6 weeks in patients with elevated CRP levels at baseline
- Safety Objective for the Induction Phase
- To determine the safety profile of vedolizumab induction treatment

Exploratory Objectives for the Induction Phase

- To analyze key endpoints in the subgroup of patients with previous exposure to TNF α antagonist therapy and in the subgroup of patients defined as having failed TNF α antagonist therapy
- To analyze key endpoints in the subgroups of patients on concomitant therapies
- To correlate Crohn's Disease Activity Index (CDAI) scores with Harvey-Bradshaw Index (HBI) scores

Maintenance Phase

Primary Objective for the Maintenance Phase

- To determine the effect of vedolizumab maintenance treatment on clinical remission at 52 weeks

Secondary Objectives for the Maintenance Phase

- To determine the effect of vedolizumab maintenance treatment on enhanced clinical response at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on corticosteroid-free remission at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on durability of clinical remission

Safety Objective for the Maintenance Phase

- To determine the safety profile of maintenance vedolizumab treatment

Outcomes/endpoints

Induction phase:

Primary Endpoints for the Induction Phase

- Proportion of patients in clinical remission at Week 6
- Proportion of patients with enhanced clinical response at Week 6

Secondary Endpoint for the Induction Phase

- Change in serum CRP levels at Week 6

Maintenance Phase

Primary Endpoint for the Maintenance Phase

- Proportion of patients in clinical remission at Week 52

Secondary Endpoints for the Maintenance Phase

- Proportion of patients with enhanced clinical response at Week 52
- Proportion of patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at Week 52
- Proportion of patients with durable clinical remission

Sample size

Approximately 1059 patients were planned to be enrolled into this study from approximately 500 sites worldwide. An initial cohort (Cohort 1) of 370 patients was to be randomized in the Induction Phase, based on the sample size requirements of the Induction Study. Approximately 689 patients were then to be enrolled in Cohort 2. The number of patients to be enrolled in Cohort 2 was determined by the sample size requirements of the Maintenance Study. The protocol allowed for up to 100 additional patients to be enrolled into Cohort 2 (increasing the total number of study participants to 1159), depending on the observed overall response rate in the combined cohorts, to ensure that at least 501 patients with clinical response at Week 6 to vedolizumab treatment were randomized in the Maintenance Phase.

Randomisation

The IVRS provided treatment assignments based on randomization numbers.

Blinding (masking)

All patients and all study personnel except for those directly involved with study drug preparation (e.g., the site pharmacist) were to be blinded to study drug assignment for the entire study. Study drug was to be masked by the unblinded site pharmacist using IV bag covers to maintain blinding.

Statistical methods

Induction study: The primary endpoints (proportion of patients with clinical remission at Week 6 and proportion of patients with enhanced clinical response at Week 6 in the ITT Population) were tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification based on the following stratification factors: concomitant use of oral corticosteroids [yes/no] and previous exposure to TNF α antagonists or concomitant immunomodulator use [yes/no]. The CMH chi-square p value and the risk difference, along with its 95% confidence interval (CI), were provided. In addition, the relative risk was provided with the 95% two-sided CI. The Hochberg method was used to preserve alpha for the 2 primary endpoints. For the Induction Study, there was 1 secondary assessment of clinical efficacy (mean CRP levels), which compared the treatment difference between vedolizumab and placebo. To further maintain the overall Type I error rate at 5%, the secondary endpoint was to be tested only if at least 1 of the primary comparisons was significant.

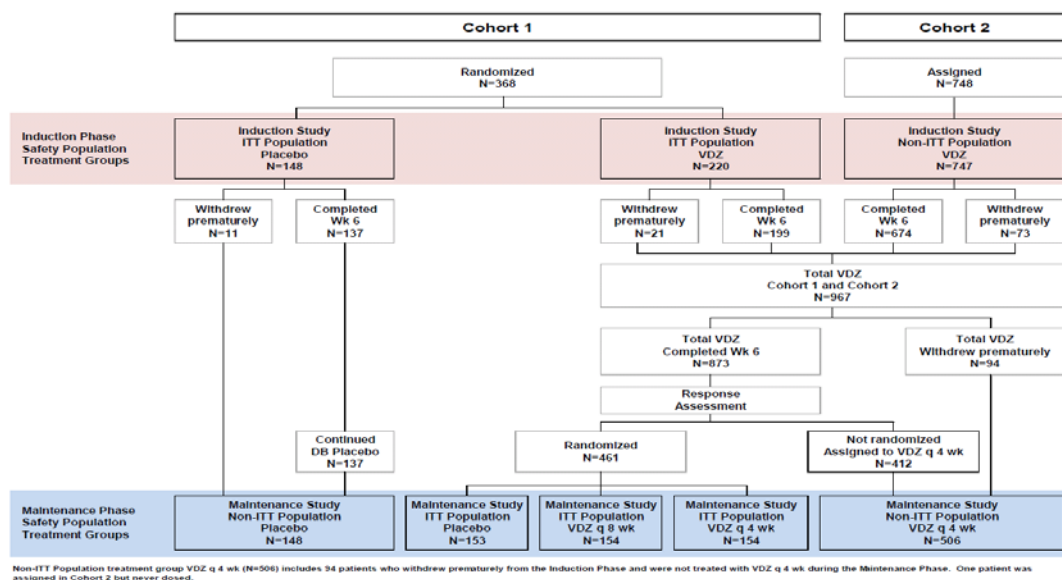
Maintenance study: for the 2 dose regimen assessments of the primary endpoint (proportion of patients with clinical remission at Week 52), the CMH chi-square test was used to compare the 2 treatment groups at the 5% level of significance with stratification according to the randomization stratification factors (enrollment in Cohort 1 or 2 in the Induction Phase, concomitant use of oral corticosteroids [yes/no], and previous exposure to TNF α antagonists or concomitant immunomodulator use [yes/no]). The CMH chi-square p value and the absolute treatment difference along with its 95% two-sided CI are provided. In addition, the relative risks are provided along with the 95% two-sided CI estimate. For both assessments of the primary endpoint, the Hochberg method was applied to control the overall Type I error rate at a 5% significance level. The secondary efficacy endpoints were analyzed using closed testing procedures. To maintain the overall Type I error rate at 5% for the 2 dose regimen comparisons for each secondary endpoint, the Hochberg method was used as described above. To further maintain the overall Type I error rate at 5%, the secondary assessments were also performed sequentially. The first secondary endpoint was to be tested only if 1 or both of the primary comparisons were significant and the next secondary endpoint was to be tested only if the previous secondary endpoint was significant for at least 1 dose. For the proportion-based exploratory analyses, the proportions and absolute treatment differences were provided along with their corresponding 95% two-sided CIs. For continuous variables, the changes from baseline (Week 0) over time were summarized. Changes in HRQOL were assessed by analyses of the IBDQ, SF-36, and EQ-5D questionnaire scores. The mean changes from baseline (Week 0) in IBDQ, SF-36 and EQ-5D scores are presented by treatment arm along with 95% two-sided CIs

for the differences in mean changes from baseline (Week 0) based on an analysis of covariance (ANCOVA) model.

Results

Participant flow

Figure 26 Overview of Treatment Groups in Induction Phase and Maintenance Phase Safety Populations Study C13007



Recruitment

First Patient Enrolled: 23 December 2008

Last Patient Completed: 08 May 2012

Conduct of the study

Four amendments have been done at the original protocol version (26 June 2008) of which two were specific for US (Amendment 2 - 28 October 2008 and Amendment 4 - 21 April 2009).

Protocol Deviations:

- Induction Study ITT Population, a total of 23 patients (8 placebo; 15 vedolizumab) had at least 1 unmet entry criterion, mainly criterion number 2.

An additional 63 patients in the open label vedolizumab group had violations of inclusion/exclusion criteria, the most common failure was to meet the inclusion criterion for baseline CDAI score.

- Maintenance study ITT population, a total of 32 patients (8 placebo; 12 vedolizumab Q8W and 12 vedolizumab Q4W). All the inclusion/exclusion criteria deviations occurred in $\leq 2\%$ of vedolizumab combined group as well as non-ITT placebo group. The most common deviations concerned the inclusion criterion number 2 and number 6.

Baseline data

Baseline Demographics and disease characteristics (induction phase)

The population consisted of 47% males and 89% of the population were white Caucasian. The mean age was 36.1 years (range 18-77 yrs) mean weight was 69.8 kg (range 30-167 kg) and the geographical distribution was 36% from North America, 23% from Western/Northern Europe, 19% from Central Europe, 8% from Eastern Europe and 14% from Asia/Australia/Africa. The baseline demographics were well balanced between the treatment groups.

The mean duration of disease was 9.0 years (median 7.0 years) and the mean baseline disease activity, as assessed by the baseline CDAI score, was 323.6. It is noted that median (minimum values) includes CDAI value of 132. Baseline CDAI scores were >330 in 44% of the patients. The majority of patients had a baseline CRP >10 mg/L (53%), a baseline fecal calprotectin 500 µg/g (56%), and disease involvement of both the ileum and colon (55%). A history of prior surgery for CD was reported for 42% of patients. The majority of the patients had no history of fistulizing disease (63%); 15% of the patients had a draining fistula at baseline. Extraintestinal manifestations of the disease were present at baseline in 62% of patients; 82% of patients had a history of extraintestinal manifestations. Most patients had never smoked or were former smokers (73%).

The baseline disease characteristics of the treatment groups in the Induction Study ITT Population were generally comparable, although the VDZ group had greater proportions of patients with CD duration of ≥7 years (50%) and with a history of prior surgery for CD (45%) compared to the placebo group (43% and 36%, respectively). The baseline disease characteristics of the open-label VDZ group were generally similar to those observed in the Induction Study ITT Population.

Table 19 Baseline Crohn's Disease Characteristics -- Induction Phase Safety Population

Crohn's Disease Characteristic	Induction Cohort 1 ITT Population ^a		Induction Cohort 2 ^b Open-label	Combined VDZ N = 967	Total N = 1115
	PLA N = 148	VDZ N = 220	VDZ N = 747		
Duration of CD (yrs) ^c					
Mean (Std Dev)	8.2 (7.80)	9.2 (8.18)	9.2 (7.63)	9.2 (7.76)	9.0 (7.77)
Median	6.1	7.1	7.2	7.2	7.0
Minimum, maximum	0.3, 42.0	0.5, 43.6	0.2, 42.5	0.2, 43.6	0.2, 43.6
Duration of CD - categorical, n (%)					
< 1 year	12 (8)	12 (5)	45 (6)	57 (6)	69 (6)
≥ 1 - < 3 years	27 (18)	48 (22)	126 (17)	174 (18)	201 (18)
≥ 3 - < 7 years	45 (30)	49 (22)	191 (26)	240 (25)	285 (26)
≥ 7 years	64 (43)	111 (50)	385 (52)	496 (51)	560 (50)
Baseline disease activity – CDAI ^d					
n	147	219	743	962	1109
Mean (Std Dev)	324.6 (78.08)	327.3 (70.67)	322.2 (67.17)	323.4 (67.98)	323.6 (69.37)
Median	319.0	324.0	320.0	321.0	321.0
Minimum, maximum	155, 584	132, 500	93, 548	93, 548	93, 584
Baseline disease activity – categorical, n (%)					
CDAI ≤ 330	81 (55)	119 (54)	418 (56)	537 (56)	618 (55)
CDAI > 330	66 (45)	100 (45)	325 (44)	425 (44)	491 (44)
Missing	1	1	4	5	6
Baseline CRP (mg/L)					
n	147	220	747	967	1114
Mean (Std Dev)	23.6 (27.85)	24.1 (27.23)	20.4 (27.40)	21.2 (27.39)	21.5 (27.45)

Crohn's Disease Characteristic	Induction Cohort 1 ITT Population ^a		Induction Cohort 2 ^b Open-label	Combined	Total
	PLA N = 148	VDZ N = 220	VDZ N = 747	VDZ N = 967	N = 1115
Median	13.7	15.3	10.2	10.6	11.5
Minimum, maximum	0.2, 159.0	0.2, 164.0	0.2, 295.0	0.2, 295.0	0.2, 295
Baseline CRP - categorical, n (%)					
≤ 2.87 mg/L	20 (14)	37 (17)	130 (17)	167 (17)	187 (17)
> 2.87 to ≤ 5 mg/L	14 (9)	25 (11)	75 (10)	100 (10)	114 (10)
> 5 to ≤ 10 mg/L	28 (19)	38 (17)	160 (21)	198 (20)	226 (20)
> 10 mg/L	85 (57)	120 (55)	382 (51)	502 (52)	587 (53)
Missing	1	0	0	0	1
Baseline fecal calprotectin n	142	210	719	929	1071
Mean (Std. Dev)	1421.2 (2076.11)	1839.9 (2624.92)	1050.1 (1558.93)	1228.7 (1881.84)	1254.2 (1908.82)
Median	652.6	852.2	656.8	688.3	685.8
Minimum, maximum	23.8, 12429.0	23.8, 13672.5	23.8, 18607.5	23.8, 18607.5	23.8, 18607.5
Baseline fecal calprotectin - categorical, n (%)					
≤ 250 µg/g	34 (23)	51 (23)	201 (27)	252 (26)	286 (26)
> 250 to ≤ 500 µg/g	27 (18)	25 (11)	112 (15)	137 (14)	164 (15)
> 500 µg/g	81 (55)	134 (61)	406 (54)	540 (56)	621 (56)
Missing	6	10	28	38	44
Disease localization, n (%)					
Ileum only	21 (14)	37 (17)	123 (16)	160 (17)	181 (16)
Colon only	43 (29)	62 (28)	211 (28)	273 (28)	316 (28)
Ileocolonic (both ileum and colon)	84 (57)	121 (55)	413 (55)	534 (55)	618 (55)
Other (extra ileum, extra colon)	0	0	0	0	0
History of prior surgery for CD, n (%)	54 (36)	98 (45)	314 (42)	412 (43)	466 (42)
History of fistulizing disease, n (%)	56 (38)	90 (41)	264 (35)	354 (37)	410 (37)
Draining fistula at baseline, n (%)					
Yes	23 (16)	38 (17)	104 (14)	142 (15)	165 (15)
All closed	2 (1)	1 (< 1)	8 (1)	9 (< 1)	11 (< 1)
No	123 (83)	181 (82)	635 (85)	816 (84)	939 (84)
Smoking status, n (%)					
Current smoker	34 (23)	54 (25)	210 (28)	264 (27)	298 (27)
Nonsmoker (never smoked)	85 (57)	120 (55)	351 (47)	471 (49)	556 (50)

Crohn's Disease Characteristic	Induction Cohort 1 ITT Population ^a		Induction Cohort 2 ^b Open-label	Combined	Total
	PLA N = 148	VDZ N = 220	VDZ N = 747	VDZ N = 967	N = 1115
Former smoker	29 (20)	46 (21)	185 (25)	231 (24)	260 (23)
Missing	0	0	1	1	1
Baseline extraintestinal manifestations, n (%)	107 (72)	133 (60)	456 (61)	589 (61)	696 (62)
History of extraintestinal manifestations, n (%)	123 (83)	177 (80)	619 (83)	796 (82)	919 (82)

Source: Table 14.1.1.6CP.

Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ITT = intent-to-treat; PLA = placebo; Std Dev = standard deviation; VDZ = vedolizumab.

a All patients enrolled in Cohort 1 who were randomized to blinded induction treatment with vedolizumab or placebo.

b All patients enrolled in Cohort 2 who received open-label vedolizumab induction treatment.

c Duration of CD is defined as (1 + first dose date – diagnosis date)/365.25.

d Baseline disease activity represents the baseline CDAI score.

Approximately half of the patients in the Induction Study ITT Population (placebo 49%; VDZ 50%) reported prior TNF α antagonist use. Of the 368 patients in the Induction Study ITT Population, 21% had failed 1 TNF α antagonist, 21% had failed 2 TNF α antagonists, and 5% had failed 3 TNF α antagonists. The proportions of patients who had previously failed TNF α antagonist therapy or were naïve to TNF α antagonist therapy were similar between the treatment groups. In addition, the treatment groups were similar with respect to the number of TNF α antagonist therapies patients had previously failed.

In the Induction Study ITT Population, 79% of the patients used at least 1 concomitant IBD medication during the study. Corticosteroids were the most commonly used (49%), followed by 5-ASAs (46%) and immunomodulators (35%).

Baseline Demographics and disease characteristics maintenance phase

All patients who completed the Induction Phase entered the Maintenance Phase. The Maintenance Study ITT Population includes VDZ-treated patients who had a clinical response at Week 6; at the start of the Maintenance Phase, these patients were randomized to 1 of 2 VDZ IV dosing regimens (300 mg Q4W or Q8W) or placebo.

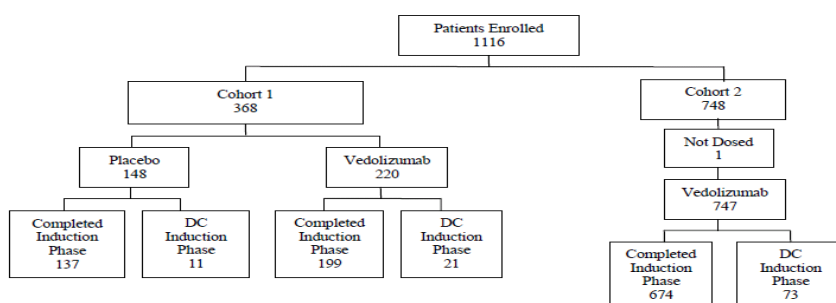
The demographic characteristics of the all VDZ combined group were generally consistent with those observed in the Maintenance Study ITT Population, including the greatest proportion of patients enrolling from sites in North America (39%). In addition, the demographic characteristics of the non-ITT VDZ patients (Week 6 non-responders) were consistent with those of the Maintenance Study ITT Population (Week 6 responders).

Although the majority of patients in each of the treatment groups had baseline CDAI scores \leq 330, the frequency was highest in the VDZ Q4W group (62%), followed by the placebo (56%) and the VDZ Q8W (51%) groups. Median CDAI scores in the Maintenance Study ITT population followed a similar pattern with a median score of 322.0 in the VDZ Q8W group, 316.0 in the VDZ Q4W group, and 315.0 in the placebo group.

Numbers analysed

Induction phase

Figure 9 Study Drug Assignment and Disposition of All Patients in Induction Phase – Study C13007



Patient disposition is summarized for the ITT Population (Cohort 1) by randomized treatment group (placebo or VDZ), the open-label VDZ treatment group (Cohort 2), and all VDZ patients combined (VDZ groups from Cohort 1 and Cohort 2) in Table 17.

Table 17 Patient Disposition – Induction Phase

	Induction Cohort 1 ITT Population ^a		Induction Cohort 2 ^b Open-label	VDZ Combined N = 967	Total N = 1115
	PLA N = 148	VDZ N = 220	N = 747 ^c		
Randomized/ assigned	148	220	748 ^c	968	1116
Safety Population ^d	148 (100)	220 (100)	747 (100)	967 (100)	1115 (100)
ITT Population ^e	148 (100)	220 (100)		220 (23)	368 (33)
Per-Protocol Population ^f	141 (95)	205 (93)		205 (21)	346 (31)
Completed Induction Phase ^g	137 (93)	199 (90)	674 (90)	873 (90)	1010 (91)
Discontinued (reason)	11 (7)	21 (10)	73 (10)	94 (10)	105 (9)
Adverse event ^h	7 (5)	9 (4)	24 (3)	33 (3)	40 (4)
Protocol violation(s)	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Lack of efficacy	1 (< 1)	3 (1)	28 (4)	31 (3)	32 (3)
Study terminated by sponsor	0	0	0	0	0
Withdrawal of consent	3 (2)	9 (4)	15 (2)	24 (2)	27 (2)
Lost to follow-up	0	0	3 (< 1)	3 (< 1)	3 (< 1)
Other	0	0	2 (< 1)	2 (< 1)	2 (< 1)

Source: Table 14.1.1.2BP.

Abbreviations: ITT = Intent-to-Treat; PLA = placebo; VDZ = vedolizumab.

a All patients enrolled in Cohort 1 who were randomized to blinded induction treatment with vedolizumab or placebo.

b All patients enrolled in Cohort 2 who received open-label vedolizumab induction treatment.

c One patient enrolled in Cohort 2 withdrew from the study prior to dosing and is excluded from all analyses.

d Safety Population consists of all patients who received any amount of study drug during the Induction Phase based on what they actually received.

e ITT Population consists of all randomized patients who received any amount of blinded study drug during the Induction Phase based on what they were randomized to receive.

f Per-Protocol Population consists of all randomized patients who met prespecified criteria (Section 10.2.2-I).

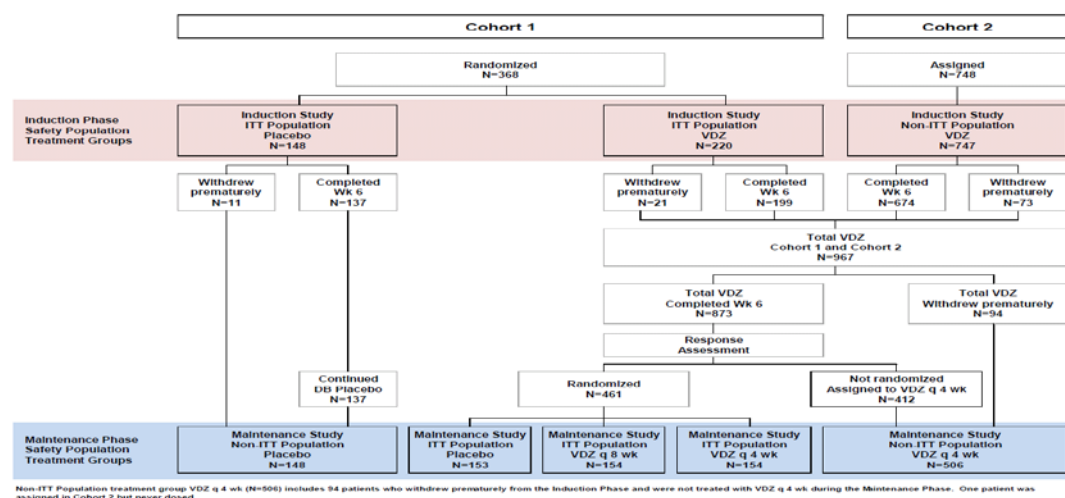
g Defined as completed dosing at Weeks 0 and 2 and completed the predose assessments at Week 6.

h One additional ITT placebo patient is presented in Table 33 as discontinuing due to an AE; this patient is not counted here as the AE that led to discontinuation was not treatment emergent.

Maintenance phase

All patients who completed the Induction Phase entered the Maintenance Phase. Figure 10 summarizes the flow of patients from the Induction Phase into the Maintenance Phase treatment groups and summarizes the composition of the Maintenance Phase Safety Population treatment groups. The Maintenance Study ITT Population includes VDZ-treated patients who had a clinical response at Week 6; at the start of the Maintenance Phase, these patients were randomized to 1 of 2 VDZ IV dosing regimens (300 mg Q4W or Q8W) or placebo.

Figure 10 Overview of Treatment Groups in Induction Phase and Maintenance Phase Safety Populations



The Maintenance Non-ITT Population includes 2 additional treatment groups: placebo and VDZ administered Q4W.

The non-ITT placebo group comprises those patients who were randomized to placebo in the Induction Phase; these patients remained on placebo in the Maintenance Phase, per the study design.

The non-ITT VDZ group comprises those patients who received VDZ in the Induction Phase and were assessed by the investigator as not having achieved clinical response at Week 6; these patients received VDZ 300 mg Q4W for the duration of the study. These patients contribute to the safety analyses in the Maintenance Phase, and exploratory efficacy analyses were done for this population.

Table 18 Patient Disposition – Maintenance Phase Safety Population

	Maintenance ITT ^a (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA ^b (from Week 6) N = 148	VDZ Q4W ^c (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Completed induction treatment	153 (100)	154 (100)	154 (100)	137 (93)	412 (81)	290 (96)	720 (88)
Randomized/assigned	153 (100)	154 (100)	154 (100)	148 (100)	507 (100)	301 (100)	815 (100)
Randomized but not dosed	0	0	0	0	1 (< 1)	0	1 (< 1)
Safety Population ^d	153 (100)	154 (100)	154 (100)	148 (100)	506 (100)	301 (100)	814 (100)
ITT Population ^e	153 (100)	154 (100)	154 (100)			153 (51)	308 (38)
Per-Protocol Population ^f	147 (96)	149 (97)	144 (94)			147 (49)	293 (36)
Completed study ^g	64 (42)	73 (47)	82 (53)	42 (28)	163 (32)	106 (35)	318 (39)
Discontinued (reason)	89 (58)	81 (53)	72 (47)	106 (72)	343 (68)	195 (65)	496 (61)
Adverse event	15 (10)	12 (8)	9 (6)	14 (9)	71 (14)	29 (10)	92 (11)
Protocol violation(s)	1 (< 1)	2 (1)	3 (2)	0	5 (< 1)	1 (< 1)	10 (1)
Lack of efficacy	64 (42)	58 (38)	48 (31)	80 (54)	208 (41)	144 (48)	314 (39)
Study terminated by sponsor	0	0	0	0	0	0	0
Withdrawal of consent	7 (5)	6 (4)	9 (6)	10 (7)	48 (9)	17 (6)	63 (8)
Lost to follow-up	1 (< 1)	3 (2)	2 (1)	2 (1)	8 (2)	3 (< 1)	13 (2)
Other	1 (< 1)	0	1 (< 1)	0	3 (< 1)	1 (< 1)	4 (< 1)
Enrolled into C13008	127 (83)	126 (82)	122 (79)	107 (72)	244 (48)	234 (78)	492 (60)

Source: Table 14.1.1.2AM.

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; VDZ = vedolizumab.

Patient C13007-24030-701 is included in this table and not in Table 14.4.1.1M, because the AE that led to discontinuation was not treatment emergent.

a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance Study ITT Population at Week 6.

b Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.

c Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

d Safety Population consists of all patients who received any amount of study drug during the Maintenance Phase based on what they actually received.

e ITT Population consists of all randomized patients who received any amount of blinded study drug during the Maintenance Phase based on what they were randomized to receive.

f Per-Protocol Population consists of all randomized patients who met prespecified criteria (Section 10.2.2-M).

g Completed study is defined as patients who completed the Maintenance Phase.

