Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Vedolizumab (rch)

Proprietary Product Name: Entyvio/Kynteles

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

Date of CER:

First round: 12 November 2013

Second round: 12 February 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AZA	azathioprine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
CLL	linear pathway clearance
Cmax	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CNS	central nervous system
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variability
DAE	discontinuation due to adverse event

Abbreviation	Meaning
DC	discontinuation
EMA	European Medicines Agency
EESA	European Efficacy Supplemental Analysis
Emax	maximum effect
Eo	effect at baseline
EU	European Union
HAHA	human anti-human antibodies
HBI	Harvey-Bradshaw Index
HIRD℠	HealthCore Integrated Research Database
HLT	high level term
HRQOL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IgG1	immunoglobulin G1
IM	intramuscular
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
LDP-02	Millennium's humanized monoclonal antihuman α4β7 integrin antibody, also known as MLN0002 (Process A) and MLN02
MAA	Marketing Authorization Application
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MLN0002	vedolizumab, Millennium's humanized monoclonal antihuman α4β7 integrin antibody, formerly LDP-02 and MLN02
MTX	methotrexate
NSO	a mouse myeloma cell line

Abbreviation	Meaning
PCP	pneumocystis carinii pneumonia
PD	pharmacodynamics
PDCO	Pediatric Development Committee
PIP	Pediatric Investigational Plan
PK	pharmacokinetics
PLA	placebo
PML	progressive multifocal leukoencephalopathy
PT	preferred term
PV	Pharmacovigilance plan
Q	intercompartmental clearance
Q4W	every 4 weeks
Q8W	every 8 weeks
RAMP	Risk Assessment and Minimization for PML
SAE	serious adverse event
SF-36	Short Form-36 questionnaire
SmPC	Summary of Product Characteristics
SOC	system organ class
t½	half-life
TB	tuberculosis
TEAE	treatment emergent adverse event
TNFα	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
V	volume of distribution

Abbreviation	Meaning
VCAM-1	vascular cell adhesion molecule-1
VDZ	vedolizumab
WBC	white blood cell
5-ASA	five aminosalicylic acid
6-MP	six mercaptopurine

1. Introduction

This is a submission for registration of a new biological entity, vedolizumab (ENTYVIO / VEDOLIZUMAB TAKEDA[1]) 300 mg powder for injection.

Vedolizumab is a humanized IgG1 monoclonal antibody, selectively targeting human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to gastrointestinal (GI) mucosa and gut-associated lymphoid tissue through adhesive interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1). The novel mechanism of action of vedolizumab allows it to bind exclusively to the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and thereby impairing the migration of leukocytes into GI mucosa. The gut-selective, anti-inflammatory activity of vedolizumab enables targeted therapy without generalized immunosuppression.

Vedolizumab is a recombinant humanized IgG1 antibody to the human α4β7 integrin produced in Chinese hamster ovary cells. 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.

The proposed indication is:

> *Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.*
>
> *Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.*

2. Clinical rationale

The Sponsor's Clinical Overview states: *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 TNFα 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*.

[1] The additional trade name was subsequently amended by the sponsor to 'Kynteles'

2.1. Guidance

There was no formal pre-submission meeting but there was some correspondence between the Sponsor and the TGA with regard the contents of the Dossier.

The Sponsor has undertaken discussions with the EMA with regard to any deviations from:

- CHMP Guideline on the Development of New Medicinal Products for Ulcerative Colitis (CHMP/EWP/18463/2006; effective August 2008)
- CHMP Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease (CPMP/EWP/2284/99 Rev. 1; effective February 2009)

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 14 clinical pharmacology studies, including 14 that provided pharmacokinetic data and 12 that provided pharmacodynamic data.
- 2 population pharmacokinetic analyses.
- 3 pivotal efficacy/safety studies.
- 2 other efficacy/safety studies.
- Integrated Summary of Efficacy, Integrated Summary of Safety

Module 2:

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission did not include paediatric data.

The Sponsor submitted a Pediatric Investigational Plan (PIP) for vedolizumab to the Pediatric Development Committee (PDCO) in July 2009 (PIP Procedure EMEA-000645- PIP01-09). On 11 June 2010, the PDCO agreed to defer studies with vedolizumab in children ≥4 years to <18 years of age with UC and CD until more information regarding the safety of vedolizumab in adults has been accumulated, and also waived the obligation to conduct studies in children <4 years of age (EMA/PDCO/315251/2010). The PDCO Opinion was endorsed in the European Medicines Agency Decision P/145/2010.

3.3. Good clinical practice

The studies submitted in the dossier are stated to have been conducted according to GCP. It is the Evaluator's belief that the Sponsor has adhered to GCP when conducting these studies.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Study C13001
		Study L297-007
		Study C13012
		Study C13013
	General PK Multiple dose	Study CPH-001
	Absolute bioavailability	Study C13010
	Bioequivalence† - Single dose	Study C13009
PK in special populations	Target population§- Single dose	Study L297-006
	Target population§ - Multi-dose	Study C13002 Study L299-016 Study M200-022 Study M200-021 Study L297-005
	Body size (in healthy adults)	Study C13005
Population PK analyses	Target population	Projections Research Population PKPD Report
		Metrum Research Group Population PKPD Report

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

[Note: The table above has been amended from the original CER to correct study numbers and to locate the studies against the appropriate topics]

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

4.2.1.1.1. Sites and mechanisms of absorption

In the present application, vedolizumab has been developed solely for intravenous use.

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

In Study C13010, the mean (80% CI) absolute bioavailability of vedolizumab by subcutaneous administration was 74.6 (66.6 to 83.6) % and by IM injection was 79.9 (72.1 to 88.5) %. Tmax was increased to 7 days for subcutaneous injection and 5 days for intramuscular injection. Cmax was similar for both subcutaneous and intramuscular routes, but was decreased compared with intravenous.

In Study L297-007 the bioavailability of a SC dose of 0.15 mg/kg was approximately 50% of the same IV dose.

4.2.1.2.2. Bioequivalence of clinical trial and market formulations

Bioequivalence was demonstrated between the Process C and Process B products of vedolizumab: geometric mean ratio (90% CI) Process B/Process C for $AUC_{0\text{-}inf}$ was 1.037 (0.944 to 1.140) and for Cmax 0.995 (0.908 to 1.091) (Study C13009).

4.2.1.2.3. Bioequivalence of different dosage forms and strengths

In the Projections Population PKPD analysis the NSO and CHO formulations had similar estimates for PK parameters.

4.2.1.2.4. Dose proportionality

Cmax and AUC were dose proportional in the comparison of 300 mg and 600 mg doses.

In Study C13001, the intravenous PK of vedolizumab were linear in the dose range 2.0 to 10.0 mg/kg. In the dose range 0.2 to 2.0 mg/kg there was some non-linearity, but this may have been due to problems with the assay for vedolizumab as half of the subjects in the 0.2 and 0.5 mg/kg dose groups were excluded from the PK analysis.

In Study L297-007 the PK of LPD-02 did not appear to be linear in the dose range 0.15 to 2.5 mg/kg IV. There was increased exposure relative to dose as the dose increased.

In Study C13013 for a 750 mg IV dose, AUC and Cmax were dose proportional to a 600 mg dose from a previous study.

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

At the 300 mg dose level Vss was 4.49 L (Study C13009).

In Study C13001, mean Vz was in the range of 2.89 to 4.02 L.

4.2.1.3.2. Plasma protein binding

No data were provided for plasma protein binding. This is unlikely to be significant as vedolizumab is an immunoglobulin.

4.2.1.3.3. Tissue distribution

In Study C13009, Vedolizumab plasma concentration data fitted to a two compartment model, with an initial redistribution phase lasting approximately 5 days.

In Study C13012 vedolizumab was not detectable in the CSF at Week 5 post-dose.

4.2.1.4. Metabolism

Vedolizumab is an antibody and is not expected to undergo biotransformation.

4.2.1.5. Excretion

4.2.1.5.1. Routes and mechanisms of excretion

At the 300 mg dose level CL was 0.15 L/day (Study C13009).

In Study C13001, mean CL was in the range 0.140 to 0.413 L/day.

At the 300 mg dose level T1/2 was 17.9 days (Study C13009).

In Study C13001, mean t½ was in the range 14.8 to 6.79 days.

In Study C13013 for a 750 mg IV dose, the mean t½ was 26.21 days.

The Metrum population PKPD study used a dual linear and nonlinear elimination model. The final typical parameter estimates were:

- 0.159 L/day for UC CLL
- 0.155 L/day for CD CLL
- 3.19 L for Vc
- 1.66 L for Vp
- 0.274 mg/day for Vmax
- 0.119 L/day for Q
- 0.974 mg/mL for Km
- half-life of 25.5 days for the linear elimination phase

4.2.1.5.2. Mass balance studies

Mass balance studies were not performed but would not normally be expected for an antibody.

4.2.1.5.3. Renal clearance

Vedolizumab is not expected to undergo renal elimination.

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics

At the 300 mg dose level, CV% for CL was 12.2%, t1/2 was 22.1% and Vss was 18.9% (Study C13009).

In the Projections Population PKPD analysis for the CHO formulation, the typical value for CL was 0.00784 L/hour with inter-individual variance of 26.1 %CV and inter-occasion variance of 21.8 %CV. The typical value for volume of distribution was 3.76 L, with inter-individual variance of 18.0 %CV.

The Metrum population PKPD study estimated the variance parameters as being indicative of moderate to large unexplained inter-individual variability with estimates of:

- CLL (34.6 %CV)
- Vc (19.2 %CV)

· Vmax (105 %CV)

4.2.2. Pharmacokinetics in the target population

In Study L297-005 in subjects with severe UC, two subjects who received the 0.15 mg/kg dose has measurable concentrations of LDP-2 at Day 60.

In Study L297-006 in a population of subjects with moderately active severe UC, the PK of LDP-02 was linear in the IV dose range 0.15 mg/kg to 2.0 mg/kg. CL was in the range of 3.61 to 6.60 mL/day/kg; t½ was in the range of 5.72 to 16.72 days; and Vz was in the range of 83.08 to 95.15 mL/kg. At the 0.15 mg/kg dose level bioavailability appeared to be complete by the SC route compared with the IV.

In Study M200-021, in subjects with mild to moderately active UC, the PK of LDP-02 was linear in the dose range 0.5 to 2.0 mg/kg IV. Mean half life was 8.7 days for the 0.5 mg/kg dose and 11.5 days for the 2.0 mg/kg dose.

In Study C13002, mean (SD) t½ was 15.1 (2.0) hours for the 2.0 mg/kg dose, 22.0 (6.7) hours for the 6.0 mg/kg dose and 20.6 (7.2) hours for the 10.0 mg/kg dose. In Study C13002, Cmax and AUC were dose proportional in the range 2.0 mg/kg to10.0 mg/kg IV.

In Study CPH-001 in Japanese subjects with UC the PK parameters for vedolizumab were not dose dependent in the range 150 mg to 300 mg. For the 300 mg dose level, the mean (SD) t½ was 226.8 (23.626) hours, CL was 0.01088 (0.00176) L/hour and Vz was 3.423 (0.431) L. For the 300 mg dose, the accumulation factor for AUC was 1.5785 and for Cmax was 1.2872.

In Study L299-016 there were insufficient data to determine any PK parameter other than Cmax. In subjects with CD, Cmax was dose proportional and there was no apparent accumulation after the second dose.

In Study M200-022 for LDP-02, Cmax and AUC were dose proportional in the range 0.5 mg/kg to 2.0 mg/kg.

In Study C13007 in subjects with CD administered vedolizumab on Weeks 0, and 2, median (range) serum trough concentrations at Week 6 were 24.1 (0.2 to 142.0) µg/mL. During the maintenance phase for 300 mg administered 8 weekly the median (range) steady state trough concentrations (at Week 52) were 16.7 (1.6 to 78.9) µg/mL and for 4 weekly administration were 46.3 (10.0 to 108.0) µg/mL.

In Study C13006 in subjects with UC administered vedolizumab on Weeks 0, and 2, median (range) serum trough concentrations at Week 6 were 24.9 (0.9 to 65.6) µg/mL. During the maintenance phase for 300 mg administered 8 weekly the median (range) steady state trough concentrations (at Week 52) were 14.6 (0.5 to 254.0) µg/mL and for 4 weekly administration were 55.6 (0.0 to 164.0) µg/mL.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

No data were submitted for subjects with impaired hepatic function but this would not be expected to affect the PK of vedolizumab.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

No data were submitted for subjects with impaired renal function but this would not be expected to affect the PK of vedolizumab.

4.2.3.3. Pharmacokinetics according to age

There were limited data for PK in older persons.

4.2.3.4. Pharmacokinetics related to genetic factors

No data were submitted for subjects with regard to genetic factors but this would not be expected to affect the PK of vedolizumab.

4.2.3.5. Pharmacokinetics according to body weight

In Study C13005 clearance was similar for low body weight and high body weight subjects: mean (SD) 0.161 (0.083) L/day for low body weight and 0.225 (0.054) L/day for high body weight. Half-life was similar for low body weight and high body weight subjects: mean (SD) 17.0 (3.92) days for low body weight and 18.6 (4.08) days for high body weight.

In Study C13005 Vz was greater in high body weight subjects compared with low body weight: mean (SD) Vz 5.84 (1.15) L for high body weight and 3.74 (1.26) for low body weight. There was higher exposure to vedolizumab in high body weight subjects compared with low body weight at a 6.0 mg/kg dose level: mean (SD) Cmax 112 (23.7) for low body weight and 173 (29.7) for high body weight; AUC(0-inf) 2440 (668) day.µg/mL for low body weight and 3260 (526) day.µg/mL for high body weight. This indicates that weight based dosing results in higher exposure in high body weight subjects.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

In the Metrum Population PKPD study AZA, MTX, MP and aminosalicylates did not have statistically significant effects on CL.

4.3. Evaluator's overall conclusions on pharmacokinetics

- The pharmacokinetics of vedolizumab have been adequately characterised.
- Vedolizumab has a half-life of around 26 days, CL of around 0.16 L/day and volume of distribution around 4.5 L[2]. The PK conformed to a two compartment model. The typical value of volume of distribution from the Metrum population PK study was 3.19 L for the central volume, 1.66 L for the peripheral volume, giving a total volume of distribution of 4.85 L. Inter-individual variance for CL was around 25 %CV and inter-occasion variance was around 22 %CV. Inter-individual variance for volume of distribution was around 18 %CV. The PK of vedolizumab appeared to be dose proportional at the dose range recommended by the Sponsor.
- The PK in subjects with UC and CD were similar to those in healthy volunteers for the final formulation intended for marketing. The exposure to vedolizumab for the proposed induction and maintenance regimen (300 mg at zero, two and six weeks and then every eight weeks thereafter) was similar for subjects with CD and UC. This was also demonstrated for the once every 4 week maintenance regimen.
- Weight based dosing results in higher exposure in high body weight subjects. This gives some support to the use of a single dose level in adults, and does not support weight based dosing.
- In the Metrum population PK study, the covariate modelling indicated that prior treatment with TNFα inhibitors increased CL, as did the presence of HAHA. AZA, MTX, MP and aminosalicylates did not have [clinically] significant effects on CL. Clearance was decreased in subjects with low serum albumin at baseline. Age and gender did not have a significant effect upon clearance.

[2] Volume of distribution data from Study C13009

- As vedolizumab is a humanised antibody, is not a cytokine modulator and is gut selective, CYP mediated drug interactions are, in the opinion of the Evaluator, unlikely. Effects on PK of hepatic or renal insufficiency are also unlikely. Hence, in the opinion of the Evaluator it is a reasonable approach not to have performed studies in subjects with impaired hepatic or renal function.
- The numbers of elderly subjects in the PK studies requires clarification.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

Table 2: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on ACT-1 and MAdCAM	Study C13009
		Study C13001
		Study L297-007
		Study L297-005
		Study L297-006
		Study M200-021
		Study C13002
		Study CPH-001
		Study L299-016
		Study M200-022
Secondary Pharmacology	Effect on CSF CD4+/CD8+	Study C13012
	Effect on immunogenicity	Study C13013
Population PD and PK-PD analyses	Target population	Projections Research Population PKPD Report
		Metrum Research Group Population PKPD Report

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

No clinical data were provided on mechanism of action.

5.2.2. Pharmacodynamic effects

Two validated, flow cytometric assays: (1) ACT-1 Binding Interference Assay, and (2) MAdCAM-1-Fc Binding Interference Assay, were used to demonstrate the presence of vedolizumab on the surface of cells bearing α4β7 integrin and to assess the time course of α4β7 receptor saturation.

5.2.2.1. Primary pharmacodynamic effects

In Study C13009, at both the 300 mg and 600 mg dose levels, maximal inhibition of ACT-1 and MAdCAM-1-Fc was achieved within 24 hours. There was little difference in overall effect between the 300 mg and 600 mg dose levels. For ACT1 binding the mean Emax was 99.8% for 300 mg, and 99.7% for 600 mg; and AUCE was 13100% and 13100% respectively. For MAdCAM binding the mean Emax was 99.2% for 300 mg, and 98.0% for 600 mg; and AUCE was 12500% and 12800% respectively. There were increases from baseline to Day 8 in the subset of lymphocytes expected to be affected by vedolizumab: CD4+, CD45RO+ bright, CD25+, β7+ bright cells, and CD8+, CD45RO+ bright, CD25+, β7+ bright cells. There were no changes in the placebo group and no changes in total lymphocyte counts.

In Study C13001, near maximal inhibition was reached for ACT-1 and MAdCAM for all doses in the range 0.2 to 10.0 mg/kg. However, for AUCE there was an increase with dose, up to the 6.0 mg/kg level with some flattening to the 10 mg/kg dose level. Maximal or near maximal inhibition of ACT-1 and MAdCAM persisted to Day 113 for the 2.0 and 6.0 mg/kg doses and to Day 169 for the 10.0 mg/kg dose.

In Study L297-007 where a dose range of 0.15 to 2.5 mg/kg was investigated, occupancy of α4β7 binding sites on both B-cells and T-cells was greatest for the 2.5 mg/kg dose with maximal binding for up to 125 days. There were no significant effects on serum concentrations of IgA, IgG and IgM at Day 7. There were no significant effects on serum concentrations of TNFα, IL-2, IL-6, and γ-interferon.

In Study L297-005 in subjects with severe UC, at both the 0.15 mg/kg and 0.5 mg/kg dose levels, maximum effect on ACT-1 binding persisted to Day 22.

In Study L297-006 in a population of subjects with moderately active severe UC, maximal or near maximal inhibition of ACT-1 binding was maintained to Day 14 for the 0.15 mg/kg IV dose, Day 60 for the 0.5 and 2.0 mg/kg dose levels and, paradoxically, Day 180 for the 0.15 mg/kg SC dose. However, the efficacy outcomes did not correlate with inhibition of ACT-1. The dose group with the best clinical response was the 0.5 mg/kg dose level.

In Study M200-021, in subjects with mild to moderately active UC, maximum binding of α4β7 was maintained to Day 55 (three weeks after the second dose) for both 0.5 and 2.0 mg/kg dose groups in subjects negative for HAHA, but was not maintained after Day 29 (second dose) in subjects positive for HAHA. There were no statistically significant differences in efficacy between the study groups, but there did appear to be clinical benefit in the active treatment groups.

In Study C13013, maximal or near maximal binding of α4β7 was maintained to Day 74.

In Study C13002, maximal or near maximal inhibition of ACT-1 and MAdCAM was achieved for all the dose levels, from 2.0 mg/kg to 10.0 mg/kg. A plateau in effect appeared to occur at the 6.0 mg/kg dose level, but there was little difference between all the dose levels. Duration of effect was similar for the 6.0 mg/kg and 10.0 mg/kg dose levels, but for both was greater than

for the 2.0 mg/kg dose level. Two subjects developed HAHA and for one of these subjects there was shorter duration of effect. Efficacy, as measured by the Partial Mayo Score was similar for the 6.0 mg/kg and 10.0 mg/kg dose levels. At Day 253, response was coded for seven (58%) in the 2.0 mg/kg group, eight (73%) in the 6.0 mg/kg group, eight (73%) in the 10.0 mg/kg group and three (33%) in the placebo. There was no dose effect for faecal calprotectin, or apparent treatment effect.

In Study CPH-001 in Japanese subjects with UC to Day 43 there was no difference between the 150 mg dose level and the 300 mg in inhibition of MAdCAM. However, duration of maximum effect was up to 155 days for the 300 mg dose level but only to Day 99 for the 150 mg dose level.

In Study L299-016, in subjects with CD treated with LDP-02 duration of effect was greater for the 2.0 mg/kg group and the presence of HAHA decrease duration of effect for both dose levels. At Day 57 there was clinical response (≥70 point reduction from baseline CDAI score) for 49.1% subjects in the 0.5 mg/kg group, 53.1% in the 2.0 mg/kg and 41.4% in the placebo. Clinical remission (reduction in CDAI score to ≤150 points) was recorded for 29.5% subjects in the 0.5 mg/kg group, 36.9% in the 2.0 mg/kg and 20.7% in the placebo.

In Study M200-022 inhibition of α4β7 was greater for the 2.0 mg/kg dose compared with the 0.5 mg/kg, and duration of effect was decreased by the presence of HAHA. Remission on Day 43 was achieved by 19 (33%) subjects in the 0.5 mg/kg group, 19 (32%) in the 2.0 mg/kg group and nine (14%) in the placebo. Remission was less likely in the presence of HAHA. At Day 43 there was a significant decrease in Total Ulcerative Colitis Clinical Score from baseline compared with placebo for both LDP-02 groups: LS mean difference (95% CI) -1.61 (-2.66 to -0.56) for the 0.5 mg/kg group and -1.27 (-2.33 to -0.21) for the 2.0 mg/kg group. At Day 43 there was a significant decrease in Modified Baron Score from baseline compared with placebo for both the LDP-02 0.5 mg/kg group: LS mean difference (95% CI) -0.54 (-1.01 to -0.08) for the 0.5 mg/kg group and -0.44 (-0.91 to 0.03) for the 2.0 mg/kg group. At Day 43 there was a significant decrease in Powell Tuck Score from baseline compared with placebo for both the LDP-02 groups: LS mean difference (95% CI) -1.88 (-3.07 to -0.69) for the 0.5 mg/kg group and -1.88 (-3.07 to -0.69) for the 2.0 mg/kg group. At Day 43 there was a significant improvement in Total IBDQ from baseline compared with placebo for both the LDP-02 groups: LS mean difference (95% CI) 15.53 (3.47 to 27.59) for the 0.5 mg/kg group and 12.10 (-0.13 to 24.33) for the 2.0 mg/kg group. There was no significant difference in CRP.

5.2.2.2. Secondary pharmacodynamic effects

In Study C13012 vedolizumab had no apparent effect on CSF CD4+ or CD8+ lymphocyte count at Week 5 post-dose.

In Study C13013, vedolizumab decreased mucosal immune response but not systemic immune response. Seroconversion to Hepatitis B surface antigen at Day 74 occurred for 54 (88.5%) subjects in the vedolizumab group and 56 (90.3%) in the placebo. However, 52 (81.3%) subjects in the vedolizumab group and 60 (95.2%) in the placebo seroconverted to cholera toxin: difference in rates (95% CI) -14.0 (-24.9 to -3.1) %.

5.2.3. Time course of pharmacodynamic effects

As discussed above, the duration of effect for the 300 mg dose level was up to 155 days. Duration of effect was decreased by the presence of HAHA.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The PKPD relationship of vedolizumab was modelled using direct effect, inhibitory sigmoid Emax models. In the Projections Population PKPD analysis basal ACT-1 was 16.7%, EC50 was 0.093 µg/mL, Emax was 0.991 and slope was 0.984. For the PD model for MAdCAM, basal activity was 17.0%, EC50 was 0.091 µg/mL, Emax was 0.984 and slope was 1.95.

In the Metrum Population PKPD analysis the final PD parameter estimates were: 12.1% for Eo; 0.093 mg/mL for EC50; 0.959 for Emax; and 0.801 for slope.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

The population PKPD studies did not detect any covariate effects for gender or age.

5.2.6. Pharmacodynamic interactions

PD interactions were not investigated in the development program, but would not be expected for an antibody, such as vedolizumab.

5.3. Evaluator's overall conclusions on pharmacodynamics

- The pharmacodynamic characteristics of vedolizumab have been adequately characterised.
- Vedolizumab given using the proposed dose regimen inhibited the PD endpoints ACT-1 and MAdCAM nearly maximally at all time points where vedolizumab was measurable and the time of maximal effect was generally the first sample time. At both the 300 mg and 600 mg dose levels, maximal inhibition of ACT-1 and MAdCAM-1-Fc was achieved within 24 hours (time of the first sample). Maximal or near maximal inhibition of ACT-1 and MAdCAM persisted to Day 113 for the 2.0 and 6.0 mg/kg doses and to Day 169 for the 10.0 mg/kg dose. The duration of effect for the 300 mg dose level was up to 155 days.
- In Study C13002, maximal or near maximal inhibition of ACT-1 and MAdCAM was achieved for all the dose levels, from 2.0 mg/kg to 10.0 mg/kg. A plateau in effect appeared to occur at the 6.0 mg/kg dose level but there was little difference between all the dose levels. Duration of effect was similar for the 6.0 mg/kg and 10.0 mg/kg dose levels, but for both was greater than for the 2.0 mg/kg dose level.
- In subjects that developed HAHA the duration of effect appeared to be decreased.

6. Dosage selection for the pivotal studies

The dosage selection for the Pivotal studies appears to have been based on the pharmacodynamic data. These support the 300 mg dose level and the choice of the 4 weekly and 8 weekly regimens tested in the Phase III studies.

7. Clinical efficacy

7.1. Crohn's disease

Efficacy was examined in two Phase 3 studies: Study C13007 and Study C13011. Induction of remission was studied in both Study C13007 and Study C13011, and maintenance of remission was studied in Study C13007. While recruitment of subjects who had prior TNF-α antagonist treatment was permitted in Study 13007, in Study C13011 enrolment was restricted such that 75% of the study population had prior TNF-α antagonist treatment[3]. In addition to these studies there was a Phase 2 study (Study L299-016, discussed under *Primary pharmacodynamic effects* above) and one long-term study with exploratory endpoints: Study C13008.

The efficacy endpoints were generally the same across the clinical study program. These were:

[3] AusPAR Clarification: The objective of Study C13011 was to determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the subgroup of patients defined as having failed TNFα antagonist therapy (TNFα antagonist failure subpopulation)

- Clinical Remission: CDAI score ≤150 points
- Clinical Response: a ≥70-point decrease in CDAI score from baseline (Week 0)
- Disease Worsening: a ≥100-point increase in CDAI score from the Week 6 value on 2 consecutive visits and a CDAI score ≥ 220 points
- Durable Clinical Remission: clinical remission at ≥80% of study visits including final visit (Week 52)
- Durable Clinical Response: clinical response at ≥80% of study visits including final visit (Week 52)
- Durable Enhanced Clinical Response: enhanced clinical response at ≥ 80% of study visits including final visit (Week 52)
- Enhanced Clinical Response: a ≥100-point decrease in CDAI score from baseline (Week 0)
- Sustained Clinical Remission: CDAI score ≤150 points at both Week 4 and Week 6
- In the long-term open-label study (Study C13008) clinical response was defined as a ≥3-point decrease in HBI score from baseline and clinical remission was defined as HBI score ≤4

The study selection and definitions for efficacy endpoints were consistent with the recommendations in the TGA adopted guideline on the development of new medicinal products for the treatment of CD. The methods of calculation for CDAI and HBI score are displayed in the dossier.