Outcomes and estimation

Induction phase results

Primary Efficacy Endpoints, Induction

Clinical Remission at Week 6 and Enhanced Clinical Response at Week 6.

Table 20 Primary Efficacy Endpoints of Clinical Remission and Enhanced Clinical Response at Week 6 – Induction Study ITT Population

	Clinical Remission ^a		Enhanced Clinical Response ^b	
	PLA N = 148	VDZ N = 220	PLA N = 148	VDZ N = 220
Number (%) achieving endpoint	10 (6.8)	32 (14.5)	38 (25.7)	69 (31.4)
95% CI	(2.7, 10.8)	(9.9, 19.2)	(18.6, 32.7)	(25.2, 37.5)
Difference from placebo ^c		7.8		5.7
95% CI for difference from placebo		(1.2, 14.3)		(-3.6, 15.0)
P-value for difference from placebo ^d		0.0206		0.2322
Relative risk ^e		2.1		1.2
95% CI for relative risk		(1.1, 4.2)		(0.9, 1.7)

Source: Table 14.3.1.2A, Table 14.3.1.4A.

Abbreviations: CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PLA = placebo; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

a Clinical remission is defined as CDAI score \leq 150 points.

b Enhanced clinical response is defined as a \geq 100-point reduction from baseline in CDAI score.

c Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

d P-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF α antagonists and/or concomitant immunomodulator use (yes/no).

e Adjusted Relative Risk and its 95% CI.

In line with the statistical plan to control the Type I error rate statistical significance has been shown on the clinical remission endpoint as the p-value of 0.0206 is less than 0.025. Statistical significance was not shown for the enhanced clinical response endpoint.

The pre-specified Hochberg method was applied to control for the overall Type I error rate at a 5% significance level for the multiple comparisons of the primary endpoints. Since the p value for the endpoint of enhanced clinical response at Week 6 was > 0.05 , the p value for the endpoint of clinical remission at Week 6 was tested at the 0.025 level of significance. As the p value for clinical remission at Week 6 was < 0.025 ($p = 0.0206$), the study is considered to have met the primary endpoint of clinical remission at Week 6.

Maintenance phase results

Efficacy Results at Week 52

	Placebo N=153*	Vedolizumab Every 8 Weeks N=154	Vedolizumab Every 4 Weeks N=154
Clinical remission	22%	39% [†]	36% [‡]
Enhanced clinical response	30%	44% [‡]	45% [‡]
Corticosteroid-free clinical remission [§]	16%	32% [‡]	29% [‡]
Durable clinical remission [¶]	14%	21%	16%

*The placebo group includes those subjects who received vedolizumab at Week 0 and Week 2, and were randomised to receive placebo from Week 6 through Week 52.

< 0.001

< 0.05

[‡]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids beginning at Week 6 and were in clinical remission at Week 52. Patient numbers were n=82 for placebo, n=82 for vedolizumab every eight weeks, and n=80 for vedolizumab every four weeks

[¶]Durable clinical remission: Clinical remission at $\geq 80\%$ of study visits including final visit (Week 52)

Study C13011 (GEMINI III): A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's Disease

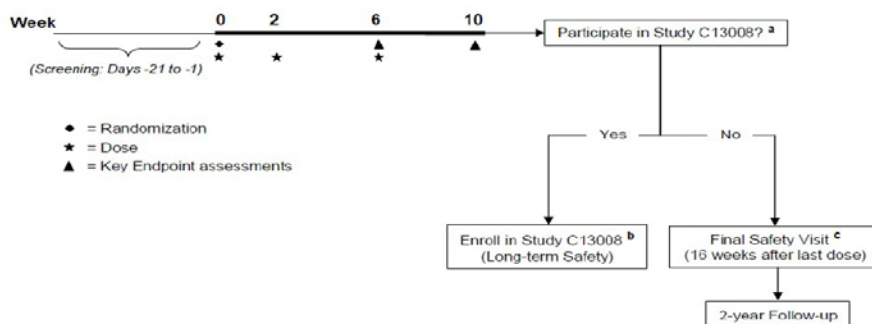
Methods

Study C13011 was a phase 3, multinational, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of VDZ for the induction of clinical response and remission in patients with moderately to severely active CD.

Of the total patients enrolled, approximately 75% were to have previously failed TNF α antagonist therapy and approximately 25% were to have been naïve to TNF α antagonist therapy.

After completing the Week 10 assessments, patients were eligible to enrol in Study C13008 (open-label, long-term safety study) if study drug was well tolerated, and no major surgical intervention for CD occurred or was required.

Figure 11 Patient Treatment Overview



- a** After completing the Week 10 assessments, patients were eligible to enroll in Study C13008 if study drug was well tolerated and no surgical intervention for CD occurred or was required.
- b** Eligible patients were to have enrolled in Study C13008 within 5 weeks after their final dose in this study.
- c** Patients who were not eligible for or declined enrollment in Study C13008 were to return for an on-study Final Safety visit (Week 22, or 16 weeks after last dose) and complete the 2-year follow-up.

Patient disposition is summarized by treatment group for the overall patient population and the TNF α antagonist failure patient subpopulation in Table 22.

Table 22 Patient Disposition

	TNF α Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
Randomized	157	158	315	207	209	416
Safety Population ^a	157 (100)	158 (100)	315 (100)	207 (100)	209 (100)	416 (100)
ITT Population ^b	157 (100)	158 (100)	315 (100)	207 (100)	209 (100)	416 (100)
Per-Protocol Population ^c	145 (92)	147 (93)	292 (93)	194 (94)	192 (92)	386 (93)
Completed study ^d	145 (92)	151 (96)	296 (94)	192 (93)	196 (94)	388 (93)
Enrolled into C13008	144 (99)	150 (99)	294 (99)	190 (99)	194 (99)	384 (99)
Discontinued (Reason)	12 (8)	7 (4)	19 (6)	15 (7)	13 (6)	28 (7)
Adverse event	6 (4)	2 (1)	8 (3)	8 (4)	4 (2)	12 (3)
Protocol violation(s)	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
Lack of efficacy	4 (3)	0	4 (1)	5 (2)	1 (< 1)	6 (1)
Withdrawal of consent	2 (1)	3 (2)	5 (2)	2 (< 1)	4 (2)	6 (1)
Lost to follow-up	0	1 (< 1)	1 (< 1)	0	3 (1)	3 (< 1)

Source: Table 14.1.1.2T, Table 14.1.1.2.

Abbreviations: ITT = Intent-to-Treat; PLA = placebo; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

Percentages are based on number of patients in the Overall ITT Population, except for the percentage of patients enrolled into Study C13008, which uses the number of patients who completed study as the denominator.

a Safety Population consists of all patients who received any amount of blinded study drug based on what they actually received.

b ITT Population consists of all randomized patients who received any amount of blinded study drug based on what they were randomized to receive.

c Per-Protocol Population consists of all randomized patients who met prespecified criteria, as defined in Section 9.10.2.3.

d Completed study is defined as patients who completed the Week 10 assessments.

Study Participants

A total of 416 patients were enrolled in this phase 3, multinational, randomized, double-blind, placebo-controlled study that was conducted to evaluate the efficacy and safety of VDZ for the induction of clinical response and remission in patients with moderately to severely active CD with inadequate response to 1 or more of the following therapies: immunomodulators, corticosteroids, and/or TNF α antagonists. Of the total patients enrolled, 75% were to have previously failed TNF α antagonist therapy, and 25% were to have been naïve to TNF α antagonist therapy and, by design, had failed corticosteroid and/or immunosuppressive therapy.

Inclusion and exclusion criteria for Study C13011 were similar to those for Study C13007. Key inclusion criteria related to CD included, but were not limited to, diagnosis of CD established at least 3 months prior to enrollment; moderately to severely active CD as determined by a CDAI score of 220 to 400 and 1 of the following:

- CRP level > 2.87 mg/L,
- ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations consistent with CD, or
- fecal calprotectin > 250 mcg/g stool during the Screening period in conjunction with CT enterography, MR enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing Crohn's ulcerations; CD involvement of the ileum and/or colon; documentation of surveillance colonoscopy within 12 months of screening visit for patients with long-term history of extensive colitis or pancolitis; inadequate response or intolerance to either immunomodulators, corticosteroid, and/or TNF α antagonists.

Treatments

Patients randomized to vedolizumab were to receive a 300-mg IV infusion at Weeks 0, 2, and 6. Patients randomized to placebo were to receive 250 mL of 0.9% sodium chloride IV at Weeks 0, 2, and 6.

Objectives

Primary Objective

- To determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the subgroup of patients defined as having failed tumor necrosis factor alpha (TNF α) antagonist therapy (TNF α antagonist failure subpopulation)

Secondary Objectives

- To determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the entire study population
- To determine the effect of vedolizumab induction treatment on clinical remission at Week 10 in the TNF α antagonist failure subpopulation and in the entire study population
- To determine the effect of vedolizumab induction treatment on sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) in the TNF α antagonist failure subpopulation and in the entire study population
- To determine the effect of vedolizumab induction treatment on enhanced clinical response at Week 6 in the TNF α antagonist failure subpopulation

Safety Objectives

- To determine the safety profile of vedolizumab induction treatment in the entire study population
- To determine the safety profile of vedolizumab induction treatment in the TNF ☐ antagonist failure subpopulation

Outcomes/endpoints

Primary Endpoint

- Proportion of patients in clinical remission at Week 6 in the TNF α antagonist failure Subpopulation

Secondary Endpoints

- Proportion of patients in clinical remission at Week 6 in the entire study population
- Proportions of patients in clinical remission at Week 10 in the TNF α antagonist failure subpopulation and in the entire study population
- Proportions of patients with sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) in the TNF α antagonist failure subpopulation and in the entire study population
- Proportion of patients with enhanced clinical response at Week 6 in the TNF α antagonist failure subpopulation

Sample size

The study was adequately powered for the primary endpoint, as well as for the key secondary endpoints. Power estimates for the primary and secondary efficacy endpoints were based on a

total sample size of 396 for the overall study population and 296 for the TNF α antagonist failure subpopulation.

Randomisation

Patients were randomized 1:1 to receive either 300 mg vedolizumab or placebo at Weeks 0, 2, and 6. Enrollment of patients was monitored by the IVRS to ensure that approximately 75% of the overall population had previously failed TNF α antagonist therapy and approximately 25% were naïve to TNF α antagonist therapy.

The randomization to treatment assignment was stratified by the presence or absence of each of the following, as entered into the IVRS at screening:

- Previous failure of TNF α antagonist therapy or naïve to TNF α antagonist therapy
- Concomitant use of oral corticosteroids
- Concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate)

Randomization schedules were generated and archived by the Biostatistics department at Millennium. Each patient who was qualified for treatment was assigned a unique randomization number. The IVRS provided treatment assignments based on these randomization numbers.

Blinding (masking)

In order to maintain the blind, all study site personnel, except the investigational pharmacist or designee, were blinded to the patient treatment assignments for the duration of the study.

Statistical methods

The proportion-based endpoints, such as clinical remission, sustained clinical remission, and enhanced clinical response, were to be tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level with stratification according to concomitant use of oral corticosteroids and concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate) for the TNF α antagonist failure subpopulation, or with stratification according to previous failure of TNF α antagonist therapy, concomitant use of oral corticosteroids, and concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate) for the overall population. The CMH chi-square p-value and the risk difference, along with its 95% two-sided confidence interval (CI), were provided. The risk difference was the primary test. In addition, the relative risk was provided along with the 95% two-sided CI estimate.

To maintain the overall Type I error rate at 5%, the secondary endpoint analyses were performed sequentially. Specifically, clinical remission at Week 6 for the overall population was to be tested only if the primary endpoint comparison was significant; the set of analyses for clinical remission at Week 10 for the TNF α antagonist failure subpopulation and the overall population was to be tested only if the endpoint of clinical remission at Week 6 for the overall population was significant. The remaining secondary endpoints were to be tested only if the comparison for the previous secondary endpoint was significant.

In addition, the Hochberg method was to be applied to each secondary endpoint pair in order to control the overall Type 1 error rate at a 5% significance level.

A logistic regression model was to include baseline CDAI score, stratification factors, and geographic region.

Analysis of covariance (ANCOVA) models of change from baseline to Week t efficacy endpoints was to include treatment group and baseline measurement. More details on the model used can be found in the final statistical analysis plan.

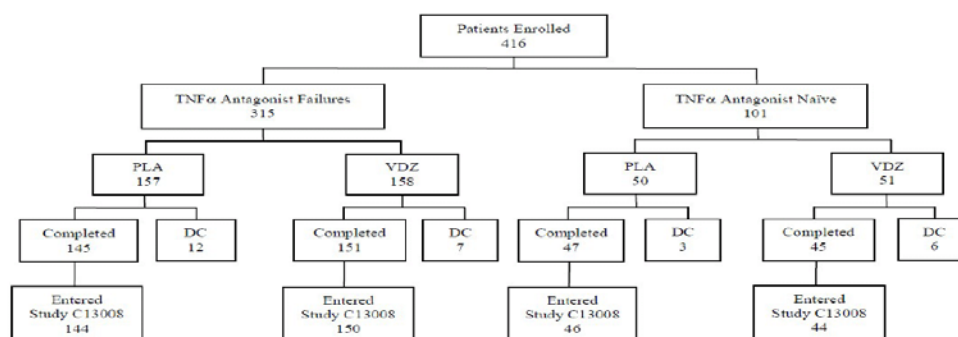
Results

Participant flow

Disposition of Patients

Among the 416 randomized patients, 315 (76%) had previously failed TNF α antagonist therapy and 101 (24%) were naïve to TNF α antagonist therapy.

Figure 35 Study Drug Assignment and Disposition of All Patients – Study C13011



Source: Table 14.1.1.2T, Table 14.1.1.2.

Abbreviations: DC = discontinued; PLA = placebo; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

Patient disposition is summarized by treatment group for the overall patient population and the TNF α antagonist failure patient subpopulation in Table 82.

Table 82 Patient Disposition

	TNF α Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
Randomized	157	158	315	207	209	416
Safety Population ^a	157 (100)	158 (100)	315 (100)	207 (100)	209 (100)	416 (100)
ITT Population ^b	157 (100)	158 (100)	315 (100)	207 (100)	209 (100)	416 (100)
Per-Protocol Population ^c	145 (92)	147 (93)	292 (93)	194 (94)	192 (92)	386 (93)
Completed study ^d	145 (92)	151 (96)	296 (94)	192 (93)	196 (94)	388 (93)
Enrolled into C13008	144 (99)	150 (99)	294 (99)	190 (99)	194 (99)	384 (99)
Discontinued (Reason)	12 (8)	7 (4)	19 (6)	15 (7)	13 (6)	28 (7)
Adverse event	6 (4)	2 (1)	8 (3)	8 (4)	4 (2)	12 (3)
Protocol violation(s)	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
Lack of efficacy	4 (3)	0	4 (1)	5 (2)	1 (< 1)	6 (1)
Withdrawal of consent	2 (1)	3 (2)	5 (2)	2 (< 1)	4 (2)	6 (1)
Lost to follow-up	0	1 (< 1)	1 (< 1)	0	3 (1)	3 (< 1)

Source: Table 14.1.1.2T, Table 14.1.1.2.

Abbreviations: ITT = Intent-to-Treat; PLA = placebo; TNF α = tumor necrosis factor alpha;

VDZ = vedolizumab.

Percentages are based on number of patients in the Overall ITT Population, except for the percentage of patients enrolled into Study C13008, which uses the number of patients who completed study as the denominator.

a Safety Population consists of all patients who received any amount of blinded study drug based on what they actually received.

b ITT Population consists of all randomized patients who received any amount of blinded study drug based on what they were randomized to receive.

c Per-Protocol Population consists of all randomized patients who met prespecified criteria, as defined in Section 9.10.2.3.

d Completed study is defined as patients who completed the Week 10 assessments.

Recruitment

First Patient Enrolled: 24 November 2010

Last Patient Completed: 12 April 2012

Conduct of the study

There were no amendments to the study protocol.

Baseline data

Baseline demographic characteristics of the Overall ITT Population and the TNF α Antagonist Failure ITT Subpopulation are summarized by treatment group in Table 23 and were generally similar between the treatment groups in the Overall ITT Population.

Table 23 Baseline Demographics – TNF α Antagonist Failure ITT Subpopulation and Overall ITT Population

Parameter	TNF α Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
Gender, n (%)						
Male	62 (39)	68 (43)	130 (41)	89 (43)	91 (44)	180 (43)
Female	95 (61)	90 (57)	185 (59)	118 (57)	118 (56)	236 (57)
Race, n (%)						
White	142 (90)	143 (91)	285 (90)	186 (90)	188 (90)	374 (90)
Black	5 (3)	4 (3)	9 (3)	5 (2)	4 (2)	9 (2)
Asian	3 (2)	5 (3)	8 (3)	9 (4)	9 (4)	18 (4)
Other	7 (4)	5 (3)	12 (4)	7 (3)	6 (3)	13 (3)
Not reported	0	1 (< 1)	1 (< 1)	0	2 (< 1)	2 (< 1)
Ethnicity, n (%)						
Hispanic or Latino	2 (1)	3 (2)	5 (2)	4 (2)	4 (2)	8 (2)
Not Hispanic or Latino	152 (97)	154 (97)	306 (97)	199 (96)	204 (98)	403 (97)
Not reported	3 (2)	1 (< 1)	4 (1)	4 (2)	1 (< 1)	5 (1)

Table 23 Baseline Demographics – TNF α Antagonist Failure ITT Subpopulation and Overall ITT Population

Parameter	TNF α Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
Age (yrs) ^a						
Mean (Std Dev)	38.4 (13.81)	38.7 (12.15)	38.6 (12.98)	37.1 (13.15)	38.6 (12.14)	37.9 (12.66)
Median	36.6	37.5	37.1	34.8	36.9	36.2
Min, Max	19, 77	20, 69	19, 77	19, 77	20, 69	19, 77
Age (yrs), n (%)						
< 35	72 (46)	64 (41)	136 (43)	105 (51)	88 (42)	193 (46)
≥ 35	85 (54)	94 (59)	179 (57)	102 (49)	121 (58)	223 (54)
Age (yrs), n (%)						
< 65	152 (97)	155 (98)	307 (97)	202 (98)	206 (99)	408 (98)
≥ 65	5 (3)	3 (2)	8 (3)	5 (2)	3 (1)	8 (2)
Body weight (kg)						
Mean (Std Dev)	71.2 (19.14)	70.3 (18.97)	70.7 (19.03)	71.3 (19.22)	69.5 (17.76)	70.4 (18.50)
Median	65.3	66.5	66.0	66.7	66.0	66.2
Min, Max	41, 125	40, 144	40, 144	41, 147	40, 144	40, 147
BMI (kg/m ²)						
Mean (Std Dev)	24.8 (6.32)	24.1 (5.38)	24.5 (5.87)	24.6 (6.13)	24.0 (5.13)	24.3 (5.65)
Median	23.3	23.3	23.3	23.3	23.3	23.3
Min, Max	15, 48	15, 43	15, 48	15, 48	15, 43	15, 48
Geographic region, n (%)						
North America	90 (57)	84 (53)	174 (55)	95 (46)	102 (49)	197 (47)
Western/Northern Europe	32 (20)	33 (21)	65 (21)	37 (18)	38 (18)	75 (18)
Central Europe	17 (11)	20 (13)	37 (12)	46 (22)	41 (20)	87 (21)
Eastern Europe	14 (9)	10 (6)	24 (8)	15 (7)	10 (5)	25 (6)
Asia/Australia/Africa	4 (3)	11 (7)	15 (5)	14 (7)	18 (9)	32 (8)

Source: Table 14.1.1.5AT, Table 14.1.1.5A.

Abbreviations: BMI = body mass index; ITT = intent-to-treat; Max = maximum; Min = minimum; PLA = placebo; Std Dev = standard deviation; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

a Age is defined as (1+first dose date – birth date)/365.25.

In the Overall ITT Population, the mean duration of disease was 10.3 years, with the majority of the patients having been diagnosed for ≥ 7 years (57%). The mean baseline disease activity, as assessed by the baseline CDAI score, was statistically significantly higher in the VDZ group (313.9) than the placebo group (301.3), with 37% of VDZ-treated patients having a baseline CDAI score > 330 compared with 29% of the placebo-treated patients. The majority of the patients had a baseline CRP > 10 mg/L (50%), a baseline fecal calprotectin $> 500 \mu\text{g/g}$ (58%), and disease involvement of both the ileum and colon (61%). A history of prior surgery for CD was reported for 44% of the patients. Twelve (12) % of the patients had a draining fistula at baseline. Extraintestinal manifestations of the disease were present at baseline in 59% of the patients. 75% of subjects had failed anti-TNF therapy.

Numbers analysed

Table 24 Summary of Analysis Populations

Data Set, n (%)	TNF α Antagonist Failure Patient Subpopulation		Overall Patient Population	
	PLA N = 157	VDZ N = 158	PLA N = 207	VDZ N = 209
Randomized patients	157	158	207	209
Safety Population ^a	157 (100)	158 (100)	207 (100)	209 (100)
ITT Population ^b	157 (100)	158 (100)	207 (100)	209 (100)
Modified ITT Population ^c	155 (99)	155 (98)	205 (99)	206 (99)
Per-Protocol Population ^d	145 (92)	147 (93)	194 (94)	192 (92)
Completers (Observed Case) Population ^e	137 (87)	147 (93)	184 (89)	191 (91)

Source: Table 14.1.1.4T, Table 14.1.1.4.

Abbreviations: CDAI = Crohn's Disease Activity Index; ITT = intent-to-treat; PLA = placebo; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

- a Safety Population consists of all patients who received any amount of blinded study drug based on what they actually received.
- b ITT Population consists of all randomized patients who received any amount of blinded study drug based on what they were randomized to receive.
- c Modified ITT Population consists of all randomized patients who received any amount of blinded study drug, and had a baseline and at least 1 post-randomization CDAI score.
- d Per-Protocol Population consists of all randomized patients who met prespecified criteria, as defined in Section 9.10.2.3.
- e Completers (Observed Case) Population consists of all randomized patients who received any amount of blinded study drug and had a baseline, Week 6, and Week 10 CDAI score.

Outcomes and estimation

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was the proportion of patients in clinical remission at Week 6 in the TNF α Antagonist Failure ITT Subpopulation.

In the TNF α Antagonist Failure ITT Subpopulation, no statistically significant difference was observed between the VDZ and placebo groups for the proportions of patients in clinical remission at Week 6. Of the 158 patients who received VDZ, 24 (15.2%) achieved clinical remission at Week 6 compared with 19 of 157 (12.1%) patients who received placebo. The treatment difference from placebo was 3.0% (95% CI: -4.5, 10.5; $p = 0.4332$), with a relative probability of achieving clinical remission at Week 6 of 1.2 (relative risk with 95% CI: 0.7, 2.2).

Study C13011 failed its primary endpoint which was for anti-TNF failure patients. This was a stringent endpoint to attempt and unlike C13007 where the primary endpoint of clinical remission at week 6 was met by a mixed setting population. Of note is that from the additional analyses presented for both CD studies it is apparent that the effect of VDZ is slower in onset than other therapies (e.g. anti-TNFs). Based on the mechanism of action as the effect is to decrease T cells entering the gut, but not affect the cells already in situ in the gut, although the levels and activity of VDZ in the gut itself are not known, this delay could be expected.

Since the primary efficacy endpoint did not reach statistical significance, formal hypothesis testing could not be performed for the ranked secondary endpoints.

Clinical Remission at Week 6 – Overall ITT Population

In the Overall ITT Population, which included patients who had previously failed or were naïve to TNF α antagonist therapy, 19.1% of VDZ-treated patients and 12.1% of placebo-treated patients achieved clinical remission at Week 6; the treatment difference from placebo was 6.9%.

Clinical Remission at Week 10 – TNF α Antagonist Failure ITT Subpopulation and Overall ITT Population

In the TNF α Antagonist Failure ITT Subpopulation, 26.6% of VDZ-treated patients and 12.1% of placebo-treated patients achieved clinical remission at Week 10; the treatment difference from placebo was 14.4%. The proportion of patients who achieved clinical remission at Week 10 increased from 15.2% at Week 6 in the VDZ group and was essentially unchanged from Week 6 (12.1%) in the placebo group.

In the Overall ITT Population, 28.7% of VDZ-treated patients and 13.0% of placebo-treated patients achieved clinical remission at Week 10; the treatment difference from placebo was 15.5%. The proportion of patients who achieved clinical remission increased from 19.1% at Week 6 in the VDZ group and showed little change from Week 6 (12.1%) in the placebo group.

This numerical difference between both the overall ITT population and the anti-TNF failure ITT population in clinical remission at week 10 compared with placebo is consistent with the delayed effect seen with VDZ and although these results have to be considered exploratory, they are biologically consistent with efficacy from VDZ and in line with the primary endpoint which was met for study C13007.

Sustained Clinical Remission – TNF α Antagonist Failure ITT Subpopulation and Overall ITT Population

In the TNF α Antagonist Failure ITT Subpopulation, 12.0% of VDZ-treated patients and 8.3% of placebo-treated patients achieved sustained clinical remission; the treatment difference from placebo was 3.7%. In the Overall ITT Population, 15.3% of VDZ-treated patients and 8.2% of placebo-treated patients achieved sustained clinical remission; the treatment difference from placebo was 7.0%.

Summary of main studies

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).