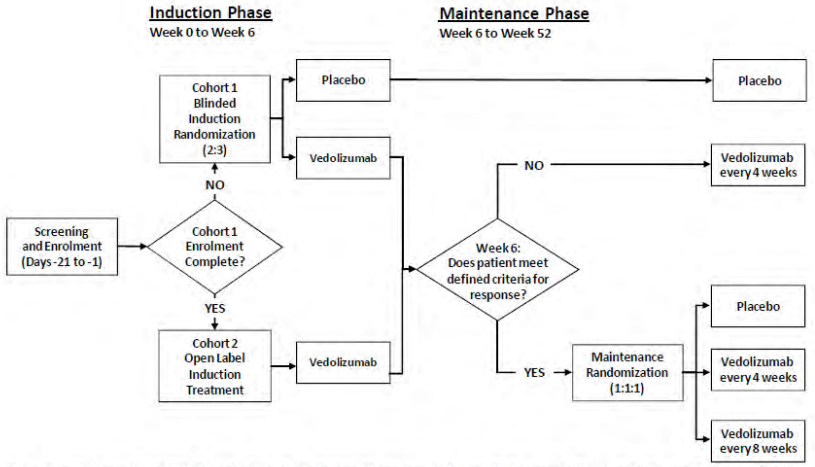
7.1.1. Pivotal efficacy studies

7.1.1.1. Study C13007

7.1.1.1.1. Study design, objectives, locations and dates

Study C13007 was a Phase 3, multicentre, randomised, placebo controlled, double blind study of the induction and maintenance of clinical remission in subjects with moderate to severe CD. The study was conducted in two phases. Subjects were initially randomised to vedolizumab or placebo for an induction phase. The vedolizumab subjects that responded were combined with additional subjects that had responded to open-label vedolizumab, then were re-randomised to vedolizumab or placebo for a maintenance phase (Figure 1). The study was conducted at 282 centres in 39 countries from December 2008 to May 2012.

Figure 1: Treatment Phases, Study Drug Randomization, and Treatment Assignment Schema (Study C13007)



Note: Prior to Amendment 5/6, the cohorts in the Induction Phase were to be enrolled sequentially, ie, patients were to be enrolled in Cohort 2 after enrollment in Cohort 1 was complete. Following Amendment 5/6, patients with a history of prior TNFα antagonist exposure were permitted to enroll into Cohort 2 if Cohort 1 enrollment had reached the limit of approximately 50% for that subpopulation.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female aged 18 to 80 years
- Female patients were: post-menopausal, surgically sterile, or agree to practice two effective methods of contraception, at the same time
- Diagnosis of CD established at least 3 months prior to enrolment by clinical and endoscopic evidence and corroborated by a histopathology report
- Moderately to severely active CD as determined by a CDAI score of 220 to 450 and: CRP level >2.87 mg/L during the Screening period; or ileocolonoscopy with photographic documentation of a minimum of three non-anastomotic ulcerations (each >0.5 cm in diameter) or ten aphthous ulcerations consistent with CD; or faecal calprotectin >250 mg/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, within 4 months prior to screening
- CD involvement of the ileum and/or colon, at a minimum
- Patients with extensive colitis or pancolitis of >8 years' duration or limited colitis of >12 years' duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of enrolment
- Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-todate on colorectal cancer surveillance (may be performed during screening)
- Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least one of the following agents: immunomodulators (6-MP (≥ 0.75 mg/kg), methotrexate (≥ 12.5 mg/week); TNFα antagonists (infliximab, adalimumab, certolizumab pegol), corticosteroids
- May be receiving a therapeutic dose of the following drugs: oral 5-ASA compounds, oral corticosteroid therapy, probiotics, antidiarrheals, azathioprine or 6-MP, methotrexate, and antibiotics used for the treatment of CD

The exclusion criteria included:

Gastrointestinal Exclusion Criteria:

- Evidence of abdominal abscess at the initial screening visit
- Extensive colonic resection, subtotal or total colectomy
- History of >3 small bowel resections or diagnosis of short bowel syndrome
- Have received tube feeding, defined formula diets, or parenteral alimentation within 21 days prior to the administration of the first dose of study drug
- Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
- Within 30 days prior to enrollment, have received any of the following for the treatment of underlying disease: non-biologic therapies (eg, cyclosporine, thalidomide), a non-biologic investigational therapy, adalimumab
- Within 60 days prior to enrollment, have received any of the following: infliximab, certolizumab pegol
- Any prior exposure to natalizumab, efalizumab, or rituximab
- Use of topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks
- Evidence of or treatment for *C. difficile* infection or other intestinal pathogen within 28 days
- Currently require or are anticipated to require surgical intervention for CD
- History or evidence of adenomatous colonic polyps that have not been removed
- History or evidence of colonic mucosal dysplasia
- Diagnosis of UC or indeterminate colitis

Infectious Disease Exclusion Criteria:

- Chronic hepatitis B or C infection
- Active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following: history of TB, a positive diagnostic TB test within 1 month of enrollment (QuantiFERON, tuberculin skin test reaction or chest X-ray)
- Any identified congenital or acquired immunodeficiency
- Any live vaccinations within 30 days
- Clinically significant extraintestinal infection (eg, pneumonia, pyelonephritis) within 30 days

General Exclusion Criteria:

- Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, haematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
- Any history of malignancy, except for the following: (a) adequately-treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to enrollment

- History of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease
- Positive PML subjective symptom checklist prior to the administration of the first dose of study drug
- Any of the following laboratory abnormalities during the Screening period: haemoglobin level <8 g/dL, WBC count <3x10^9/L, lymphocyte count 0.5< x10^9/L, platelet count <100 x10^9/L or >1200 x10^9/L, ALT, AST or ALP>3xULN, serum creatinine >2xULN
- Current or recent history (within 1 year prior to enrollment) of alcohol dependence or illicit drug use

7.1.1.1.3. Study treatments

For the induction phase the treatments were:

- Vedolizumab 300 mg
- Placebo

Treatments were administered IV at Weeks 0 and 2.

For the maintenance phase the treatments were:

- Vedolizumab 300 mg IV every 4 weeks
- Vedolizumab 300 mg IV every 8 weeks
- Placebo

Total duration of treatment was 52 weeks.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure for the Induction Phase was the proportion of patients in clinical remission or had achieved enhanced clinical response at Week 6[4]. The secondary assessment of clinical efficacy for the induction phase was mean CRP levels at Week 6.

The primary efficacy outcome measure for the Maintenance Phase was the proportion of patients in clinical remission at Week 52. The secondary efficacy outcome measures were: enhanced clinical response, corticosteroid-free remission, and durability of clinical remission.

HRQOL over time was assessed using IBDQ score, SF-36, and EQ-5D questionnaire.

Subgroup analyses were performed by: previous exposure to TNFα antagonist therapy, patients defined as having failed TNFα antagonist therapy and concomitant therapies, including corticosteroids and immunomodulators.

Exploratory endpoints were:

- The proportion of patients with clinical response at 52 weeks
- The proportion of patients with durability of clinical response over 52 weeks
- The proportion of patients with durability of enhanced clinical response over 52 weeks
- The reduction from baseline in corticosteroid use
- The proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 90 days

[4] AusPAR Clarification: the co-primary endpoints for this study were: to determine the effect of vedolizumab induction treatment on clinical remission at 6 weeks; and to determine the effect of vedolizumab induction treatment on enhanced clinical response at 6 weeks

- The proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 180 days
- The proportion of patients with clinical remission at Week 14 who did not meet the definition of clinical response at Week 6
- The proportion of patients with enhanced clinical response at Week 14 who did not meet the definition of clinical response at Week 6
- The proportion of ≥50% closure of draining enterocutaneous fistulae by Week 52 among patients with baseline fistulae
- The proportion of 100% closure of draining enterocutaneous fistulae by Week 52 among patients with baseline fistulae
- The correlation of CDAI score with HBI scores
- Change from baseline of serum CRP level in patients with an elevated CRP level at baseline
- Time to disease worsening
- Time to treatment failure
- Extra-intestinal manifestations of CD (arthritis/arthralgia; iritis/uveitis; erythema nodosum/pyoderma; anal fissure, fistula, or abscess; other fistula; fever over 37.8°C during past week)

Details of the schedule of study procedures were provided.

7.1.1.1.5. Randomisation and blinding methods

Subjects were assigned to treatment using IVRS. Blinding was maintained by masking the infusion bags.

7.1.1.1.6. Analysis populations

The Modified ITT Population for the induction analyses consisted of all randomized patients in Cohort 1 who received any amount of blinded study drug and had a baseline (Week 0) and at least 1 measurement post-randomization for CDAI score. 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. The safety population included all subjects who received any amount of study drug.

7.1.1.1.7. Sample size

The sample size calculation for the induction phase was for 370 subjects, randomised 3:2 to vedolizumab:placebo. Hence it was intended to recruit 222 subjects to the vedolizumab group and 148 to the placebo. The sample size calculation for the maintenance phase was for 501 subjects. Assuming a 55% response rate, a total of 1059 subjects were to be recruited to the study. The calculation was based on clinical response as the outcome measure.

7.1.1.1.8. Statistical methods

Hypothesis tests were performed using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the Induction Phase stratification factors. The Hochberg method was applied to control the overall Type I error rate at a 5% significance level for the multiple comparisons of the primary endpoints.

7.1.1.1.9. Participant flow

There were 220 subjects randomised to vedolizumab and 148 to placebo. A further 747 subjects were included in the open label vedolizumab group. One subject in the open-label group did not receive treatment. A total of 1010 (91%) subjects completed the induction phase: 205 (93%)[5] in the randomised vedolizumab group, 674 (90%) in the open-label and 137 (93%) in the placebo.

There were 461 subjects randomised into the maintenance phase: 154 to vedolizumab every 8 weeks, 154 to vedolizumab every 4 weeks, and 153 to placebo. A total of 73 (47%) subjects in the vedolizumab every 8 weeks, 82 (53%) in the vedolizumab every 4 weeks, and 64 (42%) in the placebo completed the study.

7.1.1.1.10. Major protocol violations/deviations

There were 15 subjects in the vedolizumab group and seven in the placebo that were excluded from the per-protocol group because of protocol violations.

7.1.1.1.11. Baseline data

In the induction group there were 595 (53%) females, 520 (47%) males and the age range was 18 to 77 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline Crohn's disease characteristics. The randomised population in the induction phase was similar in prior CD treatment and response. All subjects in the randomised groups had received prior treatment for CD, with 287 (78%) having received immunomodulators, 192 (52%) TNFα antagonists and 54 (15%) only systemic corticosteroids. In the randomised groups, 177 (80%) subjects in the vedolizumab group and 123 (83%) in the placebo had extraintestinal manifestations of CD. Concomitant treatment for CD was similar for the two groups.

For the maintenance phase, there were 239 (52%) females, 222 (48%) males and the age range was 18 to 77 years. The randomised groups were similar in demographic characteristics. There were some differences between the groups in disease localisation, but otherwise the randomised groups were similar in CD manifestations. There were 88 (57%) subjects in the 8 weekly group, 83 (54%) in the 4 weekly and 82 (54%) in the placebo with prior TNFα antagonist use. There were 82 (55%) subjects in the 8 weekly group, 77 (50%) in the 4 weekly and 78 (51%) in the placebo with prior TNFα antagonist failure. There were 124 (81%) subjects in the 8 weekly group, 124 (81%) in the 4 weekly and 125 (82%) in the placebo with extraintestinal manifestations. Concomitant CD treatment was similar for the randomised groups.

7.1.1.1.12. Results for the primary efficacy outcome

For the induction study, at Week 6 there were significantly more subjects in the vedolizumab group achieving clinical remission but not enhanced clinical response. Clinical remission was achieved by 32 (14.5%) subjects in the vedolizumab group and 10 (6.8%) in the placebo, RR (95% CI) 2.1 (1.1 to 4.2), p = 0.0206. Enhanced clinical response was achieved by 69 (31.4%) subjects in the vedolizumab group and 38 (25.7%) in the placebo, RR (95% CI) 1.2 (0.9 to 1.7), p = 0.2322. There was less efficacy in subjects with CDAI >330.

For the maintenance study, at Week 52 there were significantly more subjects in both the vedolizumab groups achieving clinical remission. Clinical remission was achieved by 60 (39.0%) subjects in the vedolizumab group 8 weekly group (RR [95% CI] 1.8 [1.3 to 2.6], p = 0.0007), 56 (36.4%) in the 4 weekly (RR [95% CI] 1.7 [1.2 to 2.4], p = 0.0042), and 33 (21.6%) in the placebo. There were no subgroup effects for this outcome measure in the vedolizumab 8

[5] Erratum: 199 (90%) in the randomised vedolizumab group completed the induction phase

weekly group, but in the 4 weekly group there appeared to be less efficacy in subjects with duration of CD <1 year.

7.1.1.1.13. Results for other efficacy outcomes

For the Induction phase:

- There was no difference between treatment groups for the change in CRP from baseline: mean (SD) -2.9 (16.28) for vedolizumab and -3.6 (30.04) for placebo.
- Clinical remission rates were lower for both placebo and vedolizumab in subjects with prior TNFα antagonist failure
- Clinical remission rates were higher for vedolizumab in subjects with concomitant corticosteroid treatment
- Clinical remission rates were not affected by concomitant immunomodulator use
- Adjusted mean (SE) change from baseline in CDAI score was -72.9 (6.18) for vedolizumab and -49.8 (7.49) for placebo
- There was no significant difference in change from IBDQ score from baseline to Week 6: mean (SE) 23.1 (2.28) for vedolizumab and 16.5 (2.75) for placebo
- There was no significant difference in change from SF-36 score from baseline to Week 6: mean (SE) change in physical component score 3.5 (0.47) for vedolizumab and 2.4 (0.56) for placebo, and mental component score 4.6 (0.71) for vedolizumab and 2.4 (0.86) for placebo
- There was no significant difference in change from EQ-5D score from baseline to Week 6: mean (SE) change in EQ-5D score -0.5 (0.10) for vedolizumab and -0.3 (0.12) for placebo, and EQ-5D VAS score 6.9 (1.38) for vedolizumab and 5.4 (1.65) for placebo

For the maintenance phase, for the secondary efficacy outcome measures:

- Enhanced clinical response at Week 52 was recorded for 67 (43.5%) subjects in the 8 weekly group, RR (95% CI) 1.4 (1.1 to 1.9), 70 (45.5%) in the 4 weekly, 1.5 (1.1 to 2.0), and 46 (30.1%) in the placebo
- Corticosteroid free clinical remission at Week 52 was recorded for 26 (31.7%) subjects in the 8 weekly group, RR (95% CI) 2.0 (1.1 to 3.6), 70 (45.5%) in the 4 weekly, 1.8 (1.0 to 3.3), and 46 (30.1%) in the placebo group[6].
- Durable clinical remission at Week 52 was recorded for 33 (21.4%) subjects in the 8 weekly group, RR (95% CI) 1.5 (0.9 to 2.4), 25 (16.2%) in the 4 weekly, 1.1 (0.7 to 1.9), and 22 (14.4%) in the placebo

For the maintenance phase, for the exploratory efficacy outcome measures:

- For subjects with previous TNFα antagonist failure, there was lesser response for vedolizumab and placebo, but vedolizumab was still superior to placebo for the key efficacy outcome measures but in subjects with loss of response to TNFα antagonists, there was no benefit for clinical remission at Week 52 in both vedolizumab groups or for enhance clinical response in the 8 weekly group.
- The number of failed therapies did not have a consistent effect on response variables.
- Concomitant systemic corticosteroid use enhanced efficacy.
- Concomitant immunomodulator use increased the rate of steroid free remission at Week 52 in the vedolizumab groups but not in the placebo.

[6] Erratum: Corticosteroid free clinical remission at Week 52 was recorded for 26 (31.7%) subjects in the 8 weekly group, RR (95% CI) 2.0 (1.1 to 3.6), 23 (28.8%) in the 4 weekly, 1.8 (1.0 to 3.3), and 13 (15.9%) in the placebo group.

- There was a 75% decrease in median corticosteroid dose to Week 52 in both vedolizumab groups and a 33.3% decrease in the placebo.
- Fistula closure was more likely in the vedolizumab 8 weekly group.
- CRP decreased to Week 52 in the vedolizumab groups compared with placebo.
- Time to disease worsening was greater in both vedolizumab groups than placebo. Time to treatment failure was greater in both vedolizumab groups than placebo.
- Mean CDAI score increased in the placebo group from Week 6, whereas it remained stable for the vedolizumab groups.
- There was no significant difference between the groups in major CD events
- There was a significant improvement in IBDQ scores relative to placebo for both vedolizumab groups: adjusted mean change (95% CI) from baseline relative to placebo 15.1 (4.4 to 25.9) for 8 weekly and 10.6 (0.3 to 21.0) for 4 weekly.
- There was a significant improvement in SF-36 physical component relative to placebo for both vedolizumab groups: adjusted mean change (95% CI) from baseline relative to placebo 3.5 (1.1 to 5.9) for 8 weekly and 2.8 (0.5 to 5.2) for 4 weekly. There was no significant difference in mental component.
- There was a significant improvement in EQ-5D VAS scores relative to placebo for both vedolizumab groups: adjusted mean change (95% CI) from baseline relative to placebo 12.4 (7.0 to 17.8) for 8 weekly and 10.0 (4.8 to 15.2) for 4 weekly. There was no significant difference in EQ-5D scores.

7.1.1.2. Study C13011

7.1.1.2.1. Study design, objectives, locations and dates

Study C13011 was a Phase 3, randomised, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of vedolizumab for the induction of clinical response and remission in subjects with moderately to severely active CD (75% of subjects were to have previously failed TNFα inhibitors and 25% were to have been naïve to TNFα inhibitors). The study was conducted at 107 centres in 19 countries from November 2010 to April 2012.

7.1.1.2.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females aged 18 to 80 years
- Female patients who were postmenopausal, surgically sterile, who agreed to practice two effective methods of contraception at the same time
- Diagnosis of CD established at least 3 months before enrollment by clinical and endoscopic evidence and corroborated by a histopathology report
- Moderately to severely active CD, as determined by a CDAI score of 220 to 400 within 7 days before enrollment and one of the following:
  - CRP level > 2.87 mg/L
  - Ileocolonoscopy with photographic documentation of a minimum of three non-anastomotic ulcerations (each > 0.5 cm in diameter) or ten aphthous ulcerations (involving a minimum of 10 contiguous cm of intestine) consistent with CD, within 4 months before enrolment
  - Faecal calprotectin >250 µg/g stool in conjunction with computed tomography enterography, magnetic resonance enterography, contrast-enhanced small bowel

radiography, or wireless capsule endoscopy revealing Crohn's ulcerations (aphthae not sufficient), within 4 months

- CD involvement of the ileum and/or colon, at a minimum
- Patients with extensive colitis or pancolitis of >8 years duration or limited colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months before enrolment
- Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance
- Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least one of the following agents: immunomodulators (AZA, 6-MP, MTX), TNFα antagonists (infliximab, adalimumab, certolizumab pegol), and, in subjects outside of the US, corticosteroids
- May be receiving a therapeutic dose of the following drugs: oral 5-ASA, oral corticosteroid therapy, probiotics, anti-diarrhoeal agents, AZA or 6-MP, MTX, antibiotics used for the treatment of CD

The exclusion criteria were similar to those for Study C13007.

7.1.1.2.3. Study treatments

The study treatments were:

- Vedolizumab 300 mg
- Placebo

The treatments were administered IV, in 250 mL normal saline, over 30 minutes on Weeks 0, 2, and 6.

7.1.1.2.4. Efficacy variables and outcomes

The primary endpoint of the study was clinical remission at Week 6 in the subpopulation of patients that had previously failed TNFα antagonist therapy.

The secondary efficacy endpoints were:

- Proportion of patients in clinical remission at Week 6 in the Overall ITT Population
- Proportion of patients in clinical remission at Week 10 in the TNFα Antagonist Failure ITT Subpopulation and in the Overall ITT Population
- Proportion of patients with sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) in the TNFα Antagonist Failure ITT Subpopulation and in the Overall ITT Population
- Proportion of patients with enhanced clinical response at Week 6 in the TNFα Antagonist Failure ITT Subpopulation

The exploratory efficacy endpoints were:

- Proportions of patients in clinical remission at Week 6, in clinical remission at Week 10, with sustained clinical remission, and with enhanced clinical response at Week 6 for the following subgroups:
  - Patients naïve to TNFα antagonist therapy (TNFα antagonist naïve subpopulation)
  - Patients defined as failed and/or intolerant of corticosteroids (prior corticosteroid failures)

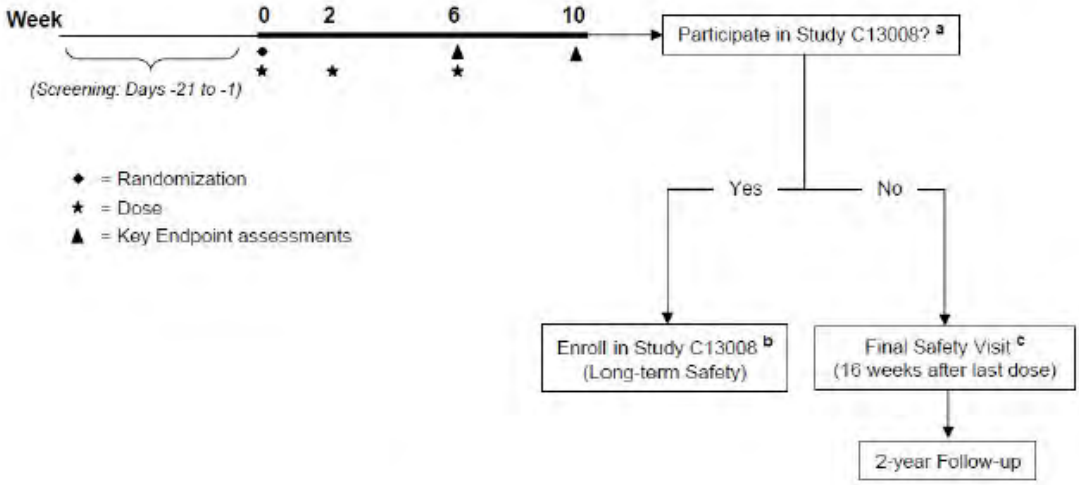
  - Patients defined as failed and/or intolerant of immunomodulators (prior immunomodulator failures)
  - Patients defined as failed and/or intolerant of TNFα antagonist therapy and immunomodulators (prior TNFα antagonist and immunomodulator failures)
  - Patients defined as failed and/or intolerant of previous CD therapy by worst prior treatment failure (worst prior treatment failure)
- Proportion of patients in clinical remission at Week 6, in clinical remission at Week 10, with sustained clinical remission, and with enhanced clinical response at Week 6 for the following subgroups:
  - Patients who did not receive concomitant corticosteroids or immunomodulators (no concomitant corticosteroids or immunomodulators)
  - Patients who received concomitant corticosteroids (concomitant corticosteroids only)
  - Patients who received concomitant immunomodulators (concomitant immunomodulators only)
  - Patients who received concomitant corticosteroids and immunomodulators (concomitant corticosteroids and immunomodulators only)
- In the subgroup of patients with a draining fistula at baseline: proportion of patients with closure of draining fistulae at Week 6 and Week 10 in the TNFα antagonist failure subpopulation and in the overall study population

The Patient Reported Outcomes were:

- IBDQ
- SF-36
- EQ-5D

The study plan is summarized in Figure 2.

Figure 2: Patient Treatment Overview (Study C13011)



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.

7.1.1.2.5. Randomisation and blinding methods

Subjects were randomized 1:1 to vedolizumab or placebo. Approximately 75% of the study population had failed previous TNFα antagonist treatment and 25% were naïve to TNFα antagonists. Randomisation was by IVRS with stratification by previous TNFα antagonist treatment, concomitant use of oral steroids and concomitant use of immunomodulators.

7.1.1.2.6. Analysis populations

The overall ITT population included all subjects who received any amount of blinded study drug. The modified ITT population included all subjects who received any amount of blinded study drug and had a baseline and at least one post-randomisation measurement for the endpoint. The safety population included all subjects who received any amount of study drug.

7.1.1.2.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure and also key secondary efficacy outcome measures. The power was >80% for each of these measures, with 93% power for the primary efficacy outcome measure. Total sample size was 396 for the overall study population and 296 for the TNFα antagonist failure subpopulation. For the primary efficacy outcome measure the assumed response rates were 5% for placebo and 17% for vedolizumab.

7.1.1.2.8. Statistical methods

The hypothesis tests for proportions used the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level with stratification by concomitant oral corticosteroid and immunomodulator use, and by previous TNF-α antagonist failure. 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. Change from baseline in efficacy endpoints was tested using ANCOVA models.

7.1.1.2.9. Participant flow

A total of 660 subjects were screened and 416 were randomized to treatment: 315 (76%) had previously failed TNFα antagonist treatment and 101 (24%) were TNFα antagonist naïve. There were 259[7] subjects randomized to vedolizumab and 207 to placebo. Twenty eight subjects did not complete the study, with 12 withdrawing due to AE.

7.1.1.2.10. Major protocol violations/deviations

Thirty subjects were excluded from the per-protocol population, 17 in the vedolizumab group and 13 in the placebo.

7.1.1.2.11. Baseline data

There were 236 (57%) females, 180 (43%) males and the age range was 19 to 77 years. There were only eight subjects aged ≥65 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in CD baseline characteristics, except for CDAI which was greater in the vedolizumab group. The treatment groups were similar in prior treatment failure, but not in the categories of treatment failure. The treatment groups were similar in CD treatment at baseline. There were 166 (79%) subjects in the vedolizumab group and 174 (84%) in the placebo with any history of extra-intestinal manifestations of CD. The treatment groups were similar in concomitant IBD treatments.

7.1.1.2.12. Results for the primary efficacy outcome

In the population of subjects with previous TNFα antagonist treatment failure there was no significant difference in efficacy between vedolizumab and placebo. There were 24 (15.2%)

[7] Erratum: the correct value is 209 subjects

subjects in the vedolizumab group and 19 (12.1%) in the placebo who achieved clinical remission: RR (95% CI) 1.2 (0.7 to 2.2), p = 0.4332.