Table 1. Summary of efficacy for trial C13006

Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis.	
Study identifier	Study C13006 Induction

Design	Phase 3 randomized, placebo-controlled, blinded, multicenter evaluation of induction and maintenance therapy in patients with moderate to severe UC.			
	Separate efficacy and safety evaluation for the Induction and Maintenance Phases. Separate randomization after the Induction Phase.			
	Duration of Induction phase:		6 weeks	
	Duration of Maintenance phase:		46 weeks (from week 6 to week 50)	
	Duration of Extension phase:		2 years follow up	
Hypothesis	Superiority of Vedolizumab vs placebo			
Treatments groups	Vedolizumab (Cohort 1 - ITT)		treatment= IV dosing, 300 mg at Weeks 0 and 2 duration = 6 weeks number randomized = 225	
	Placebo (Cohort 1 - ITT)		treatment= placebo at Weeks 0 and 2 duration = 6 weeks number randomized = 149	
	Cohort 2 non-ITT		treatment= open-label vedolizumab, 300 mg at Weeks 0 and 2	
Endpoints and definitions	Primary endpoint	Clinical response at 6 weeks	Reduction in complete Mayo score of ≥ 3 points and <input type="checkbox"/> 30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≥ 1 point	
	Secondary endpoint	Clinical remission at 6 weeks	Partial Mayo score of ≤ 2 points and no individual subscore > 1 point	
	Secondary endpoint	Mucosal healing at 6 weeks	Mayo endoscopic subscore of ≤ 1 point.	
Database lock	27 January 2012			
Results and Analysis				
Analysis description	Primary Analysis The primary comparison of the Induction Phase was tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the randomization stratification factors (concomitant use of oral corticosteroids and previous exposure to TNFa antagonists or concomitant immunomodulator [6-mercaptopurine or azathioprine] use).			
Analysis population and time point description	Intent to treat= 895, Per protocol=826, time point= week 6			
Descriptive statistics and estimate variability	Treatment group	PLA	VDZ	Difference from Placebo/RR
	Number of subject	149	225	/
	Clinical Response %	38 (25.5%)	106 (47.1%)	21.7%/1.8
	Stratified p-value (CMH chi-square test)	p<0.0001		

	Stratified Hazard Ratio (95% CI)	21.7% (95% CI: 11.6, 31.7)		
	Clinical Remission	8 (5.4%)	38 (16.9%)	11.5% / 3.1
	Stratified p-value (CMH chi-square test)	p = 0.0009		
	Stratified Hazard Ratio (95% CI)	11.5% (95% CI: 4.7, 18.3)		
	Mucosal Healing (%)	37 (24.8%)	92 (40.9%)	16.1% / 1.6
	Stratified p-value (CMH chi-square test)	p = 0.0012		
	Stratified Hazard Ratio (95% CI)	16.1% (95% CI: 6.4, 25.9)		
Analysis description	No sensitivities analyses were performed Patient Reported Outcomes (PROs) Inflammatory Bowel Disease Questionnaire (IBDQ) total and sub-scale Scores, Short Form-36 (SF-36), and EuroQol (EQ-5D) were assessed at Week 6 calculating the mean change from baseline based on an analysis of covariance (ANCOVA) model.			
Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis.				
Study identifier	Study C13006 Maintenance			
Design	Conducted as part of the phase 3, randomized, placebo-controlled, double-blind, multicenter study (C13006) of efficacy and safety with separate Induction and Maintenance Phases, including a separate randomization after the Induction Phase			
	Duration of Maintenance phase:	46 weeks (from week 6 to week 50)		
	Duration of Extension phase:	2 years follow up		
Hypothesis	Superiority> < Equivalence> <Non-inferiority> <Exploratory: specify>			

Table 2.

Treatments groups	VDZ Q4W	treatment= IV dosing, 300 mg double-blind vedolizumab every 4 weeks from Week 6 to Week 50, (ie, Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50) duration = 46 Weeks number randomized = 125 subjects
	VDZ Q8W	treatment= IV dosing, 300 mg-Q8W Vedolizumab at Weeks 6, 14, 22, 30, 38, and 46, and, to maintain blinding, placebo saline infusions at Weeks 10, 18, 26, 34, 42, and 50 duration = 46 Weeks number randomized =122

	Placebo		treatment= placebo duration = 46 Weeks number randomized =126	
Endpoints and definitions	Primary endpoint	Clinical remission at 52 weeks	clinical remission is defined as partial Mayo score of ≤ 2 points and no individual subscore > 1 point at Week 52.	
	Secondary endpoint	- Durability of clinical response - Mucosal healing at 52 weeks - Durability of clinical remission - Corticosteroid-free remission at 52 weeks	clinical response at both Weeks 6 and 52 Mayo endoscopic subscore of ≤ 1 point Clinical remission at both Weeks 6 and 52 Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at Week 52.	
Database lock	27 January 2012			
<u>Results and Analysis</u>				
Analysis description	Primary Analysis			
Analysis population and time point description	ITT population (all patients randomized at Week 6)= 373; Non ITT= 522; Per-Protocol population= 359; Time point= Q4W, Q8W			
Descriptive statistics and estimate variability	Treatment group	PLA	VDZ Q8	VDZ Q4
	Number of subject	N=126	N=122	N=125
	Clinical Remission (%)	20 (15.9%)	51 (41.8%)	56 (44.8%)
	DIFFERENCE from Placebo/RR Q8 vs. Pb Q4 vs. Pb	26.1 /2.7 (95% CI: 1.7, 4.2) 29.1 /2.8 (95% CI: 1.8, 4.4)		
	Stratified p-value (CMH chi-square test) Q8 vs. Pb Q4 vs. Pb	<0.0001 <0.0001		
	Durable Response (%)	30 (23.8%)	69 (56.6%)	65 (52.0%)
	DIFFERENCE from placebo/RR Q8 vs. Pb Q4 vs. Pb	32.8 /2.4 (95% CI: 1.7, 3.4) 28.5 /2.2 (95% CI: 1.5, 3.1)		

	Stratified p-value (CMH chi-square test) Q8 vs. Pb Q4 vs. Pb	<0.0001 <0.0001		
	Mucosal Healing (%)	25 (19.8%)	63 (51.6%)	70 (56.0%)
	DIFFERENCE from placebo/RR Q8 vs. Pb Q4 vs. Pb	32.0 /2.6 (95% CI: 1.8, 3.9) 36.3 /2.8 (95% CI: 1.9, 4.2)		
	Stratified p-value (CMH chi-square test) Q8 vs. Pb Q4 vs. Pb	<0.0001 <0.0001		
	Durable Remission (%)	11(8.7%)	25 (20.5%)	30 (24.0%)
	DIFFERENCE from Placebo/RR Q8 vs. Pb Q4 vs. Pb	11.8 /2.4 (95% CI: 1.2, 4.6) 15.3 /2.8 (95% CI: 1.4, 5.3)		
	Stratified p-value (CMH chi-square test) Q8 vs. Pb Q4 vs. Pb	0.0079 0.0009		
	Corticosteroid-free Remission (%)	10 (13.9%) n=72	22 (31.4%) n=70	33 (45.2%) n=73
	DIFFERENCE from placebo/RR Q8 vs. Pb Q4 vs. Pb	17.6 /2.3 (95% CI: 1.2, 4.4) 31.4 /3.3 (95% CI: 1.7, 6.1)		
	Stratified p-value (CMH chi-square test) Q8 vs. Pb Q4 vs. Pb	0.0120 <0.0001		
Analysis description	No sensitivities analyses were performed Patient Reported Outcomes (PROs) Inflammatory Bowel Disease Questionnaire (IBDQ) total and sub-scale Scores, Short Form-36 (SF-36), and EuroQol (EQ-5D) were assessed at Week 6 calculating the mean change from baseline based on an analysis of covariance (ANCOVA) model.			

Table 1. Summary of efficacy for trial C13007

Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Crohn's Disease.	
Study identifier	Study C13007 Induction
Design	<p>Phase 3 randomized, placebo-controlled, blinded, multicenter evaluation of induction and maintenance therapy in patients with moderate to severe CD. This study comprises 2 phases (see Synopsis Figure 1):</p> <ul style="list-style-type: none"> - The Induction Phase, designed to establish the efficacy and safety of vedolizumab for the induction of clinical response and clinical remission, and - The Maintenance Phase, designed to establish the efficacy and safety of vedolizumab for the maintenance of clinical response and clinical remission

	Duration of Induction phase:		6 weeks		
Hypothesis	Superiority of Vedolizumab vs placebo				
Treatments groups	Vedolizumab (Cohort 1)		treatment= IV dosing, 300 mg at Weeks 0 and 2 duration = 6 weeks number randomized = 220		
	Placebo (Cohort 1)		treatment= placebo at Weeks 0 and 2 duration = 6 weeks number randomized = 148		
	Cohort 2		treatment= open-label vedolizumab, 300 mg at Weeks 0 and 2		
Endpoints and definitions	Primary endpoint	Clinical remission at 6 weeks	Clinical remission is defined as CDAI score ≤ 150 points		
	Primary endpoint	Enhanced clinical response at 6 weeks	Enhanced clinical response is defined as a ≥100-point reduction from baseline in CDAI score		
	Secondary endpoint	Change in serum C-reactive protein (CRP) levels at 6 weeks	The secondary efficacy endpoint was the change from baseline in serum CRP levels at Week 6		
Database lock	17 April 2012				
Results and Analysis					
Analysis description	Primary Analysis -The primary comparison of the Induction Phase was tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the randomization stratification factors (concomitant use of oral corticosteroids and previous exposure to TNFa antagonists or concomitant immunomodulator [6-mercaptopurine or azathioprine] use). -Figure (bar-graph) of proportions and 95% CI for proportion of patients who are in enhanced clinical response at Week 6.				
	Analysis population and time point description				
Intent to treat= 148 PLA, 220 VDZ; Modified ITT= 143 PLA, 214 VDZ; Per protocol= 141 PLA, 220 VDZ; time point= week 6					
Descriptive statistics and estimate variability	Treatment group	PLA	VDZ	Adjusted Diff from Placebo/RR	p-value
	Number of subject	N=148	N=220	/	/
	Clinical Remission %	10 (6.8%)	32 (14.5%)	7.8%/ 2.1 (95% CI: 1.1, 4.2)	0.0206
	Enhanced Response (%)	38 (25.7%)	69 (31.4%)	5.7% / 1.2 (95% CI: 0.9, 1.7)	0.2322
	Secondary Endpoints				

	Mean CRP Change (µg/mL)	-3.6 (Std Dev: 30.04)	-2.9 (Std Dev: 16.28)	/	0.9288 (Wilcoxon P-value)
Analysis description	<p>Sensitivity Analysis of CRP Changes To assess the robustness of the CRP changes at Week 6, ANCOVA on the ranks of CRP change from baseline as the response variable and treatment group, baseline CRP values, stratification factors (concomitant use of corticosteroids and previous exposure to TNFα antagonists and/or concomitant use of immunomodulators) as independent variables were used using the ITT population.</p> <p>Patient Reported Outcomes (PROs) The mean changes from baseline (Week 0) to Week 6 in IBDQ, SF-36, and EQ-5D scores were presented by treatment arm along with 95% two-sided confidence intervals for the differences in mean changes from baseline (Week 0) based on an analysis of covariance (ANCOVA) model.</p>				
Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Crohn's Disease					
Study identifier	Study C13007 Maintenance				
Design	All patients who completed the Induction Phase entered the Maintenance Phase. Treatment assignments were based on the Induction Phase treatment and the investigator-assessed treatment response.				
	Duration of Maintenance phase:		46 weeks (from week 6 to week 50)		
	Duration of Extension phase:		2 years follow up		
Hypothesis	Superiority of Vedolizumab vs placebo				
Treatments groups	VDZ Q4W		treatment= IV dosing, 300 mg double-blind vedolizumab every 4 weeks from Week 6 to Week 50, (ie, Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50) duration = 46 Weeks number randomized = 154		
	VDZ Q8W		treatment= IV dosing, 300 mg-Q8W Vedolizumab every 8 weeks from Week 6 through Week 50 (i.e. at Weeks 6, 14, 22, 30, 38, and 46, and, to maintain blinding, placebo saline infusions at Weeks 10, 18, 26, 34, 42, and 50) duration = 46 Weeks number randomized =154		
	Placebo		treatment= placebo duration = 46 Weeks, iv placebo at Weeks 10, 18, 26, 34, 42, and 50 number randomized =153		
Endpoints and definitions	Primary endpoint	Clinical remission at 52 weeks	CDAI score ≤ 150 points		

	Secondary endpoint	<ul style="list-style-type: none">- Enhanced clinical response at 52 weeks- Corticosteroid-free remission at 52 weeks- Durability of clinical remission	<div>≥ 100-point reduction in CDAI score from baseline</div> <div>Corticosteroid-free clinical remission is defined patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52</div> <div>CDAI score ≤ 150 points at ≥ 80% of study visits including final visit (Week 52)</div>			
Database lock	17 April 2012					
<u>Results and Analysis</u>						
Analysis description	Primary Analysis The primary comparison of the Induction Phase was tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the randomization stratification factors (concomitant use of oral corticosteroids and previous exposure to TNFα antagonists and/or concomitant immunomodulator [6-mercaptopurine, azathioprine, or methotrexate] use).					
Analysis population and time point description	ITT population (all patients randomized at Week 6)= 461; Modified ITT= 454; Per-Protocol population= 440; Time point= Q4W, Q8W					
Descriptive statistics and estimate variability	Treatment group	PLA	VDZ Q8	VDZ Q4	DIFF/RR Q8 vs. PLA Q4 vs. PLA	p-value Q8 vs. PLA Q4 vs. PLA
	Number of subject	N=153	N=154	/	/	/
	Clinical Remission (%)	33 (21.6%)	60 (39.0%)	56 (36.4%)	17.4 /1.8 (95% CI: 1.3, 2.6) 14.7 /1.7 (95% CI: 1.2, 2.4)	0.0007 0.0042
	Enhanced Response (%)	46 (30.1%)	67 (43.5%)	70 (45.5%)	13.4 /1.4 (95% CI: 1.1, 1.9) 15.3 /1.5 (95% CI: 1.1, 2.0)	0.0132 0.0053

	Corticosteroid-free Remission (%)	n=82 23 (15.9%)	n=82 26 (31.7%)	n=80 23 (28.8%)	15.9 /2.0 (95% CI: 1.1, 3.6) 12.9 /1.8 (95% CI: 1.0, 3.3)	0.0154 0.0450
	Durable Response (%)	22 (14.4%)	33 (21.4%)	25 (16.2%)	7.2 /1.5 (95% CI: 0.9, 2.4) 2.0 /1.1 (95% CI: 0.7, 1.9)	0.1036 0.6413
Analysis description	Patient Reported Outcomes (PROs) Changes in HRQOL were assessed by analyses of the IBDQ, SF-36, and EQ-5D scores. The mean changes from baseline (Week 0) in IBDQ, SF-36 and EQ-5D scores were presented by treatment arm along with 95% two-sided confidence intervals for the differences in mean changes from baseline (Week 0) based on an ANCOVA model.					

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

Individual studies:

In support of the second line indication of vedolizumab the Applicant provided analyses on the subgroup of naïve anti-TNF-alpha patients from C13007 and C13011 studies considered either individually or pooled. In Study C13007 and C13011, approximately 52% and 25%, respectively, of the study populations were TNFα antagonist-naïve, data from these patients were included in the pooled analysis.

Efficacy results obtained in the subgroup of naïve anti-TNF alpha patients from both studies are summarized in the Figure 103.c below and briefly reported:

Naïve population, C13007 study

Remission

In study C13007 week 6 clinical remission was achieved by 17.4% of vedolizumab treated patients and 9.2% of placebo patients, with a gain over placebo of 8.2 and a NNT of 12.2. In the exploratory analysis at Week 10 of the C13007 safety population, clinical remission rates were higher for patients in both groups (27.8% for the vedolizumab group and 15.1% for the placebo group), with a difference from placebo of 12.7% and a NNT of 7.9. The difference over placebo increased from Week 6 (8.2) to week 10 (12.7) when comparing results from C13007 study and exploratory analysis of the C13007 safety population (Figure 103c).

Enhanced clinical response

In study C13007, week 6 enhanced clinical response was achieved by 42.2% of vedolizumab patients and by 30.3 placebo patients, with a gain over placebo of 11.9% and a NNT of 8.4. In the exploratory analysis at Week 10 of the C13007 safety population, enhanced clinical response was achieved by 47.4% of vedolizumab patients and by 35.6% of placebo, with a difference from placebo of 9.0 and a NNT of 11 (Figure 103c).

In order to support a similar treatment effect of vedolizumab when compared to Adalimumab and Infliximab the Applicant submitted comparison data on maintenance of clinical remission in naïve patients for VDZ (week 52), Adalimumab (week 56) and Infliximab (week 54).

Comparison of treatment periods of vedolizumab compared to adalimumab and infliximab

In order to support a similar treatment effect of vedolizumab when compared to Adalimumab and Infliximab the Applicant submitted comparison data on maintenance of clinical remission in naïve patients for VDZ (week 52), Adalimumab (week 56) and Infliximab (week 54).

Table 20.b Maintenance of Clinical Remission and Response (Percentage of Patients) in the TNF α Antagonist-Naïve Population in Study C13007 and for Remicade[®] (ACCENT-I) and Humira[®] (CHARM)

	Vedolizumab Study C13007 (ITT Population)			Infliximab (ACCENT I) ^a			Adalimumab (CHARM) ^b		
	Placebo N = 71	Vedolizumab Q8W N = 66	Vedolizumab Q4W N = 71	Placebo N = 110	5 mg/kg N = 113	10 mg/kg N = 112	Placebo N = 170	40 mg eow N = 172	40 mg ew N = 157
Clinical remission (%)	26.8	51.5	46.5	13.6	28.3	38.4	12	36	41
Difference from placebo		24.8	19.7		14.7	24.8		24	29
CDAI-100 response ^c (%)	38.0	60.6	53.5	15.5	38.1	47.7	17	41	48
Difference from placebo		22.6	15.5		22.6	9.6		24	31
Patients in steroid-free remission ^d (%)	27.5 (11/40)	39.5 (15/38)	44.4 (16/36)	11 (6/54)	25 (14/56)	34 (18/53)	6 (4/66)	29 (17/58)	23 (17/74)
Difference from placebo		12.0	16.9		14	23		23	17

a Remicade package insert⁽³⁾ and Hanauer, 2002.⁽³⁾

b Humira package insert⁽³⁾ and Colombel, 2007.⁽⁴⁾

c Defined as $\geq 25\%$ and ≥ 70 point reduction from baseline CDAI in ACCENT I and CDAI-100 response in CHARM.

d Defined as patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at Week 52 in Study C13007, at Week 54 in ACCENT I, and at Week 56 in CHARM.

Naïve population C13011 study

Remission

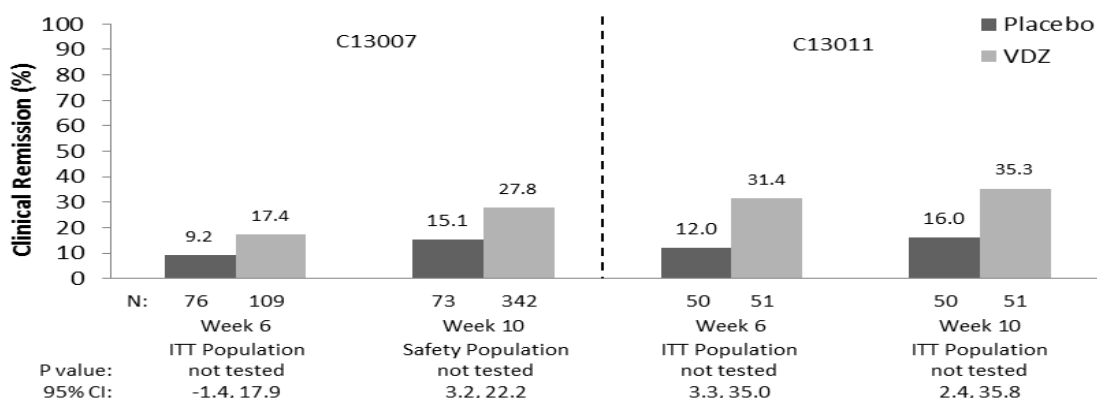
In Study C13011, Week 6 clinical remission in the naïve subpopulation was achieved by 31.4% and 12.0% of patients in the vedolizumab and placebo treatment groups, respectively, with a gain over placebo of 19.2% and a NNT of 5.2. Week 10 clinical remission was achieved by 35.3% of vedolizumab patients and 16.0% of placebo patients, with a gain over placebo of 19.1% and a NNT of 5.2.

Enhanced clinical response

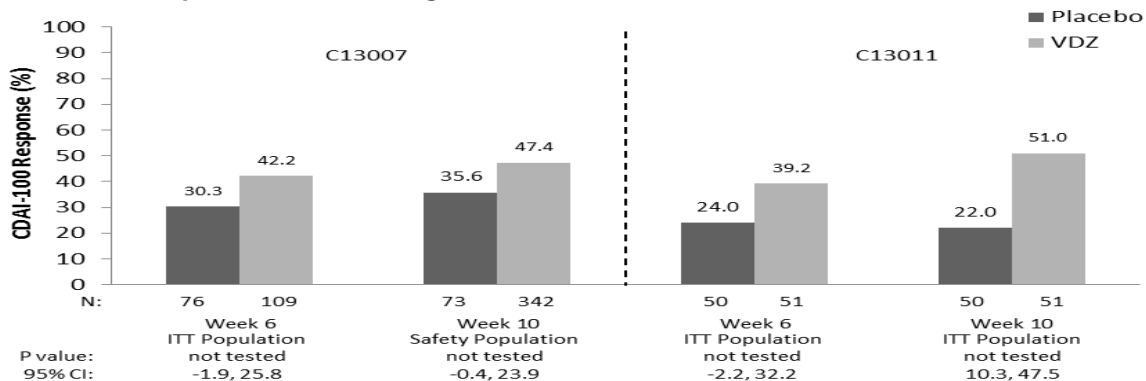
In study C13011, week 6 enhanced clinical response was achieved by 39.2% of vedolizumab patients and by 24.0% of placebo, with a gain over placebo of 15% and a NNT of 6.6. Week 10 enhanced clinical response was achieved (Figure 103c) by 51.0% of vedolizumab patients and by 22.0% of placebo, with a difference over placebo of 29%.

Clinical Remission, CDAI-100 Response, and CDAI-70 Response at Weeks 6 and 10 in Studies C13007 and C13011 (TNF α Antagonist-Naïve Patients Who Had Failed Conventional Therapy)

Clinical Remission (TNF α Antagonist-Naïve)

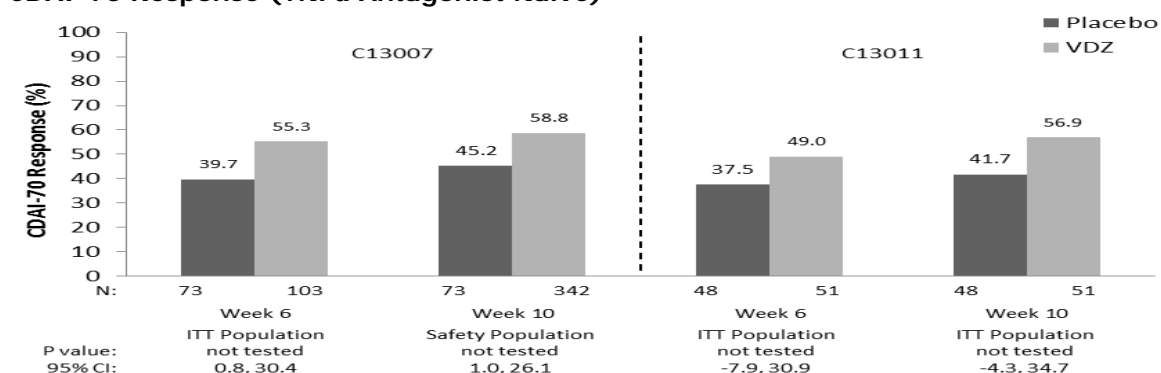


CDAI-100 Response (TNF α Antagonist-Naïve)



Clinical Remission, CDAI-100 Response, and CDAI-70 Response at Weeks 6 and 10 in Studies C13007 and C13011 (TNF α Antagonist-Naïve Patients Who Had Failed Conventional Therapy)

CDAI-70 Response (TNF α Antagonist Naïve)



5% CI is for difference from placebo.

Pooled analysis

In support of the second line indication of vedolizumab, the Applicant reported a pooled analysis already presented in the initial MAA combining TNF α antagonist-naïve patients in the ITT population of the 2 induction studies and reaching a sample size of 277 naïve patients.

From a methodological perspective the pooling was justified by the similar criteria to define failure of conventional therapy, treatment schedule and efficacy assessment for both C13007 and C13011 studies. Efficacy results indicated differences in the patient population of the 2 studies that should be considered for the pooled data. In this combined analysis, week 6 clinical remission was achieved by 22.7% of vedolizumab patients and 10.6% of placebo ($p=0.0054$), with a gain over placebo of 12.6% and a calculated NNT of 8.2. Week 6 enhanced clinical response was achieved by 40.3% of vedolizumab patients and 27.6% of placebo ($p=0.0316$), with a gain over placebo of 12.1% and a calculated NNT of 7.9.

The pooled analysis, including a larger sample size of patients, gives better results than those from the two studies separately considered with a gain over placebo of 12% when remission or enhanced clinical response are considered. (C13007: gain over placebo remission 8.2%; gain over placebo enhanced response 11.9%. C13011: gain over placebo remission 19.5%; gain over placebo enhanced response 15.2%).

Secondary Efficacy Endpoint, Induction

The secondary efficacy endpoint was the change from baseline in serum CRP levels at Week 6.

Among patients in the Induction Study ITT Population, no treatment difference was observed for changes from baseline in CRP. The median change from baseline at Week 6 in CRP was -0.5 mg/L in the placebo group and -0.9 mg/L in the VDZ group.