7.1.1.2.13. Results for other efficacy outcomes

The results for the secondary efficacy endpoints were:

- The proportion of subjects in clinical remission at Week 6 in the Overall ITT Population was 40 (19.1%) for vedolizumab and 25 (12.1%) for placebo, RR (95% CI) 1.6 (1.0 to 2.5), p=0.0478. Response was better in subjects aged <35 years, males, subjects with higher faecal calprotectin, and when disease was localised to the colon.
- The proportion of subjects in clinical remission at Week 10 was greater for vedolizumab in the TNFα Antagonist Failure ITT Subpopulation and in the Overall ITT Population. For the TNFα Antagonist Failure ITT subpopulation, Clinical remission at Week 10 was reported for 42 (26.6%) subjects in the vedolizumab group and 19 (12.1%) in the placebo, RR (95% CI) 2.2 (1.3 to 3.6), p = 0.0012; and for the Overall ITT population 60 (28.7%) subjects in the vedolizumab group and 27 (13.0%) in the placebo, RR (95% CI) 2.2 (1.4 to 3.3), p <0.0001.
- The proportion of patients with sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) had no significant difference in the TNFα Antagonist Failure ITT Subpopulation and but was superior for vedolizumab in the Overall ITT Population. For the TNFα Antagonist Failure ITT subpopulation: 19 (12.0%) subjects in the vedolizumab group and 13 (8.3%) in the placebo, RR (95% CI) 1.4 (0.7 to 2.8), p = 0.2755; and for the Overall ITT population 32 (15.3%) subjects in the vedolizumab group and 17 (8.2%) in the placebo, RR (95% CI) 1.9 (1.1 to 3.2), p = 0.0249.
- The proportion of patients with enhanced clinical response at Week 6 in the TNFα Antagonist Failure ITT Subpopulation was greater in the vedolizumab population: 62 (39.2%) for vedolizumab and 35 (22.3%) for placebo, RR (95% CI) 1.8 (1.2 to 2.5), p=0.0011.

For the exploratory efficacy endpoints:

- In the subgroup of subjects who were TNFα antagonist naïve there was greater efficacy with regard to clinical remission at Week 6 and Week 10, and for sustained clinical remission, but not for enhanced clinical response. There were too few subjects with prior corticosteroid failure or immunomodulator failure to comment on differences in efficacy and the study was not powered for this outcome measure.
- The efficacy of vedolizumab was enhanced by concomitant corticosteroid use. There was no apparent effect for concomitant immunomodulator use. However, there was lesser efficacy for vedolizumab in subjects that were on neither concomitant corticosteroids nor immunomodulators: for clinical remission at Week 6, nine (13.8%) subjects in the vedolizumab group and ten (15.2%) in the placebo.
- Similar proportions of subjects in the vedolizumab and placebo groups achieved closure of draining fistulae at Week 6 (15.8% and 12.5%, respectively) or at Week 10 (15.8% and 11.1%, respectively).

For patient reported outcomes:

- There was improvement in IBDQ total score for both populations at both Week 6 and Week 10. The difference (95% CI) in adjusted mean change from baseline, vedolizumab - placebo was 13.6 (7.3 to 19.9).
- For SF-36 there was an improvement in mental component but not physical component scores at Week 10: difference (95% CI) in adjusted mean change from baseline, vedolizumab - placebo 3.6 (1.6 to 5.7).

- There was no significant difference in EQ-5D scores but there was a significant improvement in EQ-5D VAS: at Week 10 difference (95% CI) in adjusted mean change from baseline, vedolizumab - placebo was 9.2 (5.3 to 13.1).

There were too few subjects that were positive for HAHA to make meaningful conclusions about the effect of HAHA on efficacy.

7.1.2. Other efficacy studies

7.1.2.1. Study C13008

Study C13008 was an open label, long term safety study in subjects with moderate to severe UC and CD. The study was conducted in 38 countries form May 2009 to March 2013 (safety cut-off date). The study enrolled subjects with UC or CD from Study 13004, Study C13006, Study C13007 and Study C13011. The subjects received vedolizumab 300 mg IV every 4 weeks and the study treatment is intended to be of up to 7 years duration. The study enrolled 2243 subjects, of whom 832 had withdrawn. There were 1349 subjects with CD, and 894 with UC. There were 1128 (50%) males, 1115 (50%) females, and the age range was 19 to 80 years. The efficacy data were limited by the open design of the study and lack of comparator. There was a persisting improvement in mean partial Mayo scores in the UC population, but this analysis would not have accounted for drop-outs due to lack of efficacy.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

A pooled analysis of efficacy was performed using data from Study L299-016[8], Study C13007 and Study C13011. In the analysis of clinical remission at Week 6, there were 429 subjects treated with vedolizumab and 355 with placebo. There were 72 (16.8%) in the vedolizumab group and 35 (9.9%) in the placebo that achieved clinical remission; mean (95% CI) difference 7.4 (2.6 to 12.2) %, p = 0.0027. For those subjects with prior anti-TNFα treatment failure, 35 (13.3%) subjects in the vedolizumab group and 22 (9.7%) in the placebo achieved clinical remission: mean (95% CI) difference 4.1 (-1.6 to 9.8) %, p = 0.1574. For those subjects that were anti-TNFα treatment naïve, 35 (22.7%) subjects in the vedolizumab group and 13 (10.6%) in the placebo achieved clinical remission: mean (95% CI) difference 12.6 (3.7 to 21.4) %, p = 0.0054.

7.1.4. Evaluator's conclusions on clinical efficacy for Crohn's Disease

Efficacy was demonstrated for induction of remission for subjects with moderate to severe CD for the 300 mg dose level of vedolizumab. In Study C13007, at Week 6 there were significantly more subjects in the vedolizumab group achieving clinical remission but not enhanced clinical response. Clinical remission was achieved by 32 (14.5%) subjects in the vedolizumab group and 10 (6.8%) in the placebo, RR (95% CI) 2.1 (1.1 to 4.2), p = 0.0206. Enhanced clinical response was achieved by 69 (31.4%) subjects in the vedolizumab group and 38 (25.7%) in the placebo, RR (95% CI) 1.2 (0.9 to 1.7), p = 0.2322. There was less efficacy in subjects with greater disease severity (CDAI >330).

Efficacy at Week 10 was better demonstrated than for Week 6. This supports the Sponsor's proposed regimen for induction of remission, i.e. 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. In Study C13011, the proportion of subjects in clinical remission at Week 10 was greater for vedolizumab in the TNFα Antagonist Failure ITT Subpopulation and in the Overall ITT Population. For the TNFα Antagonist Failure ITT subpopulation, Clinical remission at Week 10 was reported for 42 (26.6%) subjects in the vedolizumab group and 19 (12.1%) in the placebo, RR (95% CI) 2.2 (1.3

[8] AusPAR clarification: Data from Study L299-016 were presented individually, but not pooled with the data from Studies C13007 and C13011 due to substantial differences in study design, patient population, and dose/dosing regimen.

to 3.6), p = 0.0012; and for the Overall ITT population 60 (28.7%) subjects in the vedolizumab group and 27 (13.0%) in the placebo, RR (95% CI) 2.2 (1.4 to 3.3), p <0.0001.

In Study C13007, at Week 6 clinical remission rates were lower for both placebo and vedolizumab in subjects with prior TNFα antagonist failure. In those subjects with intolerance or lack of response to TNFα inhibitors there was a significant benefit for vedolizumab. However, in subjects that had previously lost response to TNFα antagonist treatment, there did not appear to be efficacy for vedolizumab. In Study C13011, in the population of subjects with previous TNFα antagonist treatment failure there was no significant difference in efficacy between vedolizumab and placebo. Hence, in subjects that had initially responded to TNFα antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.

In both Study C13007 and Study C13011, clinical remission rates were higher for vedolizumab in subjects with concomitant corticosteroid treatment. However, clinical remission rates were not affected by concomitant immunomodulator use.

The pooled analysis of efficacy of data from Study L299-016[9], Study C13007 and Study C13011 indicated a mean (95% CI) difference, vedolizumab-placebo in remission rate of 7.4 (2.6 to 12.2) %, p = 0.0027.

Maintenance of remission was demonstrated for up to 52 weeks. Clinical remission was achieved by 60 (39.0%) subjects in the vedolizumab group 8 weekly group (RR [95% CI] 1.8 [1.3 to 2.6], p = 0.0007), 56 (36.4%) in the 4 weekly (RR [95% CI] 1.7 [1.2 to 2.4], p = 0.0042), and 33 (21.6%) in the placebo.

The secondary efficacy outcome measures were supportive of the primary efficacy outcome measures.

There was little difference in efficacy between the 4 weekly administration regimen for maintenance and the 8 weekly regimen. Hence the recommendation to increase dosing frequency from 8 weekly to 4 weekly in patients who do not respond requires further justification.

The choice of a 14 week time period from initiation of treatment to determine response, and therefore initiation of maintenance treatment, does make sense given the proposed dosing regimen. Were there a 10 week assessment, patients would be making an additional visit to their health provider that would not influence the likelihood of ongoing treatment.

There were too few subjects that were positive for HAHA to make meaningful conclusions about the effect of HAHA on efficacy.

7.2. Ulcerative colitis

Efficacy was examined in one Phase 3 study: Study C13006. Induction of remission and maintenance of remission were studied in Study C13006. Study C13006 recruited subjects with inadequate response to, loss of response to, or intolerance of at least one of the following agents: immunomodulators, TNFα antagonists and corticosteroids. In addition to these studies there were two Phase 2 studies (Study C13002 and Study M200-022 both discussed in the Section on *Primary pharmacodynamic effects*, above) and one long-term study with exploratory endpoints: Study C13008.

The efficacy endpoints were generally the same across the clinical study program. These were:

- Clinical Remission by Complete Mayo Score: a complete Mayo score of ≤2 points and no individual subscore >1 point

[9] AusPAR clarification: Data from Study L299-016 were presented individually, but not pooled with the data from Studies C13007 and C13011 due to substantial differences in study design, patient population, and dose/dosing regimen.

- Clinical Remission by Partial Mayo Score: a partial Mayo score of ≤2 points and no individual subscore > 1 point
- Clinical Response by Complete Mayo Score: a reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
- Clinical Response by Partial Mayo Score: a reduction in partial Mayo score of ≥2 points and ≥25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
- Corticosteroid-free Remission: Clinical remission in patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52
- Durable Clinical Remission: Clinical remission at Weeks 6 and 52
- Durable Clinical Response: Clinical response at Weeks 6 and 52
- Durable Mucosal Healing: a Mayo endoscopic subscore ≤1 at both Week 6 and Week 52
- Sustained Clinical Response: a clinical response at both Weeks 4 and 6 based on partial Mayo score (defined as reduction in partial Mayo score of ≥ 2 points and ≥ 25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤ 1 point).

The study selection and definitions for efficacy endpoints were consistent with the recommendations in the TGA adopted guideline on the development of new medicinal products for the treatment of UC.

The Complete Mayo Score is a composite index of 4 disease activity variables (stool frequency, rectal bleeding, findings on sigmoidoscopy, and physician's global assessment), each scored on a scale from 0 to 3 (higher scores indicate greater disease activity). The method for calculating the Mayo score is displayed in Table 3. The partial Mayo score excludes the endoscopy score.

Table 3: Mayo Scoring System for the Assessment of Ulcerative Colitis Activity (Study C13006)

Category[a]
Stool frequency[b] 0 = Normal no. of stools for this patient 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Sub score, 0 to 3
Rectal bleeding[c] 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes Sub score, 0 to 3
Findings on endoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration) Sub score, 0 to 3; 0 = Normal or inactive disease
Physician's global assessment[d] 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Sub score, 0 to 3

a The Mayo score ranges from 0–12, with higher scores indicating more severe disease. Partial Mayo score excludes endoscopy and ranges from 0–9.[25]
b Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
c The daily bleeding score represents the most severe bleeding of the day.
d The physician's global assessment acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

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

7.2.1. Pivotal efficacy studies

7.2.1.1. Study C13006

7.2.1.1.1. Study design, objectives, locations and dates

Study C13006 was a Phase 3, multicentre, randomised, placebo controlled, double blind study of the induction and maintenance of clinical remission in subjects with moderate to severe UC. The study was similar in design to Study C13007 (above). The study was conducted in two phases. Subjects were initially randomised to vedolizumab or placebo for an induction phase. The vedolizumab subjects that responded were combined with additional subjects that had responded to open-label vedolizumab, and were re-randomised to vedolizumab or placebo for a maintenance phase. The study was conducted at 211 centres in 34 countries from January 2009 to March 2012.

7.2.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female aged 18 to 80 years

- Female patients were: post-menopausal, surgically sterile, or agree to practice two effective methods of contraception, at the same time
- Diagnosis of UC established at least 6 months prior to enrollment by clinical and endoscopic evidence and corroborated by a histopathology report
- 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
- Evidence of UC extending proximal to the rectum (≥15 cm of involved colon)
- Patients with extensive colitis or pancolitis of > 8 years' duration or limited colitis of > 12 years' duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of enrolment
- Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to date on colorectal cancer surveillance (may be performed during screening)
- Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least one of the following agents: immunomodulators: 6-MP (≥ 0.75 mg/kg), methotrexate (≥ 12.5 mg/week); TNFα antagonists: infliximab, adalimumab, and certolizumab pegol; and corticosteroids
- May be receiving a therapeutic dose of the following drugs: oral 5-ASA compounds, oral corticosteroid therapy, probiotics, antidiarrheals, and azathioprine or 6-MP

The exclusion criteria included:

Gastrointestinal Exclusion Criteria:

- Evidence of abdominal abscess or toxic megacolon at the initial screening visit
- Extensive colonic resection, subtotal or total colectomy
- Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
- Within 30 days prior to enrolment, have received any of the following for the treatment of underlying disease: non-biologic therapies (eg, cyclosporine, thalidomide), a non-biologic investigational therapy
- Within 60 days prior to enrolment, have received any of the following: infliximab
- Any prior exposure to natalizumab, efalizumab, or rituximab
- Use of topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks
- Evidence of or treatment for *C. difficile* infection or other intestinal pathogen within 60 days or other intestinal pathogen within 30 days
- Currently require or are anticipated to require surgical intervention for UC
- History or evidence of adenomatous colonic polyps that have not been removed
- History or evidence of colonic mucosal dysplasia
- Diagnosis of Crohn's colitis or indeterminate colitis

Infectious Disease Exclusion Criteria:

- Chronic hepatitis B or C infection

- Active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following: history of TB, a positive diagnostic TB test within 1 month of enrolment (QuantiFERON, tuberculin skin test reaction or chest X-ray)
- Any identified congenital or acquired immunodeficiency
- Any live vaccinations within 30 days
- Clinically significant extraintestinal infection (eg, pneumonia, pyelonephritis) within 30 days

General Exclusion Criteria:

- Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, haematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
- Any surgical procedure requiring general anaesthesia within 30 days
- Any history of malignancy, except for the following: (a) adequately-treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to enrolment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to enrolment
- History of any major neurological disorders, including stroke, multiple sclerosis, brain tumour, or neurodegenerative disease
- Positive PML subjective symptom checklist prior to the administration of the first dose of study drug
- Any of the following laboratory abnormalities during the Screening period: haemoglobin level <8 g/dL, WBC count <3x109/L, lymphocyte count 0.5< $x10^9$/L, platelet count <100 $x10^9$/L or >1200 $x10^9$/L, ALT, AST or ALP>3xULN, serum creatinine >2xULN
- Current or recent history (within 1 year prior to enrolment) of alcohol dependence or illicit drug use

7.2.1.1.3. Study treatments

For the induction phase the treatments were:

- Vedolizumab 300 mg
- Placebo

Treatments were administered IV at Weeks 0 and 2. Treatment duration for the induction phase was 6 weeks.

For the maintenance phase the treatments were:

- Vedolizumab 300 mg IV every 4 weeks
- Vedolizumab 300 mg IV every 8 weeks
- Placebo

Total duration of treatment was 52 weeks.

7.2.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure for the Induction Phase was the proportion of subjects with clinical response at Week 6. The secondary efficacy endpoints for the induction phase were:

- The proportion of subjects in clinical remission (by complete Mayo score) at Week 6
- The proportion of subjects with mucosal healing at Week 6

The primary efficacy outcome measure for the Maintenance Phase was the proportion of subjects in clinical remission at Week 52. The secondary efficacy outcome measures were:

- The Proportion of subjects with durable clinical response (by complete Mayo score)
- The proportion of subjects with mucosal healing at Week 52
- The proportion of subjects with durable clinical remission
- The proportion of subjects using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52

HRQOL over time was assessed using IBDQ score, SF-36, and EQ-5D questionnaire.

Exploratory endpoints were:

- Time to disease worsening
- Reduction in oral corticosteroid use
- Reduction in fecal calprotectin
- Proportion of patients with clinical response by Week 14
- Proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 90 days
- Proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 180 days
- Serum and stool samples were to be analyzed for protein biomarkers associated with UC disease activity
- Genomic deoxyribonucleic acid (DNA) was to be analyzed for polymorphisms associated with therapeutic response to vedolizumab
- Key endpoints in the subgroup of patients with previous exposure to TNFα antagonist therapy and in the subgroup of patients defined as having failed TNFα antagonist therapy
- Key endpoints in the subgroups of patients on concomitant therapies

The schedule of study procedures was similar to that for Study C13007.

7.2.1.1.5. Randomisation and blinding methods

Subjects were assigned to treatment using IVRS. Blinding was maintained by masking the infusion bags. Randomisation for the induction phase was in the ratio 3:2 vedolizumab to placebo and stratified by:

- Concomitant use of oral corticosteroids
- Previous exposure to TNFα antagonists or concomitant immunomodulator (6-MP or AZA) use

Randomisation to the maintenance phase was in the ratio 1:1:1 for vedolizumab 8 weekly, vedolizumab 4 weekly and placebo, with stratification for:

- Enrollment in Cohort 1 or Cohort 2 in the Induction Phase
- Concomitant use of oral corticosteroids
- Previous exposure to TNFα antagonists or concomitant immunomodulator use

7.2.1.1.6. Analysis populations

The Modified ITT Population for the induction analyses consisted of all randomized patients in Cohort 1 who received any amount of blinded study drug and had a baseline (Week 0) and at least 1 measurement post-randomization for CDAI score. 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. The safety population included all subjects who received any amount of study drug.

7.2.1.1.7. Sample size

The sample size calculation for the induction phase was for 375 subjects, randomised 3:2 to vedolizumab:placebo. Hence it was intended to recruit 225 subjects to the vedolizumab group and 150 to the placebo. The sample size calculation for the maintenance phase was for 826 subjects, but many of these subjects were recruited for safety analysis. The study required 372 responders to be recruited (124 in each treatment group) for the efficacy analysis. This assumed a 55% response rate for the induction phase. The calculation was based on clinical response as the primary outcome measure, but also provided sufficient power for key secondary endpoints.

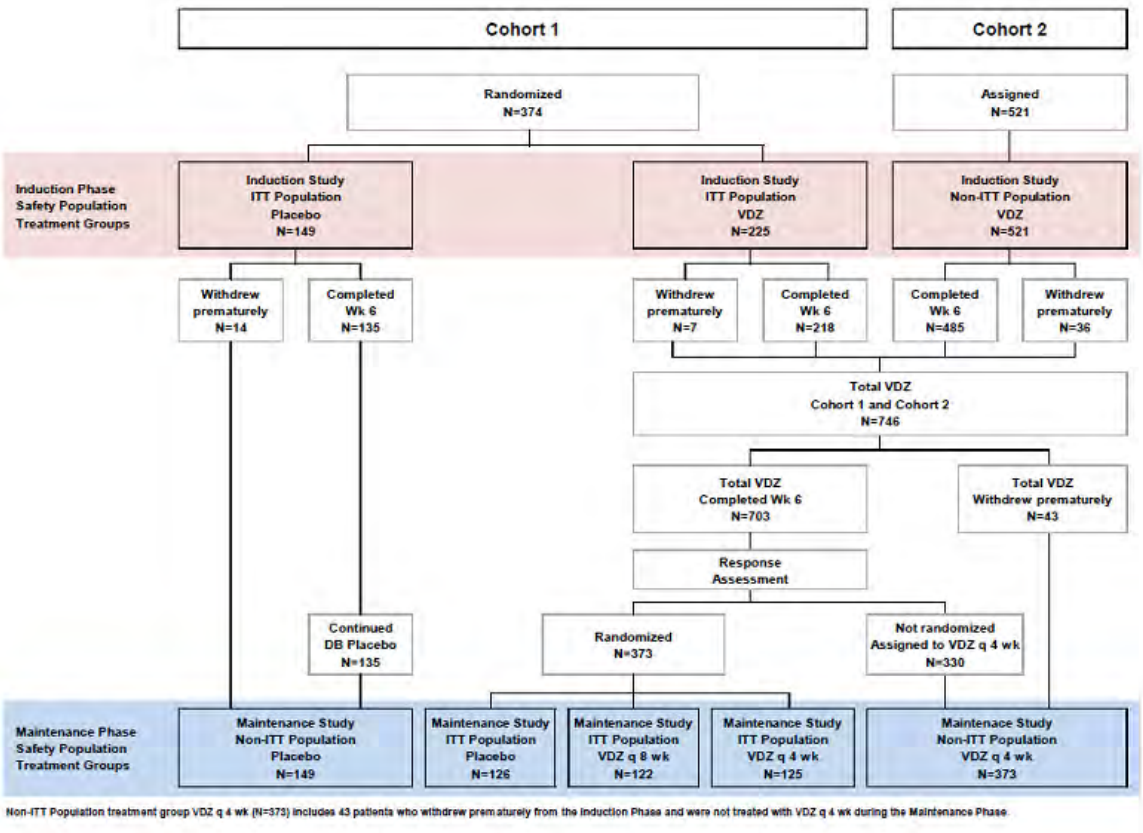
7.2.1.1.8. Statistical methods

Hypothesis tests were performed using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the Induction Phase stratification factors. The Hochberg method was applied to control the overall Type I error rate at a 5% significance level for the multiple comparisons of the primary endpoints.

7.2.1.1.9. Participant flow

A total of 1406 subjects were screened. In the induction phase, there were 374 subjects randomised: 225 subjects randomised to VDZ and 149 to placebo (Figure 3). A further 521 subjects were included in the open label vedolizumab group. A total of 838 (94%) subjects completed the induction phase: 218(97%) in the randomised vedolizumab group, 485 (93%) in the open-label and 135 (91%) in the placebo.

Figure 3: Overview of Treatment Groups in Induction Phase and Maintenance Phase Safety Populations (Study C13006)



There were 373 subjects randomised into the maintenance phase: 122 to vedolizumab every 8 weeks, 125 to vedolizumab every 4 weeks, and 126 to placebo. A total of 77 (63%) subjects in the vedolizumab every 8 weeks, 84 (67%) in the vedolizumab every 4 weeks, and 48 (38%) in the placebo completed the study.

7.2.1.1.10. Major protocol violations/deviations

For the induction period, one subject in each of the randomised groups discontinued because of protocol violation.

7.2.1.1.11. Baseline data

In the induction group there were 525 (59%) males, 370 (41%) females and the age range was 18 to 78 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline UC characteristics. The randomised population in the induction phase was similar in prior UC treatment failure. Concomitant treatment for UC was similar for the two groups at baseline, but during the study more subjects in the placebo group were treated with 5-aminosalicylic acids and more subjects in the vedolizumab group were treated with immunomodulators. In the double blind population, 74 (33%) subjects in the vedolizumab group and 44 (30%) in the placebo had extraintestinal manifestations of UC.

For the maintenance phase, there were 364 (59%) males, 256 (41%) females and the age range was 19 to 78 years. The randomised groups were similar in demographic characteristics. The randomised groups were similar in UC manifestations. Prior UC treatment was similar for the randomised treatment groups. There were 46 (38%) subjects in the 8 weekly group, 48 (38%) in the 4 weekly and 39 (31%) in the placebo with extraintestinal UC manifestations. Concomitant 5-aminosalicylic acid treatment [was: placebo 77%, Q8W 70%, Q4W 78%].

7.2.1.1.12. Results for the primary efficacy outcome

For the induction study, at Week 6 there were significantly more subjects in the vedolizumab group achieving clinical response. Clinical response was achieved by 106 (47.1%) subjects in the vedolizumab group and 38 (25.5%) in the placebo, RR (95% CI) 1.8 (1.4 to 2.5), p <0.0001. There was no apparent difference in clinical response if the disease was extensive colitis.

For the maintenance study, at Week 52 there were significantly more subjects in both the vedolizumab groups achieving clinical remission. Clinical remission was achieved by 51 (41.8%) subjects in the vedolizumab group 8 weekly group (RR [95% CI] 2.7 [1.7 to 4.2], p <0.0001), 56 (44.8%) in the 4 weekly (RR [95% CI] 2.8 [1.8 to 4.4], p <0.0001), and 20 (15.9%) in the placebo. There appeared to be fewer subjects with clinical remission in the Asian subgroup for vedolizumab 8 weekly group, and in the 4 weekly group there no apparent benefit in subjects with duration of UC ≥1 and <3 year.

7.2.1.1.13. Results for other efficacy outcomes

For the Induction phase, the results of the secondary efficacy analysis were:

- Clinical remission at Week 6 was achieved by 38 (16.9%) subjects in the vedolizumab group and eight (5.4%) in the placebo, RR (95% CI) 3.1 (1.5 to 6.6), p = 0.0009
- Mucosal healing at Week 6 was achieved by 92 (40.9%) subjects in the vedolizumab group and 37 (24.8%) in the placebo, RR (95% CI) 1.6 (1.2 to 2.3), p = 0.0012

For the maintenance phase, for the secondary efficacy outcome measures:

- The proportion of subjects with durable clinical response was 69 (56.6%) subjects in the vedolizumab 8 weekly group (p <0.0001 compared to placebo), 65 (52.0%) in the 4 weekly (p <0.0001) and 30 (23.8%) in the placebo
- The proportion of subjects with mucosal healing at Week 52 was 63 (51.6%) subjects in the vedolizumab 8 weekly group (p <0.0001 compared to placebo), 70 (56.0%) in the 4 weekly (p <0.0001) and 25 (19.8%) in the placebo
- The proportion of subjects with durable mucosal healing was 52 (42.6%) subjects in the vedolizumab 8 weekly group (p <0.0001 compared to placebo), 54 (43.2%) in the 4 weekly (p <0.0001) and 22 (17.5%) in the placebo
- The proportion of subjects with durable clinical remission was 30 (24.0%) subjects in the vedolizumab 8 weekly group (p = 0.0079 compared to placebo), 25 (20.0%) in the 4 weekly (p = 0.0009) and 11 (8.7%) in the placebo[10]
- The proportion of subjects using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52 was 33 (45.2%) subjects in the vedolizumab 8 weekly group (p = 0.0120 compared to placebo), 22 (31.4%) in the 4 weekly (p <0.0001) and 10 (13.9%) in the placebo[11]

For the maintenance phase, for the exploratory efficacy outcome measures:

- Time to disease worsening was similar for both vedolizumab groups, which were significantly better than placebo
- The mean (SE) change in oral corticosteroid use was -9.5 (1.46) mg/day for vedolizumab 8 weekly, -11.6 (1.33) mg/day for 4 weekly and -4.6 (1.49) mg/day for placebo. The adjusted

[10] Erratum: correct values are: 30 (24.0%) subjects in the vedolizumab every 4 weeks group (p = 0.0009 compared to placebo), 25 (20.5%) in the vedolizumab every 8 weeks group (p = 0.0079) and 11 (8.7%) in the placebo
[11] Erratum: correct values are: 33 (45.2%) subjects in the vedolizumab 4 weekly group (p < 0.0001 compared to placebo), 22 (31.4%) in the 8 weekly group (p = 0.0120) and 10 (13.9%) in the placebo group

mean (95% CI) difference compared with placebo was Mean (SE) -4.7 (-7.9 to -1.4) mg/day for vedolizumab 8 weekly and -7.1 (-10.3 to -3.8) mg/day for 4 weekly

- At Week 52 faecal calprotectin ≤250 µg/g was reported for 56 (75%) subjects in the vedolizumab 8 weekly group, 52 (68%) in the 4 weekly and 22 (50%) in the placebo
- The proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 90 days was greatest for the vedolizumab 4 weekly group: 45.2% for 4 weekly, 30.0% for 8 weekly and 13.9% for placebo
- The proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 180 days was greatest for the vedolizumab 4 weekly group: 42.5% for 4 weekly, 28.6% for 8 weekly and 11.1% for placebo
- When comparing key endpoints in the subgroup of patients with previous exposure to TNFα antagonist therapy and in the subgroup of patients defined as having failed TNFα antagonist therapy, there was better response in the vedolizumab treated groups compared with placebo, but for all groups there was better response in those subjects that had not previously failed TNFα antagonist treatments
- For key endpoints in the subgroups of patients on concomitant therapies, responses were better for subjects without concomitant immunomodulator use for all treatment groups, but treatment effect for vedolizumab was preserved. Concomitant corticosteroid use did not affect response.