C13007 Maintenance phase results

Table 21 Primary and Secondary Maintenance Efficacy Endpoints at Week 52 – Maintenance Study ITT Population (C13007 Maintenance Study)

Maintenance Endpoints	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
Primary Endpoint			
Clinical Remission^a			
Number (%) achieving endpoint	33 (21.6)	60 (39.0)	56 (36.4)
95% CI	(15.1, 28.1)	(31.3, 46.7)	(28.8, 44.0)
Difference from placebo ^b		17.4	14.7
95% CI for difference from placebo		(7.3, 27.5)	(4.6, 24.7)
P value for difference from placebo ^c		0.0007	0.0042
Relative risk ^d		1.8	1.7
95% CI for relative risk		(1.3, 2.6)	(1.2, 2.4)
Secondary Endpoints			
Enhanced Clinical Response^e			
Number (%) achieving endpoint	46 (30.1)	67 (43.5)	70 (45.5)
95% CI	(22.8, 37.3)	(35.7, 51.3)	(37.6, 53.3)
Difference from placebo ^b		13.4	15.3
95% CI for difference from placebo		(2.8, 24.0)	(4.6, 26.0)
P value for difference from placebo ^c		0.0132	0.0053

Maintenance Endpoints	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
Relative risk ^d		1.4	1.5
95% CI for relative risk		(1.1, 1.9)	(1.1, 2.0)
Corticosteroid use at baseline^f	N = 82	N = 82	N = 80
Corticosteroid-free Clinical Remission^g			
Number (%) achieving endpoint	13 (15.9)	26 (31.7)	23 (28.8)
95% CI	(7.9, 23.8)	(21.6, 41.8)	(18.8, 38.7)
Difference from placebo ^b		15.9	12.9
95% CI for difference from placebo		(3.0, 28.7)	(0.3, 25.5)
P value for difference from placebo ^c		0.0154	0.0450
Relative risk ^d		2.0	1.8
95% CI for relative risk		(1.1, 3.6)	(1.0, 3.3)
Durable Clinical Remission^h			
Number (%) achieving endpoint	22 (14.4)	33 (21.4)	25 (16.2)
95% CI	(8.8, 19.9)	(14.9, 27.9)	(10.4, 22.1)
Difference from placebo ^b		7.2	2.0
95% CI for difference from placebo		(-1.5, 16.0)	(-6.3, 10.2)
P value for difference from placebo ^c		0.1036	0.6413
Relative risk ^d		1.5	1.1
95% CI for relative risk		(0.9, 2.4)	(0.7, 1.9)

Source: Study C13007, Table 14.3.1.2AM; Study C13007, Table 14.3.1.4AM; Study C13007, Table 14.3.1.8AM; and Study C13007, Table 14.3.1.7AM.

Abbreviations: CDAI = Crohn's Disease Activity Index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PLA = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; TNF α = tumor necrosis factor alpha; VDZ = vedolizumab.

a Clinical remission is defined as CDAI score \leq 150 points.

b Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

c P value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF α antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

d Adjusted Relative Risk and its 95% CI.

e Enhanced clinical response is defined as a \geq 100-point reduction in CDAI score from baseline.

f Number of patients with corticosteroid use at baseline is obtained from the IVRS

g Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52.

h Durable clinical remission is defined as CDAI score \leq 150 points at \geq 80% of study visits including final visit (Week 52).

Supportive studies

UC

Study M200-022: This is a phase 2 placebo-controlled, randomized, double-blind, parallel group, multicenter, study which involves patients with mild to moderate active ulcerative colitis (UC). One-hundred-eighty-one (181) patients were enrolled and randomized in 3 arms: placebo, 0.5 mg/kg LDP-02, or 2.0 mg/kg LDP-02. The aim of the study was to evaluate whether the two doses of LDP-02 (0.5 and 2.0 mg/kg) reduced UC disease activity in patients who were not receiving corticosteroid or immunosuppressive therapy and to assess the safety and tolerability of LDP-02. As a secondary objective, the study was aimed to obtain PK/PD information. The primary endpoint was the proportion of patients who underwent in remission after treatment, (defined as a 0 or 1 in the total UCCS score Modified Baron score with no evidence of rectal bleeding at the Day 43).

Clinical remission was also evaluated at Day 29.

The primary endpoint was met: the percentage of patients with clinical remission at day 43 was higher in both 0.5mg/kg and 2mg/kg LDP-02 arms than in the placebo. Similar differences from placebo are noted when the two doses are compared.

No statistically significant difference in remission rate at day 29 was reported between treatment groups and placebo.

A positive effect of VDZ is supported by results from secondary endpoints, which are consistent with those from the primary endpoint. Overall these findings support the anti-inflammatory activity of VDZ in the colon, but not at systemic level (i.e. CRP serum concentration levels), with a peak of activity at week 6 similarly achieved by the use of both LDP-02 doses. The Applicant discussed the reasons for not observing differences in CRP serum concentrations after VDZ treatment and recognized that a later effect of vedolizumab treatment when compared to that of TNF α antagonist could depend on the different mechanism of action of these drugs and in particular, for active UC data do not support CRP as a useful marker in vedolizumab treated patients.

Both VDZ doses showed a significant improvement in UC disease-related parameters as compared to placebo at Day 43.

The reduced drug effect after day 43 could be expected since probably related to VDZ PK/PD characteristics (half-life of 25 days). Indeed, the posology proposed by the Applicant is doubled (300mg) for each administration and performed at day 0, 14 and 42. In line with the characteristic behaviour of UC inflammatory activity, patients in the placebo group showed an improvement of the condition after 43 days.

CD

Study L299-016

Study L299-016 is a phase 2, LDP-02 (VDZ), randomized, double-blind, parallel group, multicenter, study that involves patients with mildly to moderately active CD, who were not treated with corticosteroids and/or immunosuppressives. A total of 185 patients were enrolled and randomly divided into 3 treatment groups: placebo, 0.5 mg/kg LDP-02, or 2.0 mg/kg LDP-02. All patients received the medical product in two different intravenous (IV) administration on Days 1 and 29. The study was aimed to evaluate whether LDP-02 reduced CD activity and to obtain PK/PD data.

Endpoints:

Primary: evaluation of the percentage of patients with a clinical response at Day 57, defined as a reduction from baseline in the CDAI score of at least 70 points.

Secondary: 1) the proportion of patients with a clinical remission at Day 57 (CDAI score ≤ 150); 2) proportion of patients at each visit who met the criteria for clinical remission and clinical response; 3) changes in mean CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ) scores; 4) changes in the serum concentration of C-reactive protein (CRP); 5) time to relapse, remission and response (Kaplan-Meier time-to-event); 6) proportion of patients who met the criteria of treatment failure at Day 29.

Results: The proportion of patients achieving a clinical response at day 57 did not differ respect of placebo group (53% of patients in the 2.0 mg/kg LDP-02 group and 49% of patients in the 0.5 mg/kg LDP-02 group compared with 41% of subjects on placebo), thus indicating that the primary endpoint of the study was not met. The other secondary endpoints evaluated by the Applicant were only partially and heterogeneously met, thus making difficult the evaluation of the study. Overall, it seems that there is an improvement in the disease activity only in some evaluation days and those days are often discontinuous thus suggesting that there was no relationship between the treatment and the amelioration of the pathology.

In this case the improvement of the clinical parameters analysed could be associated to the relapsing/remitting nature of this pathology and not to the effect of VDZ. As seen in other studies, CRP plasma concentration was not reduced by the treatment with VDZ.

The other secondary endpoints were not met. However the doses used in this study were far lower than the phase 3 clinical trials.

2.5.3 Discussion on clinical efficacy

Design and conduct of clinical studies

Ulcerative Colitis

The demonstration of the efficacy of VDZ in UC patients is based on one phase 3 pivotal trial, Study C13006, conducted under a single protocol but analyzed as 2 studies: the C13006 Induction Study (week 0-6) and the C13006 Maintenance Study (week 6-52). Supportive evidence is derived by two phase II studies: the proof-of-concept and pharmacokinetic/pharmacodynamic (PK/PD) M200-022, study, and the C13002 PK/PD study. Moreover, the C13008 and C13004 open-label safety studies with exploratory efficacy endpoints support long-term efficacy. The number of studies and overall the clinical development programme in UC indication are considered appropriate.

The main study C13006 (phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled trial) was designed to support treatment efficacy and safety in moderately to severely active UC patients who have failed 1 or more standard therapies, including corticosteroids, thiopurines and Infliximab). Two cohorts of patients, sequentially enrolled with identical eligibility criteria, were contained in the 6-week induction phase: Cohort 1 which included patients randomized and treated with double-blind study drug and Cohort 2 which included patients treated with open-label VDZ. Patients were enrolled in Cohort 2 to ensure that the sample size of induction responders randomized into the Maintenance Study provided sufficient power for the Maintenance Study primary efficacy analysis. These patients received open-label VDZ and did not contribute to the efficacy analyses done in the Induction Study. The use of this strategy by the Applicant in view of having an adequate sample size to evaluate efficacy in the maintenance setting is acknowledged by the CHMP.

The "enrichment design" of the study (week 6), allowing only responders to enter the double-blind maintenance phase, is acknowledged as it is commonly adopted in clinical trials conducted in IBD setting. The Maintenance Phase began at Week 6, included study drug dosing at Week 6 and every 4 weeks or 8 weeks thereafter, and concluded with Week 52 assessment. Three groups of patients were contained in the Maintenance Phase and they were assigned to

treatments arms on the basis of their induction treatment assignment and response to therapy: 1)VDZ-treated patients with treatment response at Week 6 of the Induction Phase were randomized to receive or VDZ every 4 weeks (ITT population Q4W), or every 8 weeks (ITT population Q8W), or placebo (ITT population placebo); 2) VDZ-treated patients with no treatment response at Week 6 of the Induction Phase continued treatment with VDZ, administered every 4 weeks (maintenance non-ITT population VDZ q4w); 3) patients on double-blind placebo in the Induction Study continued on double-blind placebo during the Maintenance Phase, regardless of treatment response during induction (maintenance non-ITT placebo).

The different dose regimen (every 4 weeks or 8 weeks) to which patients might have been randomized in the maintenance phase gives the opportunity to evaluate additional data and to support the choice of the dose regimen. Moreover, a prolonged treatment with VDZ in patients not responders at week 6 gives information about the potential gain in efficacy when treatment is prolonged beyond 6 weeks.

The duration of the maintenance phase of the study was from week 6 to 52, whereas EMA guideline recommends duration of at least 1 year. To address this deviation the Applicant submitted supplemental analyses which were accepted by the CHMP.

Key inclusion criteria (age, UC diagnosis, UC activity, UC extension, inadequate response or intolerance to at least 1 immunomodulators, corticosteroids, and/or a TNFalpha antagonist (Infliximab)) are generally in line with those of recent studies conducted on the same category of patients.

The study was designed against placebo, however conventional therapies (5-ASAs, corticosteroids, immunomodulators, antibiotics, probiotics, and antidiarrheals) were concomitantly administered to patients. The lack of an anti-TNF α compound comparator arm represents a limit of the study in consideration of today's standard of care.

Primary and secondary objectives of both induction and maintenance studies are clearly stated and represent those commonly studied in the UC indication. However, it is noted that in contrast with EMA guidelines and with scientific advices, the primary endpoint was the proportion of patients with clinical response at week 6 and not with clinical remission.

The exploratory endpoint, data on sustained response/remission (Partial Mayo score) at every visit (from week 6 to week 52), is agreed by the CHMP, since maintenance of remission during 52 weeks is a relevant secondary endpoint recommended by the EMA guideline.

The grading for the assessment of rectal bleeding, in the definition of clinical remission, including a rectal bleeding subscore of 0 (absence of bleeding) or 1 (minimal bleeding), although not required by the EMA guideline is acceptable to the CHMP in view of its common use in clinical trials with comparators.

Although above deviations have been identified from EMA guidance, overall the study design of both phases is considered adequate.

Baseline demographics were similar in the ITT induction and maintenance population (except for geographic region in the maintenance study). Overall, the treatment groups were comparable with respect to disease characteristics and to the extent and nature of treatment failure to UC therapies, baseline UC therapies in both induction and maintenance studies. In the induction

study, approximately 40% of patients had a history of failure to a TNF α antagonist and a similar proportion had failed immunomodulators (without TNF α antagonist failure). Fewer patients failed corticosteroids alone (17%). In the maintenance study a reasonable difference was reported in the non-ITT Q4W treatment group (e.g. Week 6 non-responders) in which a higher proportion of patients who had prior TNF α antagonist failure was recorded (49%, compared to 30%, 35%, and 32% in the ITT placebo, VDZ Q8W, and VDZ Q4W groups, respectively).

Taken together the reported characteristics reflect those of the target population of the sought indication.

The large majority of patients concluded the induction study. In the maintenance study approximately 50% of VDZ treated and 70% of placebo patients discontinued study treatment mainly due to lack of efficacy (54% placebo and 38% VDZ).

Crohn's disease

The pivotal trial for Crohn's disease included patients with moderate to severe CD and has the same design as study C13006. The trials in both indications included subjects who failed or were intolerant to immunomodulators or anti-TNF therapy. The posology was the same for all three trials with 300mg VDZ at weeks 0, 2 and 6 (induction phase) followed by 300mg every 4 or every 8 weeks thereafter until week 52.

An additional pivotal trial in Crohn's disease was conducted in predominantly those who had failed anti-TNF therapy (75%) which was an induction trial of 10 weeks (C13011) with no maintenance phase.

Following these trials patients could enter into the long-term open label study C13008.

The claimed indication: "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 tumour necrosis factor-alpha antagonist" is based on two phase 3 induction studies, C13007 and C13011 and one phase III maintenance study (C13007). These studies are supported by a phase 2 studies (L299-016) and two long-term, open-label safety studies with exploratory efficacy endpoints (C13008 and C13004). The number of studies and overall the clinical development programme in CD indication are considered appropriate.

The main C13007 Study (phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled trial) was designed to include 2 separate phases that were then analyzed as 2 separate studies (Induction study and Maintenance study). The Applicant's choice to study under two separate trials VDZ efficacy in induction and maintenance setting is in accordance with EMA guideline (CPMP/EWP/2284/99 Rev. 1).

The Induction study was a 6-week trial that included 2 cohorts with same eligibility criteria: Cohort 1, in which patients were randomized and treated with double-blind study drug; Cohort 2, in which patients were treated with open-label VDZ but were not included in the efficacy induction population. The adoption of this strategy, aimed at having an adequate sample size to evaluate efficacy in the maintenance setting, is acknowledged. The "enrichment design" of the study (week 6) allowing only responders to enter the double-blind maintenance phase is commonly adopted in clinical trials conducted in IBD setting.

The maintenance study included all CD patients (cohort 1 and 2) who completed the induction phase: the second phase of the C13007 study started at week 6 and concluded at week 52. According to pre-specified criteria, VDZ-treated patients from both cohorts who showed a clinical response at week 6 were randomized 1:1:1 to VDZ administered every 4 weeks (Q4W-ITT population), VDZ administered every 8 weeks (Q8W-ITT population), or placebo (ITT population).

The different dose regimen (every 4 weeks or 8 weeks) to which patients might have been randomized in the maintenance phase gives the opportunity to compare data and support the choice of the dose regimen.

The double blind maintenance phase for the evaluation of remission is not compliant with the EMA guideline requiring a minimum duration of 52 weeks. However, the use of disease activity data from the first study visit of the long-term safety Study C13008 can supply the missing data on remission at week 52, and so this can be accepted.

The inclusion and exclusion criteria are considered adequate for the target population. However, it is noted that:

- Among the inclusion criteria, the cut-off chosen for CRP level (>2.87 mg/L) was chosen by the Applicant based on the upper limit of normal range of used laboratories. The role of CRP as biomarker of disease inflammation in UC and CD patients treated with vedolizumab has been discussed and differences have been pointed out with regard to its sensitivity and role in the two diseases.
- The absence of mucosal healing data at the enrolment is still considered a weakness of the study, since it is a clinically relevant parameter.
- -The adopted definition of inadequate response to immunomodulators is not considered appropriate both from a regulatory (EMA CHMP/EWP/18463/2006) as well as from a clinical point of view. However, during the procedure, the applicant justified the definitions utilized for "inadequate response" and these are accepted by the CHMP.
- Definition of failure to infliximab induction treatment was considered inadequate by EMA SA (EMA/H/SA/765/1/FU/2/2010/III) since not in line with recommendations provided in the infliximab product information for ulcerative colitis. It was recognized by the Applicant that the adoption of this criterion allows the inclusion of patients not "classically" defined as TNF alpha non responders. It is noteworthy that information on previous doses of infliximab was not collected. However, data coming from the extrapolation of those from C13007 study allow concluding that this adopted definition would not favour the active treatment.
- The definition of inadequate response to Adalimumab induction dose treatment (80 mg/40mg) instead of the proper induction dose (160mg/80mg) was considered inappropriate. The Applicant justified the definition of inadequate response to Adalimumab induction dose treatment 80 mg/40mg according to SmPC posology labelling. In study C13007 roughly 40% (VDZ combined group) of patients previously failed adalimumab therapy due to inadequate response. However, it should be considered that in clinical practice the high induction dose (160/80mg) is widely used. Moreover, a recent study conducted in a nationwide real life cohort of unselected moderately to severe CD patients

reported that 73% of 720 patients started on high dose adalimumab induction (160/80mg) (Baert F, J of Crohn's and Colitis 2013).

- The definition of history of intolerance as the occurrence of a previous infection was not agreed. But the issue is considered resolved in view of the limited number of patients and of the proportional distributed between vedolizumab and placebo arms.
- The definition of inadequate response to corticosteroids lacks the specification of the time interval between the 2 failed attempts of dose tapering. This information was not collected as part of the clinical studies. However, the definition used by the applicant can be accepted as it is recognized that patients with inadequate response to corticosteroids were limited in number and equally distributed between the placebo and the vedolizumab groups across studies.

The study was designed against placebo, however conventional therapies were concomitantly administered to patients. The lack of an anti-TNF-alpha compound as comparator arm represents a limit of the study in consideration of today's standard of care.

The definitions of the primary and secondary endpoints of both induction and maintenance studies are in line with previous evidence. Induction study: the two co-primary endpoints are acknowledged for their clinical significance and for being in line with regulatory guidelines. The main secondary endpoint was aimed to evaluate the efficacy of VDZ treatment on systemic inflammatory response (CRP levels). Exploratory analyses of the induction study were aimed to evaluate the consistency of the main study endpoints in various subgroups of patients (previous exposure or failure to anti TNF-alpha; concomitant therapies) and to correlate two different disease activity scores (CDAI and HBI). Maintenance study: the primary and the main secondary endpoints of the maintenance study are considered acceptable. Exploratory analyses of the maintenance study were aimed at assessing the effect of VDZ maintenance therapy on various aspects of clinical response (achievement and durability), on other meaningful clinical aspects. Moreover, the study was aimed to correlate CD-associated genetic polymorphisms and serum biomarkers with therapeutic response to the drug.

Although above deviations have been identified from EMA guidance, overall the study design of both phases is considered adequate.

In the ITT Population of the induction study the majority of patients in each group completed the induction phase of the study, with similar reasons that led to premature discontinuation. In the ITT Population of the maintenance study 47.3% of patients completed the study and the majority of patients discontinued due to lack of efficacy (31% and 38% in the Q4W and Q8W, respectively). Overall, baseline demographics and disease activity characteristics of the induction and maintenance populations were similar among groups and might be considered representative of the target population. However, the CHMP noted that in the Induction study, about 55% of patients had a CDAI <330 indicating a population with prevalent moderate disease activity. In order to clarify if this could represent a selection bias positively influencing efficacy results, the Applicant provided the number of patients with baseline CDAI score <220, and the number of patients with levels of foecal calprotectin higher than 250 µg/g and/or CRP serum concentration higher than 2.87 mg/L in patients with CDAI score higher or lower than 330. The data provided supported that the percentage of patients was low and equally distributed in both C13007 and C13011 studies.

Efficacy data and additional analyses

Ulcerative colitis

For the UC pivotal study (induction phase) the primary endpoint was the proportion of patients in clinical response at week 6. The results were in favour of VDZ with a treatment difference from placebo (PLA) of 21.7% ($p < 0.001$).

The secondary endpoints included the proportion of patients in clinical remission at week 6 (16.9% in VDZ group vs. 5.4% PLA; $p < 0.009$) and mucosal healing at week 6 (40.9% VDZ group vs. 24.8% PLA; $p < 0.0012$). For the induction phase of study C13006 in UC the primary and secondary endpoints were clinically and statistically significant demonstrating that VDZ is effective in UC induction. Exploratory analysis included assessment of induction endpoint comparing those with and without prior anti-TNF failure. These results showed a smaller difference between VDZ and PLA in the anti-TNF failure patients (6.6% at week 6) compared with those without prior anti-TNF failure (16.5%). However the results were in favour of VDZ treatment in the anti-TNF failure group.

The primary endpoint for the maintenance phase of study C13006 was the proportion of patients in clinical remission at week 52 in those on 4 weekly (Q4W) and 8 weekly (Q8W) dosing as compared with placebo. Secondary endpoints included the proportion with durable clinical response, mucosal healing, remission and reduction in steroid usage at week 52. For the primary endpoint of clinical remission at week 52 the differences from placebo were 26.1% in the Q8W ($p < 0.0001$), 29.1% in Q4W ($p < 0.001$). All secondary endpoints for the maintenance phase were also met with similar high levels of statistical significance. Multiple additional analyses were conducted including clinical remission by study visit which showed that maintenances of remission occurred out to week 52 with no reduction in response.

Exploratory analyses in the maintenance phase also assessed response in those with prior anti-TNF failure. In keeping with the induction phase, the response and treatment difference was less for this group as compared with those without prior anti-TNF failure, but the results were in favour of the vedolizumab group.

Additional endpoints included patient reported outcomes all of which were in favour of vedolizumab. For the UC indication the available data support the applicant's revised proposal to wait until week 10 before considering continuation of therapy in anti-TNF α naïve-patients who fail to show a response. In patients non responder to anti-TNF α therapy, the option to wait till week 10 could be clinically relevant.

The Applicant discussed the proposal to wait until week 14 before considering continuation of therapy in UC anti-TNF α naïve-patients who fail to show a respond at week 6 and provided data on remission and clinical response on week 6 non responders anti TNF-alpha naïve and TNF- α failed patients at week 10 and week 14.

In the anti TNF-alpha naïve subpopulation, the gain from week 10 to week 14 was of 4.8% in the placebo group and of 2.9% in the combined VDZ group on remission and of 7.3% in the placebo and of 6.5% in the VDZ combined group on clinical response.

In patients non responder to anti-TNF alpha therapy, the gain from week 10 to week 14 was of 5.6% in the placebo group and of 2.4% in the combined VDZ group on remission and of 2.8% in the placebo and of 7.5% in the vedolizumab combined group on clinical response. The evidence generated from these results was not considered strong enough to maintain the previous SmPC proposal in UC patients to wait until week 14 to observe the therapeutic benefit and thus treatment continuation. Therefore the Applicant agreed to shorten the time period of observation to carefully reconsider continuation of therapy if no evidence of therapeutic benefit is observed by Week 10. This is reflected in the product information and agreed by the CHMP.

Crohn's disease

C13007 Induction study (naïve population, second line indication).

For the Induction phase of C13007 the primary efficacy endpoint (proportions of patients who achieved clinical remission at Week 6 (CDAI score \leq 150 points) was met, 14.5% vedolizumab group vs. 6.8% placebo group; difference from placebo 7.8% ($p=0.0206$; RR 2.1, 95%CI 1.1-4.2).

The co-primary efficacy endpoint (enhanced clinical response at Week 6, a ≥ 100 -point reduction from baseline in CDAI score) was not met (31.4% vedolizumab group vs. 25.7% placebo group; difference from placebo 5.7% - $p=0.2322$; RR 1.2, 95%CI 0.9-1.7). The results from the co-primary endpoints are in contrast from a clinical point of view. Data provided by the applicant during the procedure excluding from C13007 study 7 patients (2 placebo and 5 vedolizumab) who achieved clinical remission at Week 6 but not CDAI-100 response, showed that the gain over placebo in terms of clinical remission at week 6 is even smaller than what previously calculated (+7.1% at week 6 in the post-hoc analysis versus +7.8% at week 6 in the previous one), and consequently also more distant from the effect size considered clinical relevant for the calculation of the sample size ($\sim +16\%$). Results of a post-hoc sensitivity analysis excluding these 7 patients showed that 12.6% of VDZ patients and 5.5% of PLB patients achieved remission at week 6. In addition, the placebo response was lower than the expected (6.8% vs. the expected 21%). This enhances the potential of detecting smaller treatment effect differences as statistically significant.

Subgroup analyses for clinical remission at Week 6 in the C13007 Induction Study ITT population according to demographics and disease activity characteristics were not impressive. In particular, the difference between patients with baseline CDAI ≤ 330 (RR 3.1; 95%CI 1.3, 7.1) and patients with baseline CDAI > 330 (RR 0.8; 95% CI 0.2-3) could be an explanation of failure of one of the primary endpoints. During the procedure, the Applicant provided the forest plot for subgroup analyses of enhanced clinical response at Week 6. The relative risk for subgroup analyses of enhanced clinical response had the same trend of that for clinical remission but it was closer to 1 in many subgroups. With regard to CDAI \leq or ≥ 330 subgroups, patients having a CDAI score ≤ 330 and thus a moderate disease activity had a relative risk favouring vedolizumab whereas those having a CDAI ≥ 330 and thus a severe disease had a relative risk favouring placebo. The same trend is noted also for CRP either for values \leq or ≥ 5 than for values \leq or ≥ 1 . Taken together, data on enhanced clinical response showed that vedolizumab is more effective in patients with moderate disease activity, as shown by both CDAI score and CRP indexes, than in those with high disease activity.

The secondary endpoint of the C13007 Induction study (change in serum C-reactive protein levels at Week 6) was also not met, showing a median change from baseline at Week 6 in CRP of -0.5 mg/L in the placebo treated patients and -0.9 mg/L in the VDZ treated patients. This effect on CRP levels could reflect the scarce influence on systemic inflammatory response, which is probably due to the mechanism of action of VDZ.

Exploratory post-hoc subgroup analyses (Ancillary analyses) showed no clinically meaningful differences. In particular, no significant differences were found in the remission rates when the analysis was performed in patients who received prior/failed TNFalpha antagonist.

Exploratory analyses examined the effects of concomitant corticosteroids and immunomodulators on induction of remission with vedolizumab. Combination treatment, most notably with concomitant corticosteroids, appeared to be more effective in inducing remission in Crohn's disease than vedolizumab alone or with concomitant immunomodulators, which showed a smaller difference from placebo in the rate of remission. Clinical remission rate in GEMINI II at Week 6 was 10% (difference from placebo 2%, 95% CI: -6, 10) when administered without corticosteroids compared to 20% (difference from placebo 14%, 95% CI: -1, 29) when administered with concomitant corticosteroids. In GEMINI III at Week 6 and 10 the respective clinical remission rates were 18% (difference from placebo 3%, 95% CI: -7, 13) and 22% (difference from placebo 8%, 95% CI: -3, 19) when administered without corticosteroids compared to 20% (difference from placebo 11%, 95% CI: 2, 20) and 35% (difference from placebo 23%, 95% CI: 12, 33) respectively when administered with concomitant corticosteroids. These effects were seen whether or not immunomodulators were also concomitantly administered. This information has been included in the SmPC.

C13011 Induction study (anti-TNFalpha failed population, third line indication)

C13011 study was the supportive induction study aimed to evaluate VDZ efficacy in a subpopulation mostly composed of patients who failed anti-TNFalpha therapy. After completing the Week 10 assessments, patients were eligible to enrol in Study C13008 (open-label, long-term safety study) if study drug was well tolerated, and no major surgical intervention for CD occurred or was required. Patients who did not enrol in Study C13008, whether they completed Week 10 or withdrew early from the study, were to complete the Final Safety visit (Week 22, or 16 weeks after the last dose of study drug). In addition, after the end of the study, all patients who did not enrol in Study C13008 were to participate in a 2-year follow-up survey. Additional data with the results of the follow-up questionnaires out to June 2013 were provided by the applicant. Rates of dysplasia, colon cancer and other malignancies remained low. Rates for surgery/colectomy showed no change over time off study.

With regard to the C13011 Induction study, the primary efficacy endpoint (the proportion of patients with clinical remission at Week 6 in the TNFa antagonist failure subpopulation) was not met, showing a proportion of VDZ treated patients achieving clinical remission of 15.2% with no significant treatment difference from placebo (3.0%). Instead, clinical remission at Week 6 in the entire study population (secondary endpoint) was met.

When Clinical remission was measured at Week 10, a significant proportion of VDZ treated patients achieved this endpoint with a similar treatment difference from placebo in both the TNF alpha antagonist failure subpopulation (14.4%) and entire study population (15.5%). This result might suggest the need of an additional treatment dose (i.e. week 0, 2 and 6) and a longer time (10 weeks) of follow-up in order to observe a clinically relevant benefit.

Sustained clinical remission in the TNF α antagonist failure subpopulation was not met, whereas enhanced clinical response at Week 6 in the TNF alpha antagonist failure subpopulation was statistically significant in VDZ treated patients and increased over time (difference from placebo at week 6: 16.9%; difference from placebo at week 10: 22.0%).

In the TNF α Antagonist Failure ITT Subpopulation, 12.0% of VDZ-treated patients and 8.3% of placebo-treated patients achieved sustained clinical remission; the treatment difference from placebo was 3.7%. In the Overall ITT Population, 15.3% of VDZ-treated patients and 8.2% of placebo-treated patients achieved sustained clinical remission; the treatment difference from placebo was 7.0%. The reasons for the difference in response between the overall ITT population and the anti-TNF α failure are not known. Whether this is due to the VDZ effect requiring longer in the anti-TNF α failure patients is unclear although those with anti-TNF α failure often to have more long-standing and more severe disease. Those with shortest duration of disease had a largest treatment effect as compared with placebo, which could in part explain the difference in the anti-TNF α failure group and the overall group. During the procedure, the applicant provided evidence that there was no impact of disease location in terms of efficacy responses to VDZ.

Taken together, the main findings of C13011 induction studies are considered of weak-moderate clinical relevance.

Further evidence was provided by the Applicant to support a possible indication in third line (after both conventional therapy and anti-TNF α) e.g. week 6 compared to week 10 data on clinical remission in TNF α antagonist failure patients of Study C13007 and study C13011 and the indication for 3rd line in CD is considered acceptable particularly in view of the recognized unmet need, since no therapeutic alternatives are at present available in this anti-TNF alpha failed population. However, changes and specifications on the proposed posology have been implemented by the applicant in particular if no evidence of therapeutic benefit is observed by Week 14 then therapy should not be continued. This was agreed by the CHMP.

C13007 Maintenance study (naïve population, second line indication)

In the C13007 maintenance study, the primary endpoint (the proportion of patients with clinical remission at Week 52) was met, with a significant treatment difference from placebo (Q8W arm: 17.4% ((p = 0.0007), with a relative risk of 1.8 (95% CI: 1.3, 2.6)); Q4W arm: 14.7%) in favour of VDZ treated patients. The stratification of patients at week 6 by response status and not by remission status led to an imbalance, in terms of clinical remission, across different treatment groups with the highest proportion of patients in response in the placebo group. The above mentioned imbalance could have impacted on results.

Subgroup analyses of both Q4W and Q8W regimens, conducted according to demographic variables and disease characteristics, showed similar results. Many differences had a CI crossing the 0 and some of them supported results in contrast with a clinical expectation (i.e. for disease duration >7 years VDZ Q4W seems to give better results than for shorter disease duration; patients with CDAI at baseline >330 seem to have a better outcome if treated with Q8W regimen). Overall these results should only be considered exploratory and it is not possible to draw supplementary indication on particular subgroups that may benefit from VDZ treatment.

The proportion of patients with enhanced clinical response at Week 52 was one of the secondary endpoints and it was met with a significant treatment difference from placebo of 13.4% in Q8W

arm and 15.3% in Q4W arm. Subgroup analyses showed CI often crossing the boundary and no meaningful differences between the 2 treatment arms were noted. Ancillary analysis of durability of clinical response (i.e. durability and enhanced durability of clinical response at Week 52) were consistent with results obtained from clinical response at 52 days showing always higher and almost always significant better results in both VDZ Q4W and Q8W treatment groups as compared to placebo group.

The proportion of patients, with corticosteroids at week 6, in corticosteroid-free clinical remission at Week 52 showed a significant difference from placebo of 15.9% in Q8W arm and 12.9% in Q4W arm. Despite the intrinsic limitation of the definition of corticosteroid-free remission (i.e. how long the patient should have been off steroid and in remission to meet the endpoint), these results should be interpreted as absence of influence of either VDZ maintenance regimen Q4W or Q8W on endpoint achievement. Ancillary analysis of clinical remission and corticosteroid-free for 90 or 180 days at week 52 (patients who were using corticosteroids at baseline) reported a greater proportion of patients in remission in those treated with VDZ (significant results only in the Q8W group, with a difference from placebo of 14.6%) as compared with patients who received placebo.

A durable remission is the only and ambitious measure (secondary endpoint) of clinical remission in the timeframe comprised between week 6 and 52. The proportion of patients in durable clinical remission at Week 52 failed to show significant differences among treatment groups, although a positive trend is noted in Q8W arm. The Applicant supported the durability of vedolizumab efficacy by using less stringent endpoints i.e. CDAI-100 and CDAI-100 at >80% of study visits including week 52 and durable clinical remission for $\geq 60\%$ of study visits including week 52 and showing that the number of patients enrolled in C13007 study achieving durable clinical response (CDAI-70) and durable enhanced clinical response (CDAI-100) as well as durable clinical remission for $\geq 60\%$ of study visits was statistically higher in VDZ treated patients when compared to placebo.

In contrast to what was observed in the induction study, significant changes from baseline in CRP levels in patients with elevated CRP at baseline were noted in VDZ treated patients with respect to placebo. In light of the results obtained from induction and maintenance studies about CRP serum concentration the Applicant discussed the role of CRP as a biomarker of disease inflammatory activity in CD patients treated with VDZ. The Applicant defined the cut-off of 2.87 mg/L for CRP based on the upper limit of normal range of used laboratories. The role of CRP as biomarker of disease inflammation in UC and CD patients treated with vedolizumab has been discussed and differences have been pointed out with regard to its sensitivity and role in the two diseases.

In support of the second line indication the Applicant reported subgroup analysis of naïve anti-TNF-alpha patients from C13007 and C13011 studies considered either individually or pooled. Better results in clinical remission at week 6 were obtained in the naïve population of the C13011 study than in the C13007 study (difference from placebo 8.2% and 19.2%, NTT 5.2 vs. 12.2). The difference in the therapeutic effect of vedolizumab in the 2 studies is rather large. One reason could be the different sample size between the two studies. However, similar differences are noted also in the response of the placebo group. Data provided by the applicant highlighted that baseline disease activity in TNF α antagonist naïve patients was higher in those enrolled in Study C13007 than those in study C13011: CDAI score (316.2 and 296.8, respectively),

percentage of patients with baseline CDAI > 400 (15% and 3%, respectively). Accordingly, also baseline inflammatory indexes were higher in TNF α antagonist naïve patients of C13007 when compared to those of C13011: baseline CRP mean (SD): 22.6 (27.6) and 15.8 (16.49), respectively; baseline fecal calprotectin 1350.6 (2128.80) and 1076 (1572.91), respectively. This may limit the reliability of the pooled analysis proposed by the Applicant.

The CHMP highlighted that full response to Vedolizumab requires longer treatment periods compared to adalimumab and infliximab and that second line treatment with vedolizumab would expose patients to longer treatment with an ineffective drug before switching to other treatment options compared to what would happen if the second line drug were adalimumab or infliximab. The Applicant acknowledged the lower treatment effect of vedolizumab induction therapy in the naïve pooled C13007 and C13011 subpopulations when compared with adalimumab 160/80 mg induction dose in naïve patients or Infliximab. A similar degree of treatment effect is recognized for adalimumab 80/40mg and Vedolizumab 300mg. In order to support a similar treatment effect of vedolizumab when compared to adalimumab and Infliximab the Applicant submitted comparison data on maintenance of clinical remission in naïve patients for VDZ (week 52), adalimumab (week 56) and Infliximab (week 54). Taking into account the limitations of indirect comparisons of data across studies with different drugs, the CHMP noted that the adalimumab data reported by the Applicant referred to the overall CD population and not to the naïve subset of patients to whom the comparison should have been made. When the naïve subgroup of adalimumab patients is considered, percentages differ as follow: remission at week 56 PLB (12/89) 14%; ADA 40mg eow (36/87) 42% difference from PLB 28; ADA 40mg ew (41/86) 48% difference from PLB 36. These data suggest that efficacy rates may be higher in adalimumab patients compared to VDZ, though the limitations of cross-trial comparisons must be taken into account. The CHMP concluded that in patients with Crohn's disease, some patients may require up to 14 weeks treatment with vedolizumab to achieve remission. Possible explanations include the mechanism of action and individual patient disease factors, as this was a very treatment experienced population studied. The CHMP therefore requested the inclusion of the following information in the SmPC: "Induction of remission in Crohn's disease may take up to 14 weeks in some patients. The reasons for this are not fully known and are possibly related to the mechanism of action. This should be taken into consideration, particularly in patients with severe active disease at baseline not previously treated with TNF α antagonists".

Overall it is recognized that a later effect of vedolizumab treatment when compared to that of TNF α antagonist could depend on the different mechanism of action of these drugs. In particular, for active UC data there is little support for CRP as a useful marker in vedolizumab treated patients. On the contrary, CRP could be a useful biomarker in CD patients treated with vedolizumab but the evaluation should not be performed at an early time point, but at least beyond 6 weeks of therapy.

Although the numbers were low, in study C13011 a higher response in those with colonic involvement as compared with only ileal involvement was noted. In order to understand whether the effect of vedolizumab differs between the small and large bowel, the applicant presented the efficacy outcomes for induction and maintenance phases for patients from both studies (C13007 and C13011) by disease location and the data analysis did not reveal any consistent difference in efficacy related to disease location.

2.5.4 Conclusions on the clinical efficacy

Conclusions on clinical efficacy in Ulcerative colitis

Results from clinical studies showed a significant efficacy of VDZ in 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 antagonist. Efficacy has been clearly demonstrated for UC in both induction and maintenance. There was no difference in results between the Q4W and Q8W posology for the maintenance phase. VDZ provides an additional therapy for UC for those who have failed previous immunomodulators and to a lesser extent in those who have failed anti-TNF therapy.

On the basis of the whole data set the CHMP considers the benefit of vedolizumab sufficiently demonstrated for both UC indications (second and third line).

Conclusions on clinical efficacy in Crohn's disease

For the Induction phase of study C13007 the primary efficacy endpoint (proportions of patients who achieved clinical remission at Week 6 (CDAI score ≤ 150 points) was met. The gain over placebo (Study C13007) in terms of clinical remission (+7.8% at week 6) was small and lower than that expected (+21%).

For the maintenance phase of study C13007 the primary endpoint of clinical remission was statistically significant. Two out of the three secondary endpoints (enhanced clinical response [≥ 100 -point decrease in CDAI score from baseline] and corticosteroid-free clinical remission at Week 52) were also statistically significantly in favour of VDZ. One of the secondary endpoints (durable remission) was not met.

The rationale for the second line indication presented by the Applicant was based on the similarity of the patient populations in studies C13007 and C13011 (supporting the validity of results obtained in both studies in the overall benefit-risk assessment), the favourable safety profile of VDZ compared to anti-TNFs, the comparability of the efficacy of VDZ with anti-TNF drugs (given the limitations of comparing results between studies and the delayed action of VDZ), and the overall clinical relevance of the benefits observed for VDZ in terms of the proportion achieving remission and the length of time required for this to occur. The CHMP concluded that vedolizumab's efficacy is greater in the second line indication compared with the third line, albeit delayed and possibly less effective compared with anti-TNFalpha drug. The lack of systemic immunosuppression, with no cases of extra-pulmonary or systemic TB with VDZ in contrast to anti-TNFs, and the long-lasting efficacy in those who respond, combine to make VDZ a useful option for 2nd line CD patients. It is, however, acknowledged that there is extensive clinical experience with anti-TNFs in CD and the side effect profile is more comprehensive than is currently available for VDZ.

Evidence was provided by the Applicant to support an indication in third line (after both conventional therapy and anti-TNFalpha). The data showed that clinical remission and clinical enhanced response in the anti TNF failure populations of both C13011 and C13007 studies showed small effect of vedolizumab over placebo at Week 6 (6.2% and 0.9%, respectively) but greater percentages at Week 10 with a gain over placebo in remission of 7.4% (C13007) and 14.4% (C13011) and in enhanced response of 16.3% (C13007) and 22% (C13011). This

indication for 3rd line in CD is therefore considered acceptable by the CHMP particularly in view of the recognized unmet need, since no therapeutic alternatives are at present available in this anti-TNF alpha failed population.

Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14 as mentioned in the product information.

Exploratory analyses also suggested that vedolizumab administered in patients without concomitant corticosteroid treatment may be less effective for induction of remission in Crohn's disease than in those patients already receiving concomitant corticosteroids. As requested by the CHMP, this information is reflected in the product information.

2.6 Clinical safety

The focus of the safety evaluation is on data from the placebo-controlled 52-week induction/maintenance studies (C13006 conducted in patients with UC and C13007, conducted in patients with CD) and from an ongoing open-label, single arm, extension study C13008 (conducted in patients with UC or CD). The dose level studied in all the phase III studies was 300 mg fixed dose.

Safety data coming from phase I and phase II studies conducted both in patients and in healthy volunteers have not been included in the safety evaluation.

Phase III Studies contributing to safety database are reported in the following table.

Population	Studies	Treatment Groups
UC		
UC induction/maintenance	C13006	Placebo Vedolizumab 300 mg dosed Q4W Vedolizumab 300 mg dosed Q8W
UC overall	C13002, C13004, C13006, C13008	Vedolizumab
CD		
CD induction	C13007, C13011	Placebo Vedolizumab 300 mg
CD induction/maintenance	C13007	Placebo Vedolizumab 300 mg dosed Q4W Vedolizumab 300 mg dosed Q8W
CD overall	C13004, C13007, C13011, C13008	Vedolizumab

In order to evaluate long term safety data two long term open label safety studies were conducted.

Study 13008

Study C13008 is an ongoing, multinational, single-arm, open-label phase 3 study evaluating the long-term safety of VDZ in patients with moderate to severe UC or CD. For Study C13008, all AEs were summarized from the first dose of study drug in Studies C13004, C13006, C13007, and C13011 for the patients who received VDZ. AEs were counted during the time of active drug administration, including a pre-specified follow-up after the fixed dose of study drug. For example, AEs for patients who received VDZ in the Induction Phase and placebo in the Maintenance Phase of Studies C13006 and C13007 were counted if the AE occurred between the first dose and the last dose of the Induction Phase plus 4 weeks (i.e., through Week 6), and at any time during Study C13008. AEs were not counted during the time of placebo administration.

SAE collection continues through the Final Safety visit (16 weeks after the last on-study dose of VDZ). The addition of 16 weeks accounts for the known duration of detectable VDZ serum concentrations after the last dose.

For study C13008 the Safety Population (used for the safety analysis) is defined as all patients who participated in Studies C13004, C13006, C13007, or C13011 and who received any amount of VDZ in this study.

AEs following re-exposure to VDZ were analyzed in patients who responded to VDZ during the Induction Phase of Studies C13006 and C13007, were randomized to placebo during the Maintenance Phase, and were subsequently re-exposed to VDZ after entering Study C13008 (maintenance ITT placebo group).

Patients without prior treatment with VDZ were also enrolled in Study C13008 (i.e., de novo patients). There were no deaths reported in any de novo patient from study entry through 20 October 2012 or in any rollover patient from 16 July 2012 (cut-off date for the safety analysis) through 20 October 2012.

Ongoing Poststudy, Long-term Follow-up Survey

Since 2007, all subjects who participated in a VDZ clinical trial are to complete a 2-year telephone follow-up survey from the date of last dose of study drug. A questionnaire is administered via telephone at 6, 12, 18, and 24 months after the final dose of study drug, and it requests information on: pregnancy, infections, colorectal dysplasia or cancer, lymphoma, any other type of cancer, IBD-related surgeries, and the development of PML.

As of 08 November 2012, 1289 of 1694 (76%) patients provided responses to at least 1 post-study follow-up survey after participating in Study C13001, C13002, C13004, C13005, C13006, C13007, C13008, C13009, C13010, C13011, C13012, or C13013. Additional data with the results of the follow-up questionnaires out to June 2013 were provided by the applicant during the procedure.

The safety populations analyzed in the present Assessment Report are the following:

- The UC induction/maintenance safety population includes safety data across the Induction and Maintenance Phases of Study C13006.
- The overall UC safety population includes safety data from Studies C13002, C13004, C13006, and C13008. For a patient who participated in multiple studies (e.g., participated in

Studies C13002, C13004, and C13008), all safety data during VDZ exposure are combined for the patient.

- The CD induction safety population includes safety data from the Induction Phase of Study C13007 and from Study C13011.
- The CD induction/maintenance safety population includes safety data across the Induction and Maintenance Phases of Study C13007.
- The overall CD safety population includes safety data from Studies C13004, C13007, C13011, and C13008. For a patient who participated in multiple studies (e.g., participated in Studies C13007 and C13008), all safety data during VDZ exposure are combined for the patient.
- The overall UC and CD safety population includes safety data from Studies C13002, C13004, C13006, C13007, C13011, and C13008.
- The long-term safety of VDZ in patients with UC or CD includes data from the ongoing, single-arm extension Study C13008. Most patients in Study C13008 had participated in a qualifying VDZ study (Studies C13002, C13004, C13006, C13007, and C13011). The protocol was amended in February 2012 to allow enrolment of UC and CD patients without previous VDZ treatment (de novo patients). Because enrolment of de novo patients did not begin until May 2012, safety data from these patients in Study C13008 are not included in the SCS.
- In order to provide a comparison between placebo and continuous VDZ exposure, the safety evaluation focuses on two groups:
- patients who received placebo during induction and maintenance (non-ITT placebo)
- combined VDZ group: patients who received VDZ during induction and maintenance (patients who responded to VDZ induction treatment and were randomized to double blind VDZ Q8W or Q4W dosing in maintenance and patients who did not respond to VDZ induction treatment and were assigned to open-label VDZ Q4W dosing in maintenance).

The safety issues of special interest related to VDZ mechanism of action include infections, malignancies and PML. The most frequently reported AEs in both patients with UC and patients with CD were gastrointestinal events and infections. No PML cases were reported.

The safety profile of similar medicinal products (anti TNF alpha agents) is almost overlapping with that of VDZ, although for VDZ TBC cases were new infections and no cases of extra-pulmonary TB nor disseminated TB were noted and, at present, no cases of PML with VDZ are reported probably due to the different selectivity in the mechanism of action when compared to natalizumab.

Patient exposure

As of 16 July 2012 (cut-off date for safety data for the MAA) a total of 2708 patients had received at least one dose of VDZ (1089 patients with UC, 1619 patients with CD). Patients were exposed to VDZ for a mean of 430 days in phase 3 studies combined. Across all phase 2 and phase 3 clinical studies, 1195 patients were exposed for ≥ 12 months and 502 patients were exposed for ≥ 24 months. 621 patients with either UC or CD received ≥ 24 infusions, and 125 received ≥ 36 infusions.

Overall Safety Population: Exposure to VDZ by Month

	>= 1 dose	>= 6 mo.	>= 12 mo.	>= 18 mo.	>= 24 mo.	>= 36 mo.	>= 48 mo.
All Vedolizumab Patients ^a	2708	1677	1195	846	502	53	28
Ulcerative Colitis	1089	702	560	418	243	41	23
Crohn's Disease	1619	975	635	428	259	12	5
Vedolizumab Healthy Volunteers ^b	197	0	0	0	0	0	0
Total	2905	1677	1195	846	502	53	28

a. Patients participated in studies L297-005, L297-006, L299-016, M200-021, M200-022, C13002, C13004, C13006, C13007, C13008 and C13011.

b. Patients participated in studies L297-007, C13001, C13005, C13009, C13010 and C13012.

Discrete intervals analysis

To analyze safety in patients receiving VDZ over time, an analysis was conducted of events that occurred at discrete intervals of 3 to 6 months. These analyses were conducted in the UC overall safety population, CD overall safety population, and UC and CD combined overall safety population. For each PT within each time interval, the AE rate was calculated as the number of patients for whom the onset of the AE was within the time interval divided by the number of patients who started the time interval.

Adverse events

An overall summary of AEs for the UC (Study C13006) and CD (Study C13007) induction/maintenance patient populations is presented in the following Tables.

UC (Induction/Maintenance patient population Study C13006)

Table 3-1 Overall Summary of Adverse Events – Ulcerative Colitis Induction/Maintenance Safety Population (C13006)

Adverse Event Category, n (%)	Maintenance Study ITT ^a (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA ^b (from Week 0) N = 149	VDZ Q4W ^c (Week-6 Nonresponders) N = 373	PLA N = 275	VDZ N = 620
Excluding AEs in the Gastrointestinal Disorders SOC							
Any AE	92 (73)	97 (80)	96 (77)	102 (68)	274 (73)	194 (71)	467 (75)
Drug-related AE	40 (32)	37 (30)	35 (28)	34 (23)	121 (32)	74 (27)	193 (31)
AE resulting in study discontinuation	5 (4)	2 (2)	2 (2)	2 (1)	12 (3)	7 (3)	16 (3)
SAE	13 (10)	7 (6)	8 (6)	8 (5)	20 (5)	21 (8)	35 (6)
Drug-related SAE	4 (3)	3 (2)	1 (< 1)	1 (< 1)	8 (2)	5 (2)	12 (2)
SAE resulting in discontinuation	3 (2)	0	0	1 (< 1)	7 (2)	4 (1)	7 (1)
Deaths	0	0	0	0	1 (< 1)	0	1 (< 1)
Including AEs in the Gastrointestinal Disorders SOC							
Any AE	106 (84)	100 (82)	101 (81)	114 (77)	296 (79)	220 (80)	497 (80)
Drug-related AE	40 (32)	37 (30)	37 (30)	38 (26)	126 (34)	78 (28)	200 (32)
AE resulting in study discontinuation	15 (12)	7 (6)	6 (5)	16 (11)	23 (6)	31 (11)	36 (6)
SAE	20 (16)	10 (8)	11 (9)	17 (11)	56 (15)	37 (13)	77 (12)
Drug-related SAE	4 (3)	3 (2)	1 (< 1)	3 (2)	9 (2)	7 (3)	13 (2)
SAE resulting in discontinuation	7 (6)	2 (2)	0	6 (4)	14 (4)	13 (5)	16 (3)
Deaths	0	0	0	0	1 (< 1)	0	1 (< 1)

Source: Table 18.7.1.1 (post hoc), Study C13006, Table 14.4.1.1M.

Abbreviations: AE = adverse event; CSR = clinical study report; ITT = intent-to-treat; PLA = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; SOC = system organ class; UC = ulcerative colitis; VDZ = vedolizumab.

Treatment-emergent AEs are reported and defined as AEs occurring between the start date of the Induction Phase and the end date of Maintenance Phase.

a. Patients who were randomized into the ITT population during the Maintenance Phase.

b. Patients who received placebo during the Induction Phase and continued to receive placebo during the Maintenance Phase.

c. Patients who received vedolizumab in the Induction Phase but did not achieve clinical response at Week 6 and continued to receive vedolizumab Q4W during the Maintenance Phase.

CD (Induction/Maintenance patient population Study C13007)

Table 3-4 Overall Summary of Adverse Events – Crohn's Disease Induction/Maintenance Safety Population (C13007)

Adverse Event Category n (%)	Maintenance ITT ^a (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA ^b (from Week 0) N = 148	VDZ Q4W ^c (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Excluding AEs in the Gastrointestinal Disorders SOC							
Any AE	122 (80)	128 (83)	124 (81)	110 (74)	409 (81)	232 (77)	661 (81)
Drug-related AE	47 (31)	54 (35)	58 (38)	39 (26)	177 (35)	86 (29)	289 (36)
AE resulting in study discontinuation	3 (2)	5 (3)	4 (3)	2 (1)	30 (6)	5 (2)	39 (5)
SAE	10 (7)	12 (8)	16 (10)	10 (7)	65 (13)	20 (7)	93 (11)
Drug-related SAE	1 (< 1)	4 (3)	6 (4)	1 (< 1)	19 (4)	2 (< 1)	29 (4)
SAE resulting in discontinuation	1 (< 1)	3 (2)	2 (1)	0	15 (3)	1 (< 1)	20 (2)
Deaths	0	1 (< 1)	0	1 (< 1)	3 (< 1)	1 (< 1)	4 (< 1)
Including AEs in the Gastrointestinal Disorders SOC							
Any AE	128 (84)	135 (88)	130 (84)	118 (80)	441 (87)	246 (82)	706 (87)
Drug-related AE	51 (33)	63 (41)	63 (41)	45 (30)	191 (38)	96 (32)	317 (39)
AE resulting in study discontinuation	15 (10)	12 (8)	9 (6)	14 (9)	70 (14)	29 (10)	91 (11)
SAE	23 (15)	28 (18)	25 (16)	23 (16)	146 (29)	46 (15)	199 (24)
Drug-related SAE	4 (3)	5 (3)	6 (4)	2 (1)	24 (5)	6 (2)	35 (4)
SAE resulting in discontinuation	7 (5)	9 (6)	5 (3)	8 (5)	45 (9)	15 (5)	59 (7)
Deaths	0	1 (< 1)	0	1 (< 1)	3 (< 1)	1 (< 1)	4 (< 1)

Source: Table 18.7.2.1 (post hoc); Study C13007, Table 14.4.1.1M.