The following exploratory analyses were not performed

- Serum and stool samples were not analyzed for protein biomarkers associated with UC disease activity
- Genomic deoxyribonucleic acid (DNA) were not analyzed for polymorphisms associated with therapeutic response to vedolizumab

The results for resource utilisation were:

- The proportion of subjects with colectomies, UC related hospitalizations or UC related procedures was four (3.3%) in the vedolizumab 8 weekly group, four (3.2%) in the 4 weekly and ten (7.9%) in the placebo
- The proportion of patients with treatment failure was 28 (23%) in the vedolizumab 8 weekly group, 25 (20%) in the 4 weekly and 71 (56%) in the placebo
- The proportion of patients with disease worsening was 21 (17%) in the vedolizumab 8 weekly group, 19 (15%) in the 4 weekly and 41 (33%) in the placebo
- The proportion of patients who needed rescue medications or surgical intervention for treatment of UC was 13 (11%) in the vedolizumab 8 weekly group, 11 (9%) in the 4 weekly and 31 (25%) in the placebo
- The proportion of patients with drug-related AEs leading to discontinuation was one (<1%) in the vedolizumab 8 weekly group, two (2%) in the 4 weekly and five (4%) in the placebo

The results for HRQOL were:

- There was an improvement in IBDQ total score from baseline relative to placebo from Week 30 in both vedolizumab groups: mean (95% CI) 21.1 (11.8 to 30.4) for vedolizumab 8 weekly and 21.6 (12.4 to 30.9) for 4 weekly
- There was an improvement in SF-36 physical component score from baseline relative to placebo from at Week 52/LOCF in both vedolizumab groups: mean (95% CI) 3.3 (1.5 to 5.2) for vedolizumab 8 weekly and 2.8 (1.0 to 4.6) for 4 weekly

- There was an improvement in SF-36 mental component score from baseline relative to placebo from at Week 52/LOCF in both vedolizumab groups: mean (95% CI) 4.7 (2.3 to 7.2) for vedolizumab 8 weekly and 4.8 (2.3 to 7.2) for 4 weekly
- There was an improvement in EQ-5D score from baseline relative to placebo from at Week 52/LOCF in both vedolizumab groups: mean (95% CI) -0.4 (-0.8 to -0.1) for vedolizumab 8 weekly and -0.5 (-0.8 to -0.1) for 4 weekly
- There was an improvement in EQ-5D VAS from baseline relative to placebo from at Week 52/LOCF in both vedolizumab groups: mean (95% CI) 9.3 (4.6 to 14.0) for vedolizumab 8 weekly and 9.7 (5.0 to 14.4) for 4 weekly

There were too few subjects that were positive for HAHA to make meaningful conclusions about the effect of HAHA on efficacy. Of three subjects in the 8 weekly group none achieved remission at Week 52, and of two in the 4 weekly group one achieved remission at Week 52.

7.2.2. Other efficacy studies

7.2.2.1. Study C13008

In Study C13008 (discussed in Section 7.1.2.1), there was a persisting improvement in mean HBI scores in the CD population, but this analysis would not have accounted for drop-outs due to lack of efficacy.

7.2.3. Analyses performed across trials (pooled analyses and meta-analyses)

There were no pooled results of efficacy for UC.

7.2.4. Evaluator's conclusions on clinical efficacy for Ulcerative Colitis

Efficacy was demonstrated for induction of clinical response and maintenance of remission in subjects with moderate to severe UC. The treatment benefit was clinically significant. At Week 6 there were significantly more subjects in the vedolizumab group achieving clinical response. Clinical response was achieved by 106 (47.1%) subjects in the vedolizumab group and 38 (25.5%) in the placebo, RR (95% CI) 1.8 (1.4 to 2.5), p <0.0001. At Week 52 there were significantly more subjects in both of the vedolizumab groups achieving clinical remission. Clinical remission was achieved by 51 (41.8%) subjects in the vedolizumab group 8 weekly group (RR [95% CI] 2.7 [1.7 to 4.2], p <0.0001), 56 (44.8%) in the 4 weekly (RR [95% CI] 2.8 [1.8 to 4.4], p <0.0001), and 20 (15.9%) in the placebo.

The secondary efficacy outcome measures were supportive of the primary analyses.

Although the primary efficacy outcome measure for Study C13006 was clinical response, the study did show significant benefit for clinical remission (a secondary efficacy outcome measure). In the opinion of the Evaluator, this justifies the inclusion of clinical remission in the indication.

A higher proportion of subjects were able to discontinue oral corticosteroids with vedolizumab. This was significantly greater than placebo for both vedolizumab regimens but there was a greater, though not statistically significant, proportion of subjects able to discontinue oral corticosteroids in the 4 weekly regimen than the 8 weekly. The proportion of subjects using oral corticosteroids at baseline (Week 0) who discontinued corticosteroids and were in clinical remission at Week 52 was 33 (45.2%) subjects in the vedolizumab 4 weekly group (p < 0.0001 compared to placebo), 22 (31.4%) in the 8 weekly (p = 0.0120) and 10 (13.9%) in the placebo. The mean (SE) change in oral corticosteroid use was -9.5 (1.46) mg/day for vedolizumab 8 weekly, -11.6 (1.33) mg/day for 4 weekly and -4.6 (1.49) mg/day for placebo. The adjusted mean (95% CI) difference compared with placebo was Mean (SE) -4.7 (-7.9 to -1.4) mg/day for vedolizumab 8 weekly and -7.1 (-10.3 to -3.8) mg/day for 4 weekly. The proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 180 days was

greatest for the vedolizumab 4 weekly group: 42.5% for 4 weekly, 28.6% for 8 weekly and 11.1% for placebo.

When comparing key endpoints in the subgroup of patients with previous exposure to TNFα antagonist therapy and in the subgroup of patients defined as having failed TNFα antagonist therapy, there was better response in the vedolizumab treated groups compared with placebo, but for all groups there was better response in those subjects that had not previously failed TNFα antagonist treatments. However, efficacy was still demonstrated in the subgroup of patients that had failed previous TNF-α antagonist treatment, therefore vedolizumab treatment is justified in this subgroup.

For key endpoints in the subgroups of patients on concomitant therapies, responses were better for subjects without concomitant immunomodulator use for all treatment groups, but treatment effect for vedolizumab was preserved. Concomitant corticosteroid use did not affect response.

The results supported decreased resource utilisation and improved quality of life with both vedolizumab regimens.

There was little difference in efficacy between the 4 weekly administration regimen for maintenance and the 8 weekly regimen. Hence the recommendation to increase dosing frequency from 8 weekly to 4 weekly in patients who do not respond requires further justification.

The choice of a 14 week time period from initiation of treatment to determine response, and therefore initiation of maintenance treatment, does make sense given the proposed dosing regimen. Were there a 10 week assessment, patients would be making an additional visit to their health provider that would not influence the likelihood of ongoing treatment.

There were too few subjects that were positive for HAHA to make meaningful conclusions about the effect of HAHA on efficacy.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs)
- AEs of particular interest, including infections, gastrointestinal, neurological and infusion related were assessed.
- Laboratory tests, including HAHA

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

Other studies evaluable for safety only

Study C13004: Phase II open-label safety study of MLN0002 administered every 8 weeks. The study enrolled subjects continuing from Study C13002, and also treatment naïve subjects with UC or CD. The study was conducted at 14 centres in Canada and Russia from December 2007 to March 2010. The study enrolled 72 subjects: 53 with UC, 19 with CD. There were 38 subjects enrolled from Study C13002. There were 29 (40%) males, 43 (60%) females and the age range was 19 to 74 years.

Clinical Pharmacology Studies

The 14 clinical pharmacology studies collected data on AEs and tolerability.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.3. Patient exposure

In total, the dossier presented safety experience in 3326 subjects (including 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects) who received at least one dose of vedolizumab, of whom 903 patients with either UC or CD received ≥ 24 infusions with 4 weeks of follow-up, and 415 received ≥ 36 infusions with 4 weeks of follow-up. Exposure by study is summarized in Table 4.

Table 4: Summary of Studies (as presented in RMP Part II Section III)

Study (formulation (a))	Phase	Number Dosed	
		Placebo	Vedolizumab
Healthy Subjects			
L297-007 (Process A)	1	5	14
C13001 (Process B)	1	10	39
C13005 (Process B)	1	0	26
C13009 (Process B and C)	1	25	62
C13010 (Process C)	1	0	42
C13012 (Process C)	1	0	14
Ulcerative Colitis			
L297-005 (Process A)	1b/2a	5	9
L297-006 (Process A)	1b/2a	8	21
M200-021 (Process A)	1/2	6	24
M200-022 (Process A)	2	63	118
C13002 (Process B)	2	9	37
C13006 (Process C)	3	149	746
Crohn's Disease			
L299-016 (Process A)	2	58	127
C13007 (Process C)	3	148	967
C13011 (Process C)	3	207	209
Ulcerative Colitis and Crohn's Disease			
C13004 (Process B)	2	0	53/19[b]
C13008 (Process C)	3	0	704/1118[c]

(a) Process A is a solution for infusion; Process B is a powder for solution for infusion; Process C is a lyophilized formulation used for infusion or for injection.

(b) Of 72 enrolled patients, 53 had ulcerative colitis and 19 had Crohn's disease.

(c) Of 1822 enrolled patients, 704 had ulcerative colitis and 1118 had Crohn's disease. One Patient, who had been previously exposed to vedolizumab in Study M200-022, was granted a waiver to participate in Study C13008. Data for this patient are not included.

In the Phase 3 studies of vedolizumab there were 746 subjects with UC, with 368 subjects treated for up to 12 months; and 1176 with CD, with 421 subjects treated for up to 12 months. There were 25 subjects aged >65 years with UC and 19 with CD.

There were 2368 subjects in all the studies treated with the 300 mg dose level.

Exposure in studies conducted in subjects with CD or UC is summarised below:

- In Study L297-006 there were 21 subjects with UC exposed to a single treatment of LDP-02, five each to 0.15 mg/kg SC, 0.15 mg/kg IV. 0.5 mg/kg IV and six to 2.0 mg/kg IV.
- In Study M200-021 there were 12 subjects exposed to 0.5 mg LDP-02 IV, 11 for two doses, and 12 to 2.0 mg/kg, all to two doses.
- In Study C13002 there were twelve subjects exposed to 2.0 mg/kg, 14 to 6.0 mg/kg, and eleven to 10.0 mg/kg for up to four doses.
- In Study CPH-001 there were three Japanese subjects exposed to three doses of 150 mg and six to three doses of 300 mg.
- In Study L299-016 there were 62 subjects treated with 0.5 mg/kg, 55 (89%) of whom received two doses, and 65 received 2.0 mg/kg, 55 (85%) of whom received two doses.
- In Study M200-022 there were 58 subjects exposed to LDP-02 0.5 mg/kg, with 50 (86%) receiving two doses, and 60 exposed to 2.0 mg/kg, with 53 (88%) exposed to two doses.
- In Study C13007, during the induction phase there were there were 967 subjects exposed to vedolizumab 300 mg IV, with 941 (97%) exposed to two doses. During the maintenance phase there were 814 subjects exposed to vedolizumab 300 mg IV, with 495 exposed to six or more doses and 312 exposed to 14 or more.
- In Study C13011, there were 209 subjects exposed to vedolizumab 300 mg by IV infusion over 30 minutes, with 200 subjects exposed to three doses.
- In Study C13006, in the induction phase there were 746 subjects exposed to vedolizumab 300 mg IV with 732 subjects exposed to two doses. In the maintenance phase there were 620 subjects exposed to vedolizumab: 122 to 8 weekly and 498 to 4 weekly. There were 287 subjects exposed to ≥14 doses.
- In Study C13004, there were 72 subjects exposed to MLN0002 in the dose range 2 mg/kg to 10 mg/kg administered IV every 8 weeks, with 53 subjects exposed for ≥18 months.
- In Study C13008 there were 2243 subjects treated with vedolizumab 300 mg IV, 1349 subjects with CD and 894 with UC. There were 1350 subjects treated for ≥12 months: 802 with CD and 548 with UC. There were 835 subjects treated for ≥24 months: 425 with CD and 410 with UC.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

In Study C13007 during the 6 week induction phase, TEAEs were reported in 550 (57%) of the subjects treated with vedolizumab and 88 (59%) of the placebo group. The pattern of TEAEs was similar for the treatment groups. During the 52 week maintenance phase, TEAEs were reported in 706 (87%) subjects in the vedolizumab groups and 246 (82%) in the placebo. The pattern of TEAEs was similar for the different treatment groups.