Abbreviations: AE = adverse event; CD = Crohn's disease; CSR = clinical study report; ITT = intent-to-treat; PLA = placebo; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; SOC = system organ class; VDZ = vedolizumab.

a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT Population at Week 6.

b Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.

c Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

Gastrointestinal events (mostly worsening of the underlying CD or UC and other gastrointestinal events potentially related to underlying disease) occurred with similar frequency in UC and CD patients and in the combined VDZ and non-ITT placebo treatment groups. A post-hoc analyses was conducted by removing AEs in the gastrointestinal system organ class (SOC). This resulted in increased frequency of all other AEs, whereas the rates of SAEs and AEs leading to discontinuation substantially decreased.

UC: Drug-related AEs were approximately 30% of all AEs in all groups, with the exception of the maintenance non-ITT placebo group (23%), as expected. Excluding gastrointestinal AEs, less than 5% of AEs accounted for drug discontinuation, independently of dose regimen. The inclusion of gastrointestinal AEs, importantly increased the discontinuation rate (double or even more), indicating a lack of efficacy particularly in the placebo groups ITT and non-ITT. AEs and deaths in patients who discontinued were not relevant and almost similarly distributed.

CD: The incidence of AEs was higher in CD patients than UC patients. Including gastrointestinal disorders, AEs were 36% in the overall VDZ group vs. 26% in the non-ITT placebo group. SAEs were 7 vs. 11% in the non-ITT placebo and VDZ combined group respectively, but the frequency was more than double when gastrointestinal disorders were considered: 16% and 24% in the non-ITT placebo and VDZ combined group respectively. Of these, most resulted in the discontinuation of the drug.

AEs by SOC UC: With regard to AEs by SOC, the main difference is noted in the SOC of infections and infestations with the highest difference (11%) in the vedolizumab combined group (42%) versus non-ITT placebo group (31%), and with higher rates in VDZ Q8W versus Q4W (51% versus 45%). A smaller difference between VDZ combined and non-ITT placebo group is noted in the following SOCs: skin disorders 6%, cardiac disorders 3%, psychiatric disorders 3%, nervous system disorders 2%. No difference is reported in the SOC of blood disorders.

AEs by SOC CD: There were fewer infections and infestations reported in the VDZ combined group (39%) compared with the non-ITT placebo group (44%).

Another difference of note concerns Respiratory disorders that were more frequent in the VDZ combined group (12%) as compared to non-ITT placebo (7%)

Blood disorders were similarly reported across vedolizumab treated patients and placebo patients.

With regard to extra intestinal manifestations, the most common SOC was musculoskeletal and connective disorders which was higher in CD patients VDZ treated as compared to UC patients (44% vs. 22%). Indeed, eye disorders were similarly reported in both CD and UC but mostly described in VDZ treated patients (9%vs 4%).

AE BY PT UC (Induction/Maintenance patient population Study C13006)

In the UC Induction/Maintenance safety population (Study C13006), the most common AEs by Preferred Term (occurring in at least 3% of patients) are summarized by frequency and incidence density in the following tables taking into account the maintenance ITT and non ITT safety populations, respectively.

Table 75 Adverse Events That Occurred in > 3% of Patients in the All Vedolizumab Combined Group by Preferred Term by Frequency and Incidence Density – Maintenance Study ITT Population

Maintenance Study ITT ^a (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)									
Preferred Term, n (%)	PLA N = 126 TPY = 83.7			VDZ Q8W N = 122 TPY = 95.4			VDZ Q4W N = 125 TPY = 101.3		
	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Colitis ulcerative	29 (23)	29	0.346	15 (12)	17	0.178	18 (14)	23	0.227
Headache	15 (12)	22	0.263	16 (13)	24	0.252	17 (14)	45	0.444
Nasopharyngitis	15 (12)	20	0.239	19 (16)	22	0.231	18 (14)	26	0.257
Arthralgia	15 (12)	16	0.191	11 (9)	15	0.157	13 (10)	13	0.128
Upper respiratory tract infection	13 (10)	19	0.227	12 (10)	17	0.178	12 (10)	17	0.168
Nausea	8 (6)	9	0.108	4 (3)	6	0.063	9 (7)	13	0.128
Cough	6 (5)	6	0.072	9 (7)	9	0.094	5 (4)	6	0.059
Anaemia	5 (4)	5	0.060	5 (4)	5	0.052	5 (4)	5	0.049
Abdominal pain	2 (2)	2	0.024	9 (7)	10	0.105	9 (7)	16	0.158
Fatigue	5 (4)	5	0.060	5 (4)	5	0.052	4 (3)	10	0.099
Influenza	3 (2)	4	0.048	8 (7)	9	0.094	2 (2)	2	0.020
Vomiting	1 (< 1)	1	0.012	0	0	0.000	6 (5)	7	0.069
Oropharyngeal pain	1 (< 1)	1	0.012	7 (6)	7	0.073	6 (5)	7	0.069
Bronchitis	7 (6)	7	0.084	7 (6)	7	0.073	6 (5)	7	0.069
Pyrexia	7 (6)	7	0.084	3 (2)	3	0.031	2 (2)	2	0.020
Back pain	0	0	0.000	1 (< 1)	1	0.010	7 (6)	9	0.089
Gastroenteritis	5 (4)	9	0.108	3 (2)	3	0.031	5 (4)	7	0.069
Dizziness	3 (2)	3	0.036	1 (< 1)	1	0.010	3 (2)	4	0.039

Source: Table 14.4.1.2BM, Table 14.4.2.11FM (post hoc analysis).

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TPY = Total person time in Years; VDZ = vedolizumab.

Days for person time was defined as (end of study date - first dose date (of induction) + 1).

End of study date = last scheduled dosing date + 16 weeks for patients who do not continue onto the long-term c13008 safety study.

End of study date = last scheduled dosing date for patients who continued onto the long-term c13008 safety study.

Number of events: within the same preferred term, if the start and stop date of multiple events overlapped or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.

Incidence density: number of events / total person-time in years (TPY)

a Maintenance ITT includes patients who received vedolizumab during the induction phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT population at week 6.

Table 76 Adverse Events That Occurred in > 3% of Patients in the All Vedolizumab Combined Group by Preferred Term by Frequency and Incidence Density – Maintenance Non-ITT Groups and Combined Vedolizumab Group

Preferred Term, n (%)	Maintenance Non-ITT						Combined		
	PLA ^a (from Week 0) N = 149 TPY = 74			VDZ Q4W ^b (Week 6 Nonresponders) N = 373 TPY = 242.2			VDZ N = 620 TPY = 438.9		
	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Colitis ulcerative	29 (19)	33	0.446	64 (17)	79	0.326	97 (16)	119	0.271
Headache	13 (9)	16	0.216	47 (13)	82	0.339	80 (13)	151	0.344
Nasopharyngitis	11 (7)	11	0.149	43 (12)	60	0.248	80 (13)	108	0.246
Arthralgia	10 (7)	10	0.135	32 (9)	37	0.153	56 (9)	65	0.148
Upper respiratory tract infection	8 (5)	11	0.149	28 (8)	38	0.157	52 (8)	72	0.164
Nausea	11 (7)	14	0.189	25 (7)	36	0.149	38 (6)	55	0.125
Cough	7 (5)	8	0.108	22 (6)	23	0.095	36 (6)	38	0.087
Anaemia	11 (7)	11	0.149	25 (7)	31	0.128	35 (6)	41	0.093
Abdominal pain	8 (5)	8	0.108	17 (5)	17	0.070	35 (6)	43	0.098
Fatigue	5 (3)	5	0.068	24 (6)	25	0.103	33 (5)	40	0.091
Influenza	3 (2)	3	0.041	20 (5)	22	0.091	30 (5)	33	0.075
Vomiting	6 (4)	8	0.108	20 (5)	23	0.095	26 (4)	30	0.068
Oropharyngeal pain	2 (1)	2	0.027	13 (3)	15	0.062	26 (4)	29	0.066
Bronchitis	5 (3)	5	0.068	11 (3)	11	0.045	24 (4)	25	0.057
Pyrexia	5 (3)	5	0.068	19 (5)	23	0.095	24 (4)	28	0.064
Back pain	5 (3)	5	0.068	16 (4)	17	0.070	24 (4)	27	0.062
Gastroenteritis	0	0	0.000	11 (3)	12	0.050	19 (3)	22	0.050
Dizziness	1 (< 1)	1	0.014	15 (4)	16	0.066	19 (3)	21	0.048

Source: Table 14.4.1.2BM, Table 14.4.2.11FM (post hoc analysis).
Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TPY = Total person time in Years;
VDZ = vedolizumab.
Days for person time was defined as (end of study date - first dose date (of induction) + 1).
End of study date = last scheduled dosing date + 16 weeks for patients who do not continue onto the long-term c13008 safety study.
End of study date = last scheduled dosing date for patients who continued onto the long-term c13008 safety study.
Number of events: within the same preferred term, if the start and stop date of multiple events overlapped or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.
Incidence density: number of events / total person-time in years (TPY).
a Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.
b Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

In UC patients, among the AEs by PT reported in >3%, the following are of note:

- Respiratory infections (combining together nasopharyngitis, upper respiratory tract and bronchitis): 25% in VDZ combined group (with no difference between dose regimens) vs. 15% in non-ITT placebo (delta 10%);
- Colitis ulcerative slightly higher in the non-ITT placebo group (19%) than in the VDZ combined group (16%), suggesting a lack of efficacy;
- Headache more common in the VDZ combined group (13%) than in non-ITT placebo group (9%).

The comparison of AEs by incidence density was similar to the comparison of frequencies.

AE by PT CD (Induction/Maintenance patient population Study C13007)

For the CD induction/maintenance safety population, the most common AEs by preferred term (occurring in at least 3% of patients in the combined VDZ group) are summarized by frequency and incidence density for the ITT placebo, non-ITT placebo, and combined VDZ groups in the following Tables taking into account the maintenance ITT and non ITT safety populations, respectively:

Maintenance ITT ^a									
(Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)									
Preferred Term, n (%)	PLA N = 153 TPY = 109.2			VDZ Q8W N = 154 TPY = 108.6			VDZ Q4W N = 154 TPY = 119		
	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Crohn's disease	29 (19)	32	0.293	25 (16)	25	0.230	24 (16)	29	0.244
Arthralgia	21 (14)	30	0.275	17 (11)	21	0.193	21 (14)	29	0.244
Pyrexia	23 (15)	26	0.238	18 (12)	18	0.166	29 (19)	35	0.294
Nasopharyngitis	14 (9)	18	0.165	23 (15)	29	0.267	23 (15)	32	0.269
Headache	28 (18)	34	0.495	20 (13)	25	0.230	26 (17)	47	0.395
Nausea	18 (12)	24	0.220	18 (12)	25	0.230	22 (14)	34	0.286
Abdominal pain	18 (12)	27	0.247	15 (10)	19	0.175	19 (12)	29	0.244
Upper respiratory tract infection	6 (4)	6	0.055	7 (5)	7	0.064	13 (8)	15	0.126
Fatigue	9 (6)	11	0.101	11 (7)	14	0.129	11 (7)	14	0.118
Vomiting	13 (8)	16	0.147	9 (6)	16	0.147	8 (5)	9	0.076
Back pain	7 (5)	7	0.064	14 (9)	14	0.129	9 (6)	9	0.076
Urinary tract infection	4 (3)	4	0.037	7 (5)	10	0.092	5 (3)	6	0.050
Anaemia	5 (3)	5	0.046	5 (3)	6	0.055	4 (3)	4	0.034
Cough	4 (3)	7	0.064	7 (5)	7	0.064	7 (5)	7	0.059
Bronchitis	4 (3)	5	0.046	5 (3)	5	0.046	9 (6)	12	0.101
Diarrhoea	13 (8)	14	0.128	6 (4)	7	0.064	6 (4)	7	0.059
Influenza like illness	7 (5)	9	0.082	7 (5)	8	0.074	5 (3)	5	0.042
Dizziness	6 (4)	8	0.073	8 (5)	8	0.074	7 (5)	11	0.092
Sinusitis	4 (3)	4	0.037	5 (3)	6	0.055	8 (5)	11	0.092

Anal abscess	3 (2)	3	0.027	1 (< 1)	1	0.009	4 (3)	5	0.042
Anal fistula	0	0	0.000	2 (1)	2	0.018	5 (3)	7	0.059
Pruritus	3 (2)	3	0.027	3 (2)	3	0.028	4 (3)	4	0.034

Source: Table 14.4.1.2BM and Table 14.4.2.11FM (post hoc analysis).
Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TPY = Total Person Time in Years; VDZ = vedolizumab.
Days for Person Time was defined as (End of study date - first dose date (of induction) + 1).
End of Study Date = Last scheduled dosing date + 16 Weeks for patients who did not continue in the long-term safety study.
End of Study Date = Last scheduled dosing date for patients who did continue in the long-term safety study.
Number of Events: Within the same preferred term, if the start and stop date of multiple events overlap or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.
Incidence Density: Number of Events / Total Person-Time in Years (TPY)
a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT Population at Week 6.

Preferred Term, n (%)	Maintenance Non-ITT						Combined					
	PLA ^a (from Week 0) N = 148 TPY = 82.3			VDZ Q4W ^b (Week 6 Non-responders) N = 506 TPY = 322.4			PLA N = 301 TPY = 191.4			VDZ N = 814 TPY = 550		
	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Crohn's disease	36 (24)	41	0.498	115 (23)	140	0.434	65 (22)	73	0.381	164 (20)	194	0.353
Arthralgia	19 (13)	26	0.316	72 (14)	96	0.298	40 (13)	56	0.293	110 (14)	146	0.265
Pyrexia	17 (11)	24	0.292	56 (11)	75	0.233	40 (13)	50	0.261	103 (13)	128	0.233
Nasopharyngitis	10 (7)	12	0.146	54 (11)	63	0.195	24 (8)	30	0.157	100 (12)	124	0.225
Headache	19 (13)	39	0.474	51 (10)	64	0.199	47 (16)	93	0.486	97 (12)	136	0.247
Nausea	12 (8)	17	0.207	50 (10)	61	0.189	30 (10)	41	0.214	90 (11)	120	0.218
Abdominal pain	21 (14)	28	0.340	45 (9)	57	0.177	39 (13)	55	0.287	79 (10)	105	0.191
Upper respiratory tract infection	11 (7)	12	0.146	34 (7)	40	0.124	17 (6)	18	0.094	54 (7)	62	0.113
Fatigue	5 (3)	9	0.109	31 (6)	36	0.112	14 (5)	20	0.104	53 (7)	64	0.116
Vomiting	10 (7)	13	0.158	32 (6)	42	0.130	23 (8)	29	0.152	49 (6)	67	0.122
Back pain	5 (3)	5	0.061	15 (3)	15	0.047	12 (4)	12	0.063	38 (5)	38	0.069
Urinary tract infection	3 (2)	4	0.049	23 (5)	28	0.087	7 (2)	8	0.042	35 (4)	44	0.080
Anaemia	9 (6)	9	0.109	25 (5)	28	0.087	14 (5)	14	0.073	34 (4)	38	0.069
Cough	3 (2)	3	0.036	20 (4)	21	0.065	7 (2)	10	0.052	34 (4)	35	0.064
Bronchitis	5 (3)	6	0.073	19 (4)	21	0.065	9 (3)	11	0.057	33 (4)	38	0.069
Diarrhoea	5 (3)	8	0.097	19 (4)	21	0.065	18 (6)	22	0.115	31 (4)	35	0.064
Influenza like illness	7 (5)	7	0.085	19 (4)	25	0.078	14 (5)	16	0.084	31 (4)	38	0.069
Dizziness	7 (5)	7	0.085	14 (3)	16	0.050	13 (4)	15	0.078	29 (4)	35	0.064
Sinusitis	1 (< 1)	1	0.012	16 (3)	18	0.056	5 (2)	5	0.026	29 (4)	35	0.064

Source: Table 14.4.1.2BM and Table 14.4.2.11FM (post hoc analysis).
Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; TPY = Total Person Time in Years; VDZ = vedolizumab.
Days for Person Time was defined as (End of study date - first dose date (of induction) + 1).
End of Study Date = Last scheduled dosing date + 16 Weeks for patients who did not continue in the long-term safety study.
End of Study Date = Last scheduled dosing date for patients who did continue in the long-term safety study.
Number of Events: Within the same preferred term, if the start and stop date of multiple events overlap or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.
Incidence Density: Number of Events / Total Person-Time in Years (TPY)
a Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.
b Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

In CD patients, the most common AEs by PT reported in the combined VDZ group were CD, arthralgia and pyrexia.

Infections combined together (nasopharyngitis, upper respiratory tract bronchitis, sinusitis and urinary tract infections) occurred in 30% of VDZ combined group and in 20% of non-ITT placebo group with a difference of 10%.

AEs (occurring in at least 3% of patients in the combined VDZ group) higher in VDZ group were CD (delta 4% compared to non-ITT placebo) and fatigue (delta 4% compared to non-ITT placebo) while abdominal pain was higher (delta 4% compared to non-ITT placebo) in the placebo group. It is of note that the definition used by the Applicant for mild intensity of an AE (=Awareness of sign or symptom, but easily tolerated) appears entirely subjective and different

from the definition of the CTCAE Version 4.0, that requires the absence of intervention (=Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated).

Apart from this limitation, safety data showing a homogeneous distribution of AE by severity between VDZ treated patients and placebo group in both diseases are reassuring.

Taking into account the above mentioned limitation, approximately 30% of SAEs in UC and 25% of SAEs in CD were graded as mild, while 50% of SAEs in UC and 45% of SAEs in CD as moderate. Homogeneous distribution by severity was noted across all groups.

Severe SAEs accounted for 10% in UC and 18-19% in CD in both VDZ combined and placebo non-ITT population groups.

The most commonly reported SAEs in both diseases are gastrointestinal disorders, suggesting limited efficacy of the study drug, and infections which is well known to be an AE of special interest for VDZ as well as for biological agents used in IBD treatment.

In general, there was no clinically meaningful increase in the commonly reported AEs ($\geq 5\%$ of VDZ-treated patients) with continued VDZ treatment through 36 months.

Adverse Events of special interest:

AEs of special interest were selected based on the mechanism of action of VDZ, anticipated risks associated with study drug exposure, and known co-morbidities that occur in patients with IBD. AEs of special interest included infection AEs, gastrointestinal AEs, malignancies, nervous system AEs, and infusion-related AEs.

Infections UC: The proportion of patients with at least 1 infection in induction/maintenance safety population was higher in the combined VDZ groups (42%) compared to non-ITT placebo group (31%) with a delta of 10%. Moreover, differences among dosing regimens were noted (ITT VDZ Q8W 51%, ITT VDZ Q4W 45% and non-ITT VDZ Q4W 39%) with the highest reported in the Q8w group.

The most common infections according to HLT were: upper respiratory tract infections (VDZ combined group 25 and non-ITT placebo 15) which are the most commonly reported also in anti-TNFalfa agent patients and in general in patients treated with immunomodulant therapies; gastrointestinal infections (considered grouped: 24 in the combined VDZ and 4 in non-ITT placebo) which are related to the underlying disease. Two sepsis (1 patient each in the non-ITT placebo and combined VDZ groups) and no TB cases were reported.

Concomitant corticosteroids and/or immunomodulators did not significantly increase rates of infection.

The majority of Clostridium difficile, candida, herpes infections, although not severe in intensity, were reported in VDZ treated groups with similar frequency in Q8W and Q4W dose regimens.

In the overall safety population, commonly reported infections (i.e Upper respiratory tract infections, Lower respiratory tract and lung infections, Abdominal and gastrointestinal infections) did not increase with exposure to VDZ through 36months. In this population, one case of TB considered as primary is reported.

Infections CD: In the overall CD safety population, the distribution of AEs according to HLT in the SOC of infections and infestations was similar to that observed in UC patients. The most common were: respiratory infections (combined upper and low) 29% in the VDZ combined group and 23% in the non-ITT group; gastrointestinal 8% in the VDZ combined group and infections 5% in the non-ITT group. For these infections an increase is noted in the Q4W group.

Concomitant corticosteroids and/or immunomodulators did not significantly increase rates of infection.

Serious infections were reported in 45/814 patients (6%) of VDZ combined group and 4/148 (3%) of non-ITT placebo group.

The main SAEs grouped for clinical categories were reported in VDZ treated patients: abscess at any site (total of 30, 25 VDZ and 5 PLB), gastrointestinal infections (total of 7, all VDZ), sepsis (total of 6, 5 VDZ and 1 PLB). The occurrence of abscess and gastrointestinal infections are related to clinical complications of CD. It is of note that the number of sepsis cases is higher than that observed in UC. Moreover, the great majority of *Clostridium difficile*, *Candida* and Herpes Infections were reported in the VDZ treated patients and with a higher rate when compared to UC patients. The commonly reported infections as well as serious adverse events by SOC did not increase at discrete 3 or 6 month intervals through 36 months, the majority occurred within 12 months.

Three TB cases considered related to the study drug were reported in the overall safety population.

GI events: The majority of gastrointestinal events are consistent with the underlying disease.

Malignancies: Patients with IBD are at increased risk for colorectal cancer. A population-based study from Sweden estimated that the overall risk of colorectal cancer in inflammatory bowel disease (IBD) was 95 cases per 100,000 ([Söderlund S, et al. Gastroenterology 2009](#)). The risk of colorectal cancer in patients with UC appears to have decreased over time but it is unclear if this is due to improved medical therapy and dysplasia surveillance. The risk is related to the duration and anatomic extent of the disease

In UC, the approximate cumulative incidence of CRC is 5 to 10% after 20 years and 12 to 20% after 30 years of disease but active surgical approach in medical treatment failures and long-term use of 5-ASA drugs may have reduced the incidence. The risk of CRC in longstanding CD involving the colon is probably comparable to UC. However, not all studies reached these conclusions and thus the magnitude of risk in patients with CD remains unsettled. The severity of inflammation may also be an important marker of risk.

In the overall population, the reported cases of colon cancer (3 in UC study, 1 in CD study and 1 in the Long-Term Safety Study C13008) were all described after a mean of 9 years after diagnosis.

For all these colon cancer reported cases the Applicant provided, during the procedure, previous exposure to Immunomodulators and anti-TNFalpha therapies. One patient with CD and 3 patients with UC were diagnosed with colon cancer (one of whom diagnosed with metastases to the peritoneum). 2 patients previously to VDZ received both AZA/ 6MP and infliximab and 1 each

received AZA/ 6MP or infliximab alone. One patient received AZA 75 mg for 38 weeks concurrently to VDZ.

Nervous system (PML)

As natalizumab, an integrin antagonist indicated for the treatment of multiple sclerosis (in EU and USA) and CD (in USA) is associated with an increased risk of PML, natalizumab exposed population has been used as a benchmark to estimate the risk of PML in VDZ exposed patients. Three cases of PML out of 3116 treated patients (1/1000) were observed in the clinical trial setting with natalizumab. Following the initial identification of natalizumab's association with PML risk, three factors have been identified as increasing the risk of PML in natalizumab treated patients: positive anti-JC virus antibody status, prior use of immunosuppressants and increased duration of natalizumab treatment (especially beyond two years). The incidence of PML in natalizumab treated patients in the post-marketing setting is continuously increasing likely due to the increasing patient years of exposure to Tysabri with a greater proportion of the overall Tysabri-treated population reaching Tysabri exposures of ≥ 2 years.

As of February 2012, the estimated incidence of PML with natalizumab treated patients reaches 11.1/1000 in the highest risk patients group (JCV positive patients, exposed to Tysabri between 25 and 48 months, with prior immunosuppressant use).

The Applicant proposed a first PML risk evaluation comparing PML incidences between natalizumab and VDZ based on boundaries of confidence intervals. This method does not take into account different treatment duration between post-marketing data and clinical trial data. By applying incidence of PML derived from natalizumab trial data (incidence 1/ 1000; CI95% 0.2- 2.8), a huge number of patients would be necessary to demonstrate an inferior risk with an upper bound lower than 0.20. The second method proposed by the Applicant takes into account stratification by risk factors in estimating the incidence of PML. Using PML incidence in natalizumab treated patients stratified by risk factors, the expected cases of PML in VDZ clinical trial program is 5.17. The probability of observing 0 cases, corresponding to the above expected number, is 0.0057, showing that PML risk is significantly lower than with natalizumab.

Cardiovascular AEs

Cardiac AEs for the maintenance studies in both UC and CD showed a higher rate in the VDZ groups (4%, 3% respectively) compared with placebo (1%).

Serious adverse event/deaths/other significant events

UC: Overall in Study C13006, 11% of patients in the non-ITT placebo, 16% of patients in the ITT placebo and 12% in the combined VDZ group reported at least 1 SAE.

The frequency of SAEs was higher (15%) in patients who had not responded to VDZ during induction (non-ITT VDZ Q4W dose group) than in the ITT VDZ Q8W and in the ITT VDZ Q4W.

SAEs resulting in study discontinuation were higher in the ITT placebo (=patients who received 2 doses of VDZ during induction and placebo during maintenance) patients (6%) compared to those in the combined VDZ group (3%). The most common SAEs were in the SOC of Infections and infestations and the gastrointestinal disorders

CD: SAEs were reported with the highest percentage in the combined VDZ group (24%) and with similar frequency in the ITT placebo and non-ITT placebo groups (15% and 16%, respectively).

Among VDZ treatment groups a higher frequency (29%, delta of 10 when compared to other groups) of SAEs was observed in patients who failed to respond to VDZ at Week 6.

As previously reported, SAEs that occurred most frequently in the CD induction/maintenance safety population were in the gastrointestinal disorders SOC probably due to lack of efficacy.

Concomitant medications did not negatively influence SAEs occurrence.

The frequency of SAEs with continued VDZ treatment did not significantly increased through 36 months.

Deaths

A total of 12 deaths were reported, 4 in UC patients (all classified by investigator as not related) of which 1 in C13006 and 3 in C13008 studies and 8 in CD patients of which 5 in C13007 and 3 in C13008 studies.

Post studies deaths:

In the vedolizumab clinical program there were 9 post study deaths as of 14 March 2013. There were 2 post study deaths in Study C13006, 1 post study death in Study C13007 and C13004 and 5 post study deaths in Study C13008. The time from last dose of study drug ranged from 140 days to 659 days. Sepsis was reported in a total of 3 subjects which was the most common PT related to the fatalities. Malignancies occurred in 2 of the deaths and the remaining 4 deaths were single events. Of the 9 deaths, 2 deaths were considered related to vedolizumab.

Listing 139.a Deaths Occurring Following Completion of or Withdrawal From Participation in Vedolizumab Clinical Studies

Preferred Term	Verbatim Term	SAE Code	Protocol	Site No. Pt. ID/ Pt. Initials	Country	Gender	Age (yrs)	Intensity	Causality	Mfr. Report No.	Date of Death	Days from Last Dose ^a
Cardiac arrest	Cardiac arrest	D	C13006	28011 602/DS	Italy	Male	32	Severe	NR	2011-00325	28 APR 2011	192
Multi-organ failure	Multiple organ failure	D	C13007	04009 709/ADC	Belgium	Female	54	Severe	NR	2012-03638	22 MAR 2012	659
Sepsis	Sepsis	D	C13008	58098 701/DRR	United States	Male	59	Severe	NR	2012-00068	07 DEC 2011	405
Cardio-respiratory arrest	Cardio-pulmonary arrest	D	C13008	04006 642/VER	Belgium	Male	59	Severe	NR	2012-04633	28 APR 2012	165
Death	Death	D	C13008	28007 704/MAS	Italy	Female	38	Severe	NR	2011-04556	21 SEP 2011	140
Multi-organ failure	Multiple organ failure post surgery	D	C13008	53003 601/RB	Switzerland	Male	33	Severe	R	2010-05454	15 FEB 2012	552
Sepsis	Systemic sepsis	D	C13008	04006 647/VER	Belgium	Male	44	Severe	R	2011-04572	19 DEC 2011	152
Colon cancer metastatic ^b	Colon cancer with liver metastases	M/D	C13006	206 001/NAS	Russian Federation	Female	66	Severe	NR	2011-03865	14 AUG 2011	657
Metastases to peritoneum	Peritoneal carcinomatosis	M/D/H	C13008	02011 701/IR	Australia	Female	78	Severe	NR	2013-00730	05 MAR 2011	493
Pulmonary embolism	Pulmonary thrombo-embolism	D	C13004									
Pneumonia	Pneumonia	D	C13008									
Empyema	Empyema	D	C13008									
Sepsis	Sepsis	D	C13008									

Source: Argus Custom Report, Adverse Events by System Organ Class, MLN0002 Deaths as of 14 March 2013.

Abbreviations: D = death, H = hospitalization, ID = identifier, M = medically significant, Mfr. = manufacturer, No. = number, NR = not related, Pt. = patient, R = related; SAE = serious adverse event.

All poststudy deaths occurred in patients who received at least 1 dose of vedolizumab.

a. Number of days between last infusion of study drug and the date of death.

b. Patient's death occurred during the poststudy period; however, the onset of the fatal event occurred during the patient's on-study period.

All deaths occurred more than 140 days from the last dose of vedolizumab. The two cases which were considered as related are both UC patients with colon cancer. None of the post-study deaths can be ascribed with any reasonable degree of certainty to vedolizumab. An open

question is whether vedolizumab could play a role in accelerating tumour growth or in the long-term be associated with an increased incidence of colonic carcinoma. This question would be difficult to assess in view of the fact that UC has an increased incidence of colonic carcinoma and many patients had been pre-treated with potent immunosuppressives before receiving vedolizumab. It will be necessary for continued collection of data over time to address the possible risk as described in the RMP.

Laboratory findings

UC: The most common laboratory abnormality was absolute **lymphocyte count** $<0.5 \times 10^9/L$. In the UC induction/maintenance safety population, 5 patients (3%) from the non-ITT placebo group and 31 patients (5%) in the combined VDZ group. Of patients having absolute lymphocyte counts $<0.3 \times 10^9/L$ only one who received VDZ experienced upper respiratory tract infection. No important difference was noted in leukocyte count. Other hemocromocytometric parameters such as haemoglobin and platelets were not importantly affected. A numerically higher number of VDZ treated patients experienced increased levels of the pancreatic enzyme lipase (i.e. lipase >2 UNL: 3 non-ITT placebo 12 VDZ combined), prolongation of coagulation time (i.e. PT >1.25 UNL: 8 non-ITT placebo 26 VDZ combined). However, a higher frequency was reported in non-ITT placebo group probably due to the different size of placebo non-ITT and VDZ combined groups.

CD: Similarly to patients affected by UC, in CD patients the most common laboratory finding was lymphocyte count ($<0.5 \times 10^9/L$). In the CD induction/maintenance safety population, 13 patients (9%) from the non-ITT placebo group and 39 patients (5%) in the combined VDZ group. Of these patients 6 patients had an absolute lymphocyte counts $<0.3 \times 10^9/L$ (1 ITT placebo, 1 non-ITT placebo, and 4 combined VDZ), reporting 2 SAE (one *C. difficile* colitis in the VDZ group and one anal abscess in the non-ITT placebo).

More than in UC patients, in CD patients a numerically higher number of patients experienced increased levels of liver transaminases or pancreatic enzymes (i.e. amylase >2 UNL: 4 non-ITT placebo 13 VDZ combined; lipase >2 UNL: 3 non-ITT placebo 16 VDZ combined), prolongation of coagulation time (i.e. PT >1.25 UNL: 4 non-ITT placebo 33 VDZ combined). However, no significant difference was reported in terms of frequencies between groups or even better in non-ITT placebo probably due to the different size of placebo non-ITT and VDZ combined groups.

Vital signs: Data from induction/maintenance UC and CD studies as well from the long term safety C13008 study do not report significant abnormal ECG findings.

A similar incidence of ECG abnormalities in VDZ and in placebo treated patients was noted. Some non-specific ECG findings not related to QT changes were observed in patients treated with VDZ.

Overall, preclinical and clinical data do not raise any concern on a potential effect of the drug on QT interval.

Safety in special populations

Overall the analysis of AEs by intrinsic factors such as age, sex, race, creatinine clearance was not done due to the small size of included groups.

The Applicant analysed AEs by SOC and HTL according to body weight categories (<70 kg, ≥70 to ≤90 kg, >90 kg) for the UC and CD combined induction safety population, combined induction/maintenance safety population. The analysis of AEs according to body weight category did not show clinically important differences in the safety profile between the low (<70 kg) and the mid (≥70 to ≤90 kg) weight subgroups. The evaluation of the high weight subgroup (>90 kg) does not allow to draw conclusions due to the small number of patients in this subgroup (approximately 15% of UC and CD patients), especially in the placebo arm.

Immunological events

Investigator-defined, infusion-related events in the induction/maintenance safety populations occurred as follow:

UC: in 28 (5%) of 967 patients in the VDZ combined group and 1 patient (<1%) in the non-ITT placebo group.

CD: in 33 (4%) of 967 patients in the VDZ combined group and 8 patients (5%) in the non-ITT placebo group.

The majority of reported reactions were mild or moderate in intensity and few resulted in discontinuation of study treatment. One serious event was reported in a CD patient.

Immunogenicity: The overall HAHA rate in the combined VDZ group was of 4% during treatment. Instead the frequency of HAHA increased post treatment (5 half-lives after last dose, 16 weeks) and was approximately of 10%.

Due to small numbers of HAHA positive patients, no firm conclusions can be drawn regarding the impact of immunogenicity on the overall efficacy observed in phase 3 studies.

With regard to safety issues, infusion-related reactions were reported for 61 patients exposed to continuous VDZ in the induction/ maintenance Studies C13006 and C13007 of whom a total of 3 patients were HAHA positive (all had persistent HAHA and 2 had neutralizing antibodies).

The available data do not support a clear link between HAHA and infusion-related reactions.

Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interaction (such as immunosuppressive agents) is not of concern with the exception of safety such as infections and infestations or cancer where it is known to increase in patient taking immunosuppressant drugs.

Discontinuation due to adverse events

The most common AEs leading to discontinuation in both UC and CD patients were due to loss of efficacy. A small percentage of patients discontinued due to infections occurrence or to skin disorders.

Post marketing experience

N/A

2.6.1 Discussion on clinical safety

Safety populations from phase III studies included induction and maintenance safety populations as well as overall safety populations from Studies C13002, C13004, C13006, C13007, C13011, and C13008. Although safety data coming from phase I and phase II studies have been submitted by the Applicant, they have not been included in the safety evaluation because they represent limited and heterogeneous safety data (short term, different dose regimens, healthy subjects, small numbers).

Across all phase II and phase III trials 1195 patients with UC or CD were exposed to VDZ ≥ 12 months and 502 patients were exposed ≥ 24 months. The number of patients exposed long-term is considered adequate.

The most common AEs by SOC reported in both UC and CD patients were gastrointestinal events and infections. Gastrointestinal events (mostly worsening of the underlying CD or UC and other gastrointestinal events potentially related to underlying disease) occurred with similar frequency in UC and CD patients.

In UC patients, infections and infestations were reported with the highest difference (11%) in the VDZ combined group as compared to non-ITT placebo group, and with higher rates in VDZ Q8W versus Q4W (51% versus 45%). Moreover, a smaller difference between VDZ combined and non-ITT placebo group is noted in the following SOCs: skin disorders 6%, cardiac disorders 3%, psychiatric disorders 3%, nervous system disorders 2%. No difference is reported in the SOC of blood disorders.

Infection and infestations in CD patients were reported in 39% of the VDZ combined group and in 44% of non-ITT placebo group. Of note are also Respiratory disorders that were more frequent in the VDZ combined group (12%) as compared to non-ITT placebo (7%). Blood disorders were similarly reported across VDZ treated patients and placebo patients.

With regard to extra intestinal manifestations, the most common SOC was musculoskeletal and connective disorders which was higher in CD patients VDZ treated as compared to UC patients (44% vs. 22%). Eye disorders were similarly reported in both CD and UC but mostly described in VDZ treated patients (9% vs. 4%).

AEs by PT were mostly overlapping between UC and CD patients, with some differences linked in part to the underlying disease. In UC patients, among the AEs by PT reported in $>3\%$ of VDZ treated patients were respiratory infections (combining together nasopharyngitis, upper respiratory tract and bronchitis) and headache. In CD patients, the most common AEs by PT reported in the combined VDZ group were infections (combined together nasopharyngitis, upper respiratory tract bronchitis, sinusitis and urinary tract infections) CD, arthralgia and pyrexia. Similar frequencies in PT AEs were reported between the two VDZ dosage regimens, with the exception of pyrexia and headache most commonly described in the Q4W regimen.

No significant differences in the safety profile (AEs distribution according to PT) were highlighted combining the C13006 and C13007 studies (total of 1434 patients) as compared to results coming from the single studies. The most commonly reported AEs were headache, nasopharyngitis, arthralgia. Nasopharyngitis is the most common infection reported in these patients. Arthralgia is the most common extra-intestinal manifestation. Headache is highlighted as a very common ($>1/10$) ADR in the product information. Headache frequency did not increase

over time with continued VDZ treatment exposure. Only 1 vedolizumab treated patient experienced an AE of headache that led to discontinuation. No VDZ treated patients experienced a SAE of headache.

The AEs considered by the investigator related to study drug were those most commonly reported in both pathologies.

Approximately 30% of SAEs in UC and 25% of SAEs in CD were graded as mild while 50% of SAEs in UC and 45% of SAEs in CD as moderate. Severe SAEs accounted for 10% in UC and 18-19% in CD in both VDZ combined and placebo non-ITT population groups.

The most commonly reported SAEs in both diseases are gastrointestinal disorders, meaning lack of efficacy of the study drug, and infections which is well known to be an AE of special interest for VDZ as well as for biological agents used in IBD treatment.

In order to better clarify the reversibility rate of the reported SAE in UC and CD patients, the Applicant provided during the procedure, an updated analysis, excluding patients who were assigned to placebo after receiving VDZ during induction. The rate of unresolved SAEs was comparable amongst patients receiving placebo and VDZ.

In general, there was no clinically meaningful increase in the commonly reported AEs ($\geq 5\%$ of VDZ-treated patients) with continued VDZ treatment through 36 months in both UC and CD patients. AEs by months of VDZ exposure showed stable or decreased frequencies through 12 months with the exception of ulcerative colitis which picked at 6 <12 months, reflecting the loss of efficacy.

Among AEs of special interest in VDZ treated patients are: infections, gastrointestinal disorders, nervous system disorders. With the exception of nervous system disorders, these are similar to those reported for of anti-TNFalpha drugs.

In UC patients, the most common infections according to HLT were: upper respiratory tract infections which are the most commonly reported also in anti-TNFalpha agent patients and in general in patients treated with immunomodulant therapies; gastrointestinal infections which are related to the underlying disease. Two sepsis (1 patient each in the non-ITT placebo and combined VDZ groups) and no TB cases were reported. Concomitant corticosteroids and/or immunomodulators did not significantly increased rates of infection.

In the overall safety population, commonly reported infections did not increase with exposure to VDZ through 36months. In this population, one case of TB considered as primary is reported.

In CD patients, the distribution of AEs according to HLT in the SOC of infections and infestations was similar to that observed in UC patients. The most common were: respiratory infections (combined upper and low); gastrointestinal infections. For these infections an increase is noted in the Q4W group. Concomitant corticosteroids and/or immunomodulators did not significantly increase rates of infection.

The main infections related SAEs, grouped for clinical categories, were reported in VDZ treated patients: abscess at any site, gastrointestinal infections, sepsis (total of 6, 5 VDZ and 1 PLB). The occurrence of abscess and gastrointestinal infections are related to clinical complications of CD. It is of note that the number of sepsis cases is higher than that observed in UC.

Moreover, the great majority of *Clostridium difficile*, *Candida* and Herpes Infections were reported in the VDZ treated patients and with a higher rate when compared to UC patients. The commonly reported infections as well as serious adverse events by SOC did not increase at discrete 3 or 6 month intervals through 36 months, the majority occurred within 12 months. During the procedure the applicant demonstrated that the 4 patients that developed tuberculosis during VDZ phase 3 studies all received corticosteroids before study entry (treatment duration not known) and 2 received corticosteroids concomitantly with VDZ. Three patients used either AZA or 6-MP before study entry (treatment duration not known) and 1 patient used them concomitantly with VDZ. One patient had used infliximab more than 60 days before study entry. All 4 cases (3 cases of pulmonary TB and 1 case of latent TB, i.e. positive QuantiFERON test) appear to be new infections acquired on study, as they all had negative chest X-rays and negative QuantiFERON tests at baseline. Vedolizumab is contraindicated in patients with active tuberculosis. Before starting treatment with vedolizumab, patients must be screened for tuberculosis according to the local practice. This information is reflected in the product information.

The most common reported gastrointestinal AEs in UC patients were colitis (excluding infective), nausea and vomiting symptoms. These gastrointestinal events are consistent with the underlying UC.

In the CD induction/maintenance safety population, the most common SAE was Crohn's disease meaning lack of efficacy. These events were potentially related to the underlying disease and reported in a higher percentage of patients with CD as compared to those with UC.

Patients with IBD are at increased risk for colorectal cancer. The risk is related to the duration and anatomic extent of the disease. The severity of inflammation may also be an important marker of risk. In the overall population, the reported cases of colon cancer (3 in UC study, 1 in CD study and 1 in the Long-Term Safety Study C13008) were all described after a mean of 9 years after diagnosis. For all these colon cancer reported cases the Applicant provided during the procedure, previous exposure to Immunomodulators and anti-TNFalpha. One patient with CD and 3 patients with UC were diagnosed with colon cancer (one of whom diagnosed with metastases to the peritoneum). 2 patients previously to VDZ received both AZA/ 6MP and infliximab and 1 each received AZA/ 6MP or infliximab alone. One patient received AZA 75 mg for 38 weeks concurrently to VDZ.

Considering that, in UC and CD patients of all severities, colon cancer is more frequently observed than in the general population, the possibility of occurrence of cancer with long exposure to vedolizumab cannot be excluded. This potential risk is addressed the RMP.

The most common nervous system events were in the HLT of headaches NEC in both categories of patients. The only SAE in the Nervous system disorders SOC that occurred in a UC patient in the ITT VDZ Q4W group was syncope and in the CD population one transient ischemic attack occurred in a VDZ treated patient. No cases of PML were observed.

An adequate risk minimization action plan (RAMP algorithm) described in the RMP has been implemented in all VDZ clinical trials since 2007 and no PML case has been identified so far. Although it is acknowledged that data available up to now seem to indicate that the PML risk with VDZ is lower than with natalizumab, a residual risk of PML cannot be completely ruled out, in particular due to limited available data on long term treatment effect combined with high

frequency of prior immunosuppressive use in UC and CD patients (around 80% compared to 18% of natalizumab patients in the post-marketing setting. Only 1 healthy volunteer in study C13013 had a positive finding on the objective PML checklist on two separate occasions. Although no PML cases were identified within the vedolizumab clinical studies, PML is identified as an important potential risk in the RMP. The post marketing surveillance described in the RMP is highly important since this product is likely to be used long term (mean duration of exposure is only roughly 1 year in VDZ placebo controlled clinical trial) and there is a high frequency of prior immunosuppressive use in UC and CD patients.

Cardiac AEs for the maintenance studies in both UC and CD showed a higher rate in the VDZ groups (4%, 3% respectively) compared with placebo (1%). Although a direct cardiotoxic effect from vedolizumab is not expected based on its structure/function, non-clinical and healthy volunteer data, there was some suggestion of an increase in cardiac AEs mainly arrhythmias. However, although a slightly higher incidence of cardiac AEs compared to placebo was observed in VDZ-subjects with no cardiac history, the rates of cardiac AEs in those with a history of cardiac disease or with no cardiac disease but at least one cardiac risk factor were no higher in VDZ-treated subjects than those treated with placebo, and there was no effect of monthly or 8-weekly dosing on the incidence of events.

SAEs and deaths: The most common SAEs in both UC and CD patients were in the SOC of Infections and infestations and the gastrointestinal disorders. Among drug related SAEs there were 4 Respiratory SOC disorders (2 patients pulmonary thrombotic and embolic disorders and 2 patients pulmonary embolism). Two young patients treated with vedolizumab developed pulmonary embolism while randomized in Study C13006. Both of these patients had a long standing history of moderate to severe UC and treatment with corticosteroids which both may increase the risk of developing pulmonary embolism. In addition, one of the patients had a major surgery performed before her episode of pulmonary embolism and in the second case the patient received 4 additional doses of vedolizumab after the pulmonary embolism was considered resolved. The Applicant provided a satisfactory explanation excluding a potential effect of vedolizumab on vascular endothelium.

The frequency of SAEs was slightly higher in patients taking concomitant medications (corticosteroids and/or immunomodulators) or in patients who failed a prior anti TNFalpha therapy.

A total of 12 deaths were reported, 4 in UC patients (all classified by investigator as not related) of which 1 in C13006 and 3 in C13008 studies and 8 in CD patients of which 5 in C13007 and 3 in C13008 studies. Patients with CD reported a higher number of deaths than those with UC, with the most common cause being sepsis (3 cases out of 8, 2 adjudicated as related to study drug). Narratives highlight that sepsis occurred at the time of or following abdominal surgery for CD exacerbation/complications or due to devices implantation. It is well known that IBD patients are more prone to complications due to immunosuppression in light of the background therapy. No cases of death due to colon cancer have been reported during the induction/maintenance studies. One case of colon cancer and one of peritoneal carcinomatosis were reported as post study deaths.

Laboratory abnormalities: the most common laboratory abnormality in both UC and CD patients was the absolute lymphocyte count $<0.5 \times 10^9/L$. In the UC induction/maintenance safety

population, this AE affected 5 patients (3%) from the non-ITT placebo group and 31 patients (5%) in the combined VDZ group. Of patients having absolute lymphocyte counts $<0.3 \times 10^9/L$ only one who received VDZ experienced upper respiratory tract infection. No important difference was noted in leukocyte count.

In the CD induction/maintenance safety population, 13 patients (9%) from the non-ITT placebo group and 39 patients (5%) in the combined VDZ group had lymphocyte count $<0.5 \times 10^9/L$. Of these patients 6 patients had an absolute lymphocyte counts $<0.3 \times 10^9/L$ (1 ITT placebo, 1 non-ITT placebo, and 4 combined VDZ), reporting 2 SAE (one *C. difficile* colitis in the VDZ group and one anal abscess in the non-ITT placebo).

In both UC and CD populations, other hemocromocytometric parameters such as haemoglobin and platelets were not importantly affected.

Overall the analysis of AEs by intrinsic factors such as age, sex, race, creatinine clearance was not done due to the small size of included groups. With regard to body weight, the Applicant was advised by CHMP (2010) to put some emphasis on distinguishing the effect of body size and obesity in phase III trials given the clear relationship between body weight and clearance and since a flat dose is proposed. The analysis of AEs according to body weight category did not show clinically important differences in the safety profile between the low (<70 kg) and the mid (≥ 70 to ≤ 90 kg) weight subgroups. The evaluation of the high weight subgroup (>90 kg) does not allow to draw conclusions due to the small number of patients in this subgroup (approximately 15% of UC and CD patients), especially in the placebo arm. However, among patients receiving VDZ in the combined vedolizumab group, the frequency of patients with at least one AE was similar across the three subgroups by weight (<70 kg; ≥ 70 to ≤ 90 kg; >90 kg).

Overall higher incidence of AEs (i.e. infections, arthralgia) was associated to patients who experienced prior TNFalpha antagonist failure in both UC and CD patient's populations.

The overall HAHA rate in the combined VDZ group was of 4% during treatment. Instead the frequency of HAHA increased post treatment (5 half-lives after last dose, 16 weeks) and was approximately of 10%.

Infusion-related reactions were reported for 61 patients exposed to continuous VDZ in the induction/ maintenance Studies C13006 and C13007 of whom a total of 3 patients were HAHA positive (all had persistent HAHA and 2 had neutralizing antibodies). Infusion-related events in the induction/maintenance safety populations occurred similarly in VDZ treated patients in both UC and CD (5% and 4%, respectively) as compared to non-ITT placebo groups ($<1\%$ UC and 5% CD). The majority of reported reactions were mild or moderate in intensity and few resulted in discontinuation of study treatment. One serious event was reported in a CD patient. The recommendations reported product information are agreed by the CHMP. The available data do not support a clear link between HAHA and infusion-related reactions.

The most common AEs leading to discontinuation in both UC and CD patients were due to loss of efficacy. A small percentage of patients discontinued due to infections occurrence or to skin disorders.

2.6.2 Conclusions on the clinical safety

The safety profile of VDZ does not raise major objections and can be considered reassuring in both UC and CD indications, although differences between these two pathologies have been reported (with higher incidence of AEs in CD).

AEs of special interest, in particular infections, PML and malignancy will be carefully monitored in the post-approval safety studies as described in the RMP.

Clinical studies showed reassuring data on systemic immunosuppression in terms of response to immunization in healthy volunteers or opportunistic infections including PML and TB. However, the occurrence rate of these events with long-term exposure and in patients pre-treated with anti TNFalpha drugs and/or concomitant immunosuppressants is still not known. This lack of data is reflected in the product information and described in the RMP.

1.4. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

1.5. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2.1, the PRAC considers by consensus that the risk management system for Entyvio (Vedolizumab) 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 tumor necrosis factor-alpha (TNFα) antagonist
- 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

is acceptable with minor revisions in section III of the RMP to ensure consistency throughout the RMP in the milestones of the studies described in the PhV Plan. These issues were addressed with the submission of version 2.2 of the Risk Management Plan following the PRAC meeting in February 2014.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions (IRRs), including hypersensitivity reactions (HSRs) Upper respiratory tract infections
Important potential risks	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 progressive multifocal leukoencephalopathy (PML) Off label use Mild ulcerative colitis and Crohn's disease CD Children and adolescents Use with concomitant anti-tumour necrosis factor drugs Malignancies
Missing information	Use in Pregnancy and lactation Use in Paediatric patients Use in Elderly patients Use in Hepatic Impairment Use in Renal Impairment Use in Cardiac Impairment Long-term safety Patients with prior exposure to natalizumab or rituximab

The PRAC agreed.

- **Pharmacovigilance plans**

Table 2: Ongoing and planned studies in the PhV development plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety concerns addressed	Status Planned Started	Date for submission of interim or final reports (planned or actual)
C13008 A Phase 3, Open-label Study to Determine the	Primary Objective: To determine the safety profile of long-term vedolizumab treatment	Long-term safety of vedolizumab To determine the effect of long-term vedolizumab	Ongoing	Final study report planned 31 MAR 2017

Long-Term Safety and Efficacy of Vedolizumab in Patients with Ulcerative Colitis and Crohn's Disease	<p>Resource utilization and Patient- Reported Outcomes Objectives:</p> <p>Determine the effect of long-term vedolizumab treatment on time to major inflammatory bowel diseaserelated events (hospitalisation, surgeries and procedures)</p> <p>Examine the effect of long-term vedolizumab treatment on healthrelated quality of life measurements</p>	treatment on time to major inflammatory bowel disease-related events (hospitalisations, surgeries, and procedures) and health-related quality of life measurements		
<p>Study No. MLN 0002_401</p> <p>A prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease</p>	To augment routine pharmacovigilance activities and aid in the further characterisation of the identified and potential risks, as well as the collection of data on populations that had no or limited exposure during the conduct of the phase 3 clinical program, as compared to other biologic treatments for inflammatory bowel disease	<p>To further characterise:</p> <p>Identified risks</p> <p>Infusion-related reactions, including hypersensitivity reactions</p> <p>Upper respiratory tract infections</p> <p>Potential risks</p> <p>Infections for which the gut provides a defensive barrier</p> <p>Serious infections, including opportunistic and PML</p> <p>Missing information</p> <p>Pregnancy/lactation depending on whether or not there are exposed pregnancies</p> <p>Use in the elderly</p> <p>Use in patients with renal, hepatic, or cardiac impairment</p> <p>Prior exposure to natalizumab and rituximab depending on prior drug exposures in recruited patients</p>	Planned	<p>01 JUL 2018 (interim)</p> <p>30 JUN 2022 (final)</p>

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Table 3: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	2. Additional risk minimisation measures
Identified Risk: Infusion-related reactions (Hypersensitivity reactions)	<p>SmPC Section 4.2 Posology and Administration</p> <p>Method of administration</p> <p>Entyvio is administered as an intravenous infusion over 30 minutes. Patients should be monitored during and after infusion (see section 4.4)</p> <p>SmPC Section 4.3 Contraindications Hypersensitivity to the active substance or to any of the excipients listed in section 6.1</p> <p>SmPC Section 4.4 Special Warnings and Precautions for Use</p> <p>All patients should be observed continuously during each infusion. For the first two infusions, they should also be observed for approximately two hours following completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately one hour following completion of the infusion.</p> <p>In clinical studies, infusion-related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see section 4.8).</p> <p>If a severe IRR, anaphylactic reaction, or other severe reaction occurs, administration of Entyvio must be discontinued immediately and appropriate treatment initiated (e.g., epinephrine and antihistamines) (see section 4.3).</p> <p>If a mild to moderate IRR occurs, the infusion rate can be slowed or</p>	None

	<p>interrupted and appropriate treatment initiated. Once the mild or moderate IRR subsides, continue the infusion.</p> <p>Physicians should consider pretreatment (e.g., with antihistamine, hydrocortisone and/or paracetamol) prior to the next infusion for patients with a history of mild to moderate IRR to vedolizumab, in order to minimize their risks (see section 4.8).</p> <p>SmPC Section 4.8 Undesirable Effects In GEMINI I and II controlled studies, 4% of vedolizumab-treated patients and 3% of placebo-treated patients experienced an adverse event defined by the investigator as infusion-related reaction (IRR) (see section 4.4). No individual Preferred Term reported as an IRR occurred at a rate above 1%. The majority of IRRs were mild or moderate in intensity and <1% resulted in discontinuation of study treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion. Most infusion related reactions occurred within the first 2 hours. Of those patients who had infusion related reactions, those dosed with vedolizumab had more infusion related reactions with in the first two hours as compared to placebo patients with infusion related reactions. Most infusion related reactions were no-serious and occurred during the infusion or within the first hour after infusion is completed.</p> <p>One serious adverse event of IRR was reported in a Crohn's disease patient during the second infusion (symptoms reported were dyspnoea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) and was successfully managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone. In patients who received vedolizumab at Weeks 0 and 2 followed by placebo, no increase in the rate of IRR was seen upon retreatment with vedolizumab after loss of response.</p>	
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<p>Identified Risk: Upper respiratory tract infections)</p>	<p>SmPC Section 4.8 Undesirable effects In GEMINI I and II (C13006 and C13007) controlled studies, the rate of infections was 0.85 per patient-year in the vedolizumab-treated patients and 0.70 per patient-year in the placebo-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis and urinary tract infections. Most patients continued on vedolizumab after the infection resolved.</p>	
<p>Potential Risk:</p> <p>Infections</p> <p>Gastrointestinal infections and systemic infections (serious and nonserious) against which the gut constitutes a defensive barrier</p>	<p>SmPC Section 4.4 Special Warnings and precautions for use Vedolizumab is a gut-selective integrin antagonist with no known systemic immunosuppressive activity (see section 5.1).</p> <p>Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier (see section 4.8). Entyvio treatment is not to be initiated in patients with active, severe infections until the infections are controlled, and physicians should consider withholding treatment in patients who develop a severe infection while on chronic treatment with Entyvio. Caution should be exercised when considering the use of vedolizumab in patients with a controlled chronic severe infection or a history of recurring severe infections. Patients should be monitored closely for infections before, during and after treatment. Entyvio is contraindicated in patients with active tuberculosis (see section 4.3). Before starting treatment with vedolizumab, patients must be screened for tuberculosis according to the local practice. If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis treatment in accordance with local recommendations, before beginning vedolizumab.</p> <p>SmPC Section 4.8 Undesirable Effects In GEMINI I and II controlled studies, the rate of infections was 0.85 per patient-year in the vedolizumab-treated patients and 0.70 per patient-year in the placebo-treated patients.</p>	<p>Patient Alert Card</p> <p>To remind patients that they may be at risk of infections and should consult a health care professional if they are unwell. To alert patients to the early signs and symptoms of PML. For patients to provide Alert Card to non-IBD health care professionals to inform them of treatment with vedolizumab so that health care professionals are informed of the potential risks of serious infections, opportunistic infections, including PML</p>

	<p>The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most patients continued on vedolizumab after the infection resolved.</p> <p>In GEMINI I and II controlled studies, the rate of serious infections was 0.07 per patient year in vedolizumab-treated patients and 0.06 per patient year in placebo-treated patients. Over time, there was no significant increase in the rate of serious infections.</p> <p>In controlled and open-label studies in adults with vedolizumab, serious infections have been reported, which include tuberculosis, sepsis (some fatal), salmonella sepsis, listeria meningitis, and cytomegaloviral colitis.</p> <p>Other routine risk minimisation measures:</p> <p>Entyvio treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease. (SmPC Section 4.2).</p>	
<p>Potential Risk:</p> <p>Infections</p> <p>Other serious infections, including opportunistic infections such as PML</p>	<p>SmPC Section 4.4 Special Warnings and Precautions for Use</p> <p>Infections</p> <p>Some integrin antagonists and some systemic immunosuppressive agents have been associated with progressive multifocal leukoencephalopathy (PML), which is a rare and often fatal opportunistic infection caused by the John Cunningham (JC) virus.</p> <p>Vedolizumab binds the $\alpha 4 \beta 7$ integrin which is present on a subset of leukocytes. By binding to the $\alpha 4 \beta 7$ expressed on gut-homing lymphocytes, vedolizumab exerts an immune-suppressive effect on the gut. Although no systemic immunosuppressive effect was noted in healthy controls the effects on systemic immune system function in patients with Inflammatory Bowel Disease patients is not known. No cases of PML were reported in clinical studies of vedolizumab however, healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms as outlined in physician</p>	<p>Patient Alert Card</p> <p>To remind patients that they may be at risk of infections and should consult a health care professional if they are unwell. To alert patients to the early signs and symptoms of PML.</p> <p>For patients to provide Alert Card to non-IBD health care professionals to inform them of treatment with vedolizumab so that health care professionals are informed of the potential risks of serious infections, opportunistic infections, including PML</p> <p>Physician Educational Brochure</p> <p>A short pamphlet providing</p>

	<p>education materials, and consider neurological referral if they occur. The patient is to be given a Patient Alert Card (see section 4.2). If PML is suspected, dosing with vedolizumab must be withheld; if confirmed, dosing must be permanently discontinued</p> <p>Other routine risk minimisation measures:</p> <p>Entyvio treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease (SmPC Section 4.2).</p>	<p>information to physicians on the identified and potential risks of treatment with vedolizumab and the need to monitor patients for emerging neurological signs/symptoms</p> <p>Objectives</p> <p>To ensure that the identified and potential risks of treatment are made clear to the physician</p> <p>To aid discussion with the patient</p> <p>To ensure that physicians are aware of the need to monitor for emerging neurological signs/symptoms in view of the PML risk associated with Tysabri (natalizumab)</p>
<p>Off-label use (Mild UC/CD, use in children/adolescents/ use with concomitant biologic immuno-suppressants</p>	<p>Mild UC or CD (SmPC Section 4.1 indications for use) 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.</p> <p>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.</p> <p>Children and adolescents /Paediatric Use (SmPC Section 4.2 Posology and method of Administration) The safety and efficacy in children aged 0 to 17 years old have not been established. No data are available</p> <p>Use with concomitant Biologic immunosuppressants SmPC Section 4.4 Special Warnings and Precautions for use</p> <p>No clinical trial data for concomitant use of vedolizumab with biologic</p>	<p>None</p>

	immuno-suppressants are available. Therefore, the use of Entyvio in such patients is not recommended.	
Potential Risk: Malignancies	<p>(SmPC Section 4.4 Special Warnings and Precautions for Use)</p> <p>The risk of malignancy is increased in patients with ulcerative colitis and Crohn's disease.</p> <p>Immunomodulatory medicinal products may increase the risk of malignancy.</p> <p>SmPC Section 4.8 Undesirable Effects</p> <p>Overall, results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment; however, the number of malignancies was small and long-term exposure was limited. Long-term safety evaluations are ongoing.</p> <p>Other routine risk minimisation measures:</p> <p>Entyvio treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease. (SmPC Section 4.2).</p>	None
Missing Information: Pregnancy and Lactation	<p>SmPC Section 4.6 Pregnancy and Lactation</p> <p><u>Women of childbearing potential</u></p> <p>Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and to continue its use for 18 weeks after the last treatment with Entyvio.</p> <p><u>Pregnancy</u></p> <p>There are limited amount of data from the use of vedolizumab in pregnant women.</p> <p>Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Entyvio is to be used during pregnancy only if the benefits clearly outweigh any potential risk to both the mother and fetus.</p> <p><u>Breastfeeding</u></p> <p>It is unknown whether vedolizumab is excreted in human milk or absorbed systemically after ingestion.</p> <p>Available pharmacodynamic/toxicological data in animals have shown excretion of vedolizumab in milk (see section 5.3).</p>	

	Because maternal antibodies (IgG) are excreted in breast milk, it is recommended that a decision be made whether to discontinue breastfeeding or to discontinue/abstain from Entyvio therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
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Other routine risk minimisation measures: Entyvio treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease. (SmPC Section 4.2).	None	
Missing Information: Exposure in Elderly/Paediatric Patients Exposure in Patients with Renal, Hepatic, or Cardiac Impairment	SmPC Section 5.2 Pharmacokinetic properties <u>Special Populations</u> Age does not impact the vedolizumab clearance in ulcerative colitis and Crohn's disease patients based on the population pharmacokinetic analyses. No formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of vedolizumab	None
Missing Information: Prior exposure to natalizumab, rituximab or use with concurrent biologic immunosuppressants	SmPC Section 4.4 Special Warnings and Precautions for Use Prior and concurrent Drug Exposures No vedolizumab clinical trial data are available for patients previously treated with natalizumab or rituximab. Caution should be exercised when considering the use of Entyvio in these patients. Patients previously exposed to natalizumab should normally wait a minimum of 12 weeks prior to initiating therapy with Entyvio unless otherwise indicated by the patient's clinical condition. Other routine risk	None

	minimisation measures: Entyvio treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease. (SmPC Section 4.2).	
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The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice without changes.

2.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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

Benefits

Beneficial effects

Ulcerative Colitis

In the induction phase, a statistical significant gain was observed in the primary endpoint, the proportion of patients with clinical response at Week 6, in vedolizumab-treated patients compared to placebo (21.7%). Subgroup analyses for clinical response at Week 6 showed a consistent treatment benefit of vedolizumab across all age categories, gender and disease severity. Results on the primary endpoint were confirmed by data on the secondary endpoint showing larger percentage of patients in clinical remission in the vedolizumab arm (16.9%) compared to placebo (5.4%). Exploratory analyses indicated that efficacy is maintained in anti-TNF failure patients (6.6% at week 6), although at lower levels, compared with results in patients without prior anti-TNF failure (16.5%).

In the maintenance study, a proportion of approximately 40-45% vedolizumab-treated patients achieved remission at Week 52 (primary endpoint), with a gain over placebo of 26.1% in the Q8W dosing group and 29.1% in the Q4W dosing group, and relative risks of similar magnitude for both dosing regimens, 2.7 for Q8W, 2.8 for Q4W. The efficacy was maintained in most subgroup analyses for clinical remission at Week 52, with some non significant differences with respect to race, region foecal, and calprotectin. The benefit of vedolizumab was observed both in anti-TNF alpha naïve and experienced patients, although treatment effect was somewhat lower in the anti-TNF alpha experienced patients.

Results from secondary endpoints were consistent with those achieved in the primary endpoint, all in favour of vedolizumab treated groups with similar responses observed with both dosing

regimens. Durable clinical response (clinical response at Weeks 6 and 52), a key secondary endpoint of the Maintenance Study, was significantly higher in vedolizumab treated patients with a RR of 2.4 for Q8W dosing and of 2.2 for Q4W dosing versus placebo, respectively; mucosal healing at Week 52 was significantly better in both vedolizumab dosing regimens versus placebo (RR of 2.6 for Q8W dosing and 2.8 for Q4W dosing); corticosteroid-free remission at Week 52 in patients who were on corticosteroid at week 6 was significantly higher in vedolizumab treated patients (RR compared to placebo of 2.3 for vedolizumab Q8W and of 3.3 for vedolizumab Q4W). The proportion of patients at Week 52 who achieved clinical remission and have been corticosteroid-free for 90 days or for 180 days was shown in an exploratory analysis to be higher in vedolizumab-treated groups and in particular in Q4w dosing regimen.

Crohn's disease

Second line indication

In the C13007 Induction study, one of the co-primary endpoints, the proportion of patients with clinical remission at Week 6, was met (treatment difference from placebo of 7.8). According to the statistical plan, being the pre-defined more stringent level of significance ($p < 0.025$) reached for this endpoint the study is considered technically positive. The pooled analysis of naive C13007 and C13011 subpopulations, including a larger sample size of patients, gives better results than those from the two studies separately with a gain over placebo of 12% when remission or enhanced clinical response are considered (C13007: gain over placebo remission 8.2%; gain over placebo enhanced response 11.9%. C13011: gain over placebo remission 19.5%; gain over placebo enhanced response 15.2%).

In the maintenance phase of Study C13007, vedolizumab at both dosing regimens (300 mg Q8W and 300 mg Q4W) met the primary endpoint of clinical remission at Week 52. Positive results were also observed in 2 of the 3 secondary endpoints, i.e. enhanced clinical response and corticosteroid-free clinical remission at Week 52. These results were supported by data on durability of clinical response (i.e. durability and enhanced durability of clinical response at Week 52) from ancillary analysis.

Third line indication

The induction Study C13011 was performed on a population mainly consisting of prior anti-TNF experienced CD patients (75%). Although the study failed its primary efficacy endpoint, the proportion of patients in clinical remission at Week 6 in the TNFalpha antagonist failure subpopulation, a better benefit was shown at a later time point (week 10).

The data also showed that clinical remission and clinical enhanced response in the anti TNF failure populations of both C13011 and C13007 studies showed small effect of vedolizumab over placebo at Week 6 (6.2% and 0.9%, respectively) but greater percentages at Week 10 with a gain over placebo in remission of 7.4% (C13007) and 14.4% (C13011) and in enhanced response of 16.3% (C13007) and 22% (C13011). The efficacy in this subpopulation of anti-TNFalpha failed patients is considered acceptable in view of the limited therapeutic options available at present.

Uncertainty in the knowledge about the beneficial effects.

The beneficial effects of VDZ appeared more evident in those patients on concomitant corticosteroids, as reflected in the product information. Exploratory analyses also suggested that vedolizumab administered in patients without concomitant corticosteroid treatment may be less effective for induction of remission in Crohn's disease than in those patients already receiving concomitant corticosteroids. As requested by the CHMP, this information is reflected in the product information for consideration by the treating physician.

Data suggest that some patients with Crohn's disease may require up to 14 weeks treatment with vedolizumab to achieve remission. Possible explanations include the mechanism of action and individual patient disease factors. The CHMP therefore requested the inclusion of the following information in the SmPC: "Induction of remission in Crohn's disease may take up to 14 weeks in some patients. The reasons for this are not fully known and are possibly related to the mechanism of action. This should be taken into consideration, particularly in patients with severe active disease at baseline not previously treated with TNF α antagonists".

Crohn's disease.

Second line

In the induction study, only one of the co-primary endpoints, proportion of patients with clinical remission at Week 6, was met, whereas no statistical significance was reached in the proportion of patients with enhanced clinical response at Week 6. In addition, the gain over placebo in terms of clinical remission was small and the placebo response was lower than the expected (6.8% vs. the expected 21%). This enhances the potential of detecting smaller treatment effect differences as statistically significant. However the CHMP acknowledged that the the placebo clinical remission rate in Study C13007 is driven by the significant number of refractory patients studied.

In the anti-TNF α naïve population, better results in clinical remission at week 6 in the naïve population of the C13011 study than in study C13007 (difference from placebo 8.2% and 19.2%, NTT 5.2 vs. 12.2 respectively) were reported. The difference in the therapeutic effect of vedolizumab in the 2 studies is rather large. One reason could be the different sample size between the two studies. However, similar differences are noted also in the response of the placebo group. The data provided highlighted that baseline disease activity in TNF α antagonist naïve patients was higher in those enrolled in study C13007 than those in study C13011, which may support the hypothesis that the patient population of C13007 and C13011 studies was different.

Third line

Results from the other induction study C13011, showing a gain in clinical remission, in patients who previously failed anti-TNF α therapy, only at week 10 might suggest, together with the observation of a continuous increase in enhanced clinical response from week 6 to week 10 the need of an additional treatment dose (week 0, 2, 6) and a longer time of follow-up (10 w) in order to observe a clinical relevant benefit in the TNF α antagonist failed patients. However, it is still uncertain the magnitude of the gain over time in this refractory population. In order to avoid ineffective treatment, therapy should not be continued in patients failing to respond by week 14 as described in the product information.

In the maintenance study, the stratification of patients at week 6 by response status and not by remission status led to an imbalance, in terms of clinical remission, across different treatment groups with the highest proportion of patients in response being observed in the placebo group. It is possible that this imbalance may have favoured the placebo group in the analyses of results on clinical remission. No difference was observed in the durable remission in the timeframe comprised between week 6 and 52. However clinical remission at Week 52 was in favor of vedolizumab treated patients.

Risks

Unfavourable effects

The safety profile of VDZ does not raise major objections and could be considered reassuring in both UC and CD indications, although differences between these two pathologies have been reported (with higher incidence of AEs in CD).

In the combined studies of GEMINI I and II the adverse reactions that occurred in $\geq 5\%$ were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, cough. Infusion-related reactions were reported in 4% of patients receiving vedolizumab.

In the shorter (10-week) placebo controlled induction trial, GEMINI III, the types of adverse reactions reported were similar but occurred at lower frequency than the longer 52 week trials.

AEs of special interest, in particular infections, PML and malignancy will be carefully monitored in the post-approval safety studies as described in the RMP.

Uncertainty in the knowledge about the unfavourable effects

Clinical studies showed reassuring data on systemic immunosuppression in terms of response to immunization in healthy volunteers or opportunistic infections including PML and TB. However, the occurrence rate of these events with long-term exposure and in patients pre-treated with anti TNFalpha drugs and/or concomitant immunosuppressants is still not known. This lack of data is reflected in the product information and described in the RMP.

The incidence of certain malignancies, in particular lymphoma and colorectal cancer, may, in theory, increase in patients on long-term immunosuppressive therapies, particularly those which target cell-mediated immunity. Patients with prior exposure to immunosuppressants or immunomodulators (e.g., TNF α antagonists, natalizumab) may be at a greater risk for developing certain malignancies. This potential risk is addressed in the product information and the RMP.

The immune response to an oral vaccine (Cholera) was reduced by VDZ. It is not clear at this point whether chronic VDZ treatment may impact on immune response to systemic immunisation. This lack of data is reflected in the product information and described in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

The availability of a new agent in IBD for patients who have failed either conventional therapy or anti-TNFs is considered an important benefit for patients. This is particularly the case for an

agent with a novel mechanism of action, and a safety profile that is potentially preferable to that of anti-TNF agents.

The benefits of vedolizumab in both CD and UC have been adequately demonstrated in the clinical programme, although it is acknowledged that the magnitude of the effect is limited in the second line indication in CD, with regard to the time required for induction of remission and the effect size compared to anti-TNFs drugs. Vedolizumab administered without concomitant corticosteroids for induction of remission in Crohn's appeared less effective than in combination with concomitant corticosteroid treatment (regardless of use of concomitant immunomodulators). This information is adequately reflected in the product information.

The safety profile in both indications is at present mainly related to infections, particularly gut infections. Opportunistic infections or extra-pulmonary TB cases have not been observed. It is acknowledged that the risk of PML is potentially lower than for natalizumab, and although no cases of PML have been described in the clinical programme to date, there is an absence of long term safety data. The risk of PML will be monitored in the post-approval safety studies as described in the RMP.

Benefit-risk balance

Ulcerative Colitis. Results from both induction and maintenance study consistently indicate a benefit of vedolizumab treatment in the UC population. The benefit of vedolizumab was observed both in anti-TNF alpha naïve and experienced patients supporting both second line and third line indications. The treatment effect is considered clinically relevant, although somewhat lower in the anti-TNF alpha experienced patients and of smaller magnitude with respect to maintenance compared to previous anti-TNF-alpha drugs.

Crohn's disease. The rationale for the second line indication presented by the Applicant was based on the similarity of the patient populations in studies C13007 and C13011 (supporting the validity of results obtained in both studies in the overall benefit-risk assessment), the favourable safety profile of VDZ compared to anti-TNFs, the comparability of the efficacy of VDZ with anti-TNFs (given the limitations of comparing results between studies and the delayed action of VDZ), and the overall clinical relevance of the benefits observed for VDZ in terms of the proportion achieving remission and the length of time required for this to occur. The CHMP concluded that as efficacy is greater in the second line indication compared with the third line, albeit delayed and possibly less effective compared with anti-TNFs, the lack of systemic immunosuppression, with no cases of extra-pulmonary or systemic TB with VDZ in contrast to anti-TNFs, and the long-lasting efficacy in those who respond, combine to make VDZ a useful option for 2nd line CD patients. In the third line indication (after conventional therapy and anti-TNFalpha the data showed that clinical remission and clinical enhanced response in the anti TNF failure populations of both C13011 and C13007 studies showed small effect of vedolizumab over placebo at Week 6 (6.2% and 0.9%, respectively) but greater percentages at Week 10 with a gain over placebo in remission of 7.4% (C13007) and 14.4% (C13011) and in enhanced response of 16.3% (C13007) and 22% (C13011). This indication for 3rd line in CD is therefore considered acceptable by the CHMP particularly in view of the recognized unmet need, since no therapeutic alternatives are at present available in this anti-TNF alpha failed population.

Discussion on the benefit-risk balance

Ulcerative colitis. On the basis of the evidence generated from both induction and maintenance the efficacy of vedolizumab in the ulcerative colitis indication is considered sufficiently and robustly demonstrated. The availability of a product with demonstrated efficacy in patients not responding to anti-TNF therapy is considered valuable, and the magnitude of effect observed in both second and third line treatments, clinically significant. The significant clinical efficacy of vedolizumab treatment is considered to overcome the risk represented by limited information on the long-term safety of the drug, which is considered manageable with strict monitoring.

Crohn's disease. The efficacy of vedolizumab in the second and third line indications in CD is, on balance, considered adequate to outweigh the potential risks. The magnitude of the effect is limited in the second line indication in CD, with regard to the time required for induction of remission and the effect size compared to anti-TNFs, however the effect size compared to placebo, especially when administered with concomitant corticosteroids, is considered of clinical relevance for an agent with a different mechanism of action to existing therapies, and with a safety profile that would appear to be beneficial to that of the anti-TNF agents.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Entyvio in 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 (TNF α) antagonist" and "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 (TNF α) antagonist" is favourable and therefore recommends the granting of the marketing authorisation 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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **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 Physician's Educational Material 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:
 - Progressive weakness on one side of the body or
 - clumsiness of limbs
 - Disturbance of vision
 - 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

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that vedolizumab is qualified as a new active substance.

APPENDIX 1

DIVERGENT POSITION

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Entyvio in the claimed indications. The reasons for divergent opinion were as follows:

The magnitude of vedolizumab effect over placebo obtained in Study C13007 is considered of limited clinical value (+7.1% at week 6, sensitivity analysis) and distant from the effect size considered clinically relevant for the calculation of the sample size (~ + 16%) in the claimed second line indication where other treatment options that showed higher efficacy are available. Moreover, the only secondary endpoint was not met.

The reliability of the pooled analysis of the two studies C13007 and C13011 proposed by the Applicant to increase treatment effect and achieve statistical significant difference from placebo is questionable. Significant differences in induction of remission in response to treatment were obtained in the anti-TNFalpha naïve population of the two studies (difference from placebo 8.2% and 19.2%, NTT 5.2 vs. 12.2, in the C13007 and C13011 study, respectively). Moreover, higher response rates are observed not only in the vedolizumab arm but also in the placebo arm.

Baseline disease activity (CDAI score, % pts CDAI > 400, inflammatory indexes: mean CRP, fecal calprotectin) in TNFalpha antagonist naïve patients was higher in patients enrolled in Study C13007 than in those in Study C13011.

These observations indicate that the populations of the two studies are significantly different and thus the pooling is not acceptable.

Inadequate response to vedolizumab requires longer time periods to be recognised compared to available anti-TNF alpha drugs. This is of concern particularly for patients with high disease activity, experiencing rectal bleeding, anaemia and frequent episodes of diarrhoea who would remain symptomatic while on vedolizumab whereas other potentially more effective induction therapies are available.

Potential differences in the safety profile between anti-TNFalpha drugs and VDZ are not considered to counterbalance the lack of benefit in patients with high disease activity.

In light of all the above mentioned considerations, the clinical benefit/risk ratio of Vedolizumab in the second line indication (patients naïve to anti-TNFalpha drugs) in Crohn's disease is considered negative.

London, 20 March 2014

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Daniela Melchiorri (Italy)

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Pierre Demolis (France)