In Study C13011 TEAEs were reported in 117 (56%) subjects in the vedolizumab group and 124 (60%) in the placebo. There were fewer TEAEs of CD in the vedolizumab group, but otherwise the pattern of TEAEs was similar for the two treatment groups.

In Study C13006 in the induction phase TEAEs were reported in 337 (45%) subjects in the vedolizumab group and 69 (46%) in the placebo. The pattern of TEAEs was similar for the two

treatments. In the maintenance phase, in the randomized groups, there were 100 (83%) subjects with TEAEs in the vedolizumab 8 weekly group, 101 (81%) in the 4 weekly and 106 (84%) in the placebo. Overall, TEAEs were reported in 497 (80%) subjects treated with vedolizumab and 220 (80%) with placebo.

8.4.1.2. Other studies

In Study L297-006 TEAEs were reported in five (100%) subjects in the 0.15 mg/kg SC group, and four (80%) in the 0.15 mg/kg IV, three (60%) in the 0.5 mg/kg, five (81%) in the 2.0 mg/kg and five (63%) in the placebo. The commonest TEAEs in the active groups were: abdominal pain in six (29%) subjects, nausea in five (24%), vomiting in five (24%) aggravation of UC in four (19%) and fever in four (19%).

In Study M200-021 TEAEs were reported in ten (83%) subjects in the 0.5 mg/kg group, nine (75%) in the 2.0 mg/kg and five (83%) in the placebo. Fatigue and arthralgia were more common in the LDP-02 treated groups.

In Study C13002, TEAEs were reported in nine (75%) subjects in the 2.0 mg/kg group, nine (64%) in the 6.0 mg.kg, six (55%) in the 10.0 mg/kg group and seven (78%) in the placebo. Headache was the most commonly reported TEAE and there were no apparent dose-effects on TEAEs.

In Study CPH-001 there were 35 TEAEs reported in nine (100%) subjects. The commonest TEAE was nasopharyngitis, reported in four subjects in the 300 mg group.

In Study L299-016 TEAEs were reported in 58 (94%) subjects in the 0.5 mg/kg group, 59 (91%) in the 2.0 mg/kg and 50 (86%) in the placebo. The commonest TEAEs were headache, aggravation of CD, nausea, fatigue, abdominal pain, nasopharyngitis and pyrexia.

In Study M200-022 TEAEs were reported in 55 (95%) subjects in the 0.5 mg/kg group, 54 (90%) in the 2.0 mg/kg group and 57 (90%) in the placebo. The most commonly reported TEAEs were aggravation of UC, nausea, headache, frequent bowel movements, fatigue and nasopharyngitis.

In Study C13004 TEAEs were reported in 56 (78%) subjects. The most commonly reported TEAEs were nasopharyngitis (17% subjects) and headache (13%).

In Study C13008 TEAEs were reported in 1228 (91%) subjects in the CD population and 772 (86%) in the UC. The commonest TEAEs were: nasopharyngitis, headache, arthralgia, Crohn's Disease, abdominal pain, URTI, nausea and pyrexia.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

In Study C13007 during the induction phase, treatment related TEAEs were reported in 216 (22%) of the subjects treated with vedolizumab and 31 (21%) of the placebo group. The pattern of treatment related TEAEs was similar for the three treatment groups (Table 5). During the maintenance phase, treatment related TEAEs were reported in 317 (39%) subjects in the vedolizumab groups and 96 (32%) in the placebo.

Table 5: Treatment Emergent Drug Related Adverse Events Occurring in More Than 1% of Vedolizumab Patients by Preferred Term During Induction Phase Safety Population (Study C13007)

Preferred Term n (%)	PLA N=148	VDZ N=220	Total N=368
Headache	4 (3)	9 (4)	13 (4)
Nausea	7 (5)	5 (2)	12 (3)
Arthralgia	2 (1)	5 (2)	7 (2)
Fatigue	2 (1)	5 (2)	7 (2)
Dizziness	1 (<1)	3 (1)	4 (1)
Nasopharyngitis	1 (<1)	3 (1)	4 (1)
Abdominal pain upper	0	3 (1)	3 (<1)
Cough	0	3 (1)	3 (<1)
Pyrexia	0	3 (1)	3 (<1)
Upper respiratory tract infection	0	3 (1)	3 (<1)

In Study C13011 treatment related TEAEs were reported in 34 (16%) subjects in the vedolizumab group and 34 (16%) in the placebo. Treatment related TEAEs that occurred in >1% of vedolizumab subjects were upper respiratory tract infection (2%), headache (2%), and nausea (1%).

In Study C13006 in the induction phase treatment related TEAEs were reported in 137 (18%) subjects in the vedolizumab group and 25 (17%) in the placebo. In the maintenance phase, in the randomized groups, there were 30% subjects with TEAEs in the vedolizumab 8 weekly group, 37 (30%) in the 4 weekly and 40 (32%) in the placebo. Overall, treatment related TEAEs were reported in 200 (32%) subjects treated with vedolizumab and 78 (28%) with placebo.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In Study C13007 during the induction phase, there was one death in the vedolizumab group (myocarditis) and none in the placebo. SAEs were reported in 72 (7%) of the subjects treated with vedolizumab and nine (6%) of the placebo group. There was no apparent pattern to the SAEs. During the maintenance phase there were four deaths in the vedolizumab group (CD/sepsis, septic shock, intentional overdose, cardiorespiratory arrest) and one in the placebo (bronchopneumonia). During the maintenance phase SAEs were reported in 199 (24%) subjects in the vedolizumab group and 46 (15%) in the placebo. Infections and infestations were more common SAEs in the vedolizumab group.

In Study C13011 there were no deaths. SAEs were reported in 13 (6%) subjects in the vedolizumab group and 16 (8%) in the placebo. There were more SAEs of CD in the placebo group.

In Study C13006 in the induction phase there was one death in the open-label vedolizumab group (acute cardiac death). SAEs were reported in 25 (3%) subjects in the vedolizumab group and ten (7%) in the placebo. There was no apparent pattern to the SAEs. In the maintenance phase there was one death in the group of non-responders treated with vedolizumab (colon cancer). There were ten (8%) subjects with SAEs in the vedolizumab 8 weekly group, eleven (9%) in the 4 weekly and 20 (16%) in the placebo. Overall, SAEs were reported in 77 (12%) subjects treated with vedolizumab and 37 (13%)[12] with placebo.

[12] Erratum: correct value for the placebo group is 17 (11%)

8.4.3.2. Other studies

In Study L297-006 there were no deaths. SAEs were reported in two (40%) subjects in the 0.15 mg/kg SC group, two (40%) in the 0.15 mg/kg IV, three (60%) in the 2.0 mg/kg and two (25%) in the placebo.

In Study M200-021 there were no deaths. SAEs were reported in one (8%) subjects in the 0.5 mg/kg group, one (8%) in the 2.0 mg/kg and three (50%) in the placebo.

In Study C13002 there were no deaths reported. SAEs were reported in one (7%) subjects in the 6.0 mg/kg group (gastroduodenitis) and one (9%) in the 10.0 mg/kg group (spinal compression fractures).

In Study CPH-001 there were no deaths reported. SAEs were reported in two subjects: colon dysplasia and ileus.

In Study L299-016 there were no deaths. SAEs were reported in six (10%) subjects in the 0.5 mg/kg group, 10 (15%) in the 2.0 mg/kg group and 10 (17%) in the placebo. There was no apparent pattern to the SAEs.

In Study M200-022 there were no deaths. SAEs were reported in six (10%) subjects in the 0.5 mg/kg group, 12 (20%) in the 2.0 mg/kg and six (10%) in the placebo. There was no apparent pattern to the SAEs.

In Study C13004 there were no deaths. SAEs were reported in ten (14%) subjects. The most common group of SAEs was infections (four subjects).

In Study C13008 there were four (<1%) deaths in the CD population (traumatic intracranial haemorrhage, hepatic neoplasm malignant, completed suicide, sepsis) and three (<1%) in the UC (respiratory failure, cerebrovascular accident, pulmonary embolism). SAEs were reported in 389 (29%) subjects in the CD population and 164 (18%) in the UC. The SAEs were primarily related to the underlying disease. There were 12 subjects with malignancies.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In Study C13007 during the induction phase, DAEs occurred in 33 (3%) of the subjects treated with vedolizumab and nine (59%[13]) in the placebo group. Infections and infestations were more common DAEs in the vedolizumab group. During the maintenance phase, DAE occurred for 91 (11%) subjects in the vedolizumab groups and 29 (10%) in the placebo. A greater proportion of subjects in the vedolizumab groups discontinued because of infections or infestations.

In Study C13011 DAEs was reported for four (2%) subjects in the vedolizumab group and eight (4%) in the placebo. DAE of CD was more common in the placebo group.

In Study C13006 in the induction phase DAEs were reported in eight (1%) subjects in the vedolizumab group and four (3%) in the placebo. There was no apparent pattern to the DAEs. In the maintenance phase, in the randomized groups, there were six (5%) subjects with DAE in the vedolizumab 4 weekly group, seven (6%) in the 8 weekly and 15 (12%) in the placebo. Overall, DAEs were reported in 36 (6%) subjects treated with vedolizumab and 31 (11%) with placebo.

8.4.4.2. Other studies

- In Study L297-006 and Study C13002 there were no DAEs.

[13] Erratum: correct value is 6%

- In Study M200-021 DAE was reported for two subjects in the 0.5 mg/kg group and one in the placebo. In all cases the AE leading to discontinuation was aggravation of UC.
- In Study CPH-001 there were no DAEs.
- In Study L299-016 DAE occurred for one subject in the 0.5 mg/kg group and one in the 2.0 mg/kg; both due to aggravation of CD.
- In Study M200-022 DAE was reported for two subjects in the 0.5 mg/kg group, three in the 2.0 mg/kg and one in the placebo. For all but one subject in the 0.5 mg/kg group the reason for discontinuation was aggravation of UC.
- In Study C13004 DAEs were reported in seven (10%) subjects.
- In Study C13008 DAEs were reported in 148 (11%) subjects in the CD population and 80 (9%) in the UC. The AEs leading to withdrawal were primarily related to the underlying condition.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

In Study C13007 during the induction phase, there were seven (<1%) subjects treated with vedolizumab with elevated ALT >3xULN and one (<1%) in the placebo, and eight (<1%) subjects treated with vedolizumab with elevated AST >3xULN and none in the placebo. In Study C13007 during the maintenance phase, there were eleven (1%) subjects treated with vedolizumab with elevated ALT >3xULN and six (2%) in the placebo. There were ten (1%) subjects treated with vedolizumab with elevated AST >3xULN and four (1%) in the placebo.

In Study C13011 ALT >3xULN was reported in two (<1%) subjects in the vedolizumab group and one (<1%) in the placebo; and AST >3xULN was reported only in one (<1%) subject in the vedolizumab group.

In Study C13006 in the induction phase elevation of ALT >3xULN was reported for four (<1%) subjects treated with vedolizumab and none treated with placebo; and elevation of AST >3xULN was reported for two (<1%) subjects treated with vedolizumab and none treated with placebo. In the maintenance phase elevation of ALT >3xULN was reported for eleven (2%) subjects treated with vedolizumab and three (1%) treated with placebo; and elevation of AST >3xULN was reported for six (<1%) subjects treated with vedolizumab and three (1%) treated with placebo.

8.5.1.2. Other studies

- In Study C13002 one subject in the 10.0 mg group had elevated transaminases that resolved during the study.
- In Study L299-016 abnormalities in liver function tests were reported in one subject in the 0.5 mg/kg group, two in the 2.0 mg/kg and one in the placebo.
- In Study M200-022 one subject in the 0.5 mg/kg group, two subjects in the 2.0 mg/kg group and one in the placebo had elevations on transaminases.
- In Study C13004 one subject had elevated ALT and one had elevated AST.
- In Study C13008 an elevation of ALT >3xULN was reported for 56 (2.5%) subjects and AST >3xULN for 44 (2.0%).

8.5.2. Kidney function

There was no indication of impairment of renal function with vedolizumab.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

In Study C13007 during the induction phase, there were eight (<1%) subjects treated with vedolizumab with elevated amylase >2xULN and two (1%) in the placebo, and ten (1%) subjects treated with vedolizumab with elevated lipase >2xULN and none in the placebo. In Study C13007 during the maintenance phase, there were 13 (2%) subjects treated with vedolizumab with elevated amylase >2xULN and five (2%) in the placebo. There were 16 (2%) subjects treated with vedolizumab with elevated lipase >2xULN and four (1%) in the placebo.

In Study C13011 amylase >2xULN was reported in two (<1%) subjects in the vedolizumab group; and lipase >2xULN was reported two (<1%) subjects in the vedolizumab group and in one (<1%) subject in the placebo group.

In Study C13006 in the induction phase elevation of amylase >2xULN was reported for five (<1%) subjects treated with vedolizumab and three (2%) treated with placebo; and elevation of lipase >2xULN was reported for four (<1%) subjects treated with vedolizumab and two (1%) treated with placebo. In the maintenance phase elevation of amylase >2xULN was reported for seven (1%) subjects treated with vedolizumab and six (2%) treated with placebo; and elevation of lipase >2xULN was reported for twelve (2%) subjects treated with vedolizumab and seven (3%) treated with placebo.

8.5.3.2. Other studies

In Study L297-006 one subject in the 0.15 mg/kg SC group had elevated serum amylase and was diagnosed with pancreatitis.

In Study C13008 an elevation of amylase >2xULN was reported for 34 (2%) subjects and lipase >2xULN for 44 (2.0%).

8.5.4. Haematology

8.5.4.1. Pivotal studies

In Study C13007 during the induction phase, abnormal haematology values occurred at a similar rate for vedolizumab and placebo.

In Study C13006 in the induction phase haematological abnormalities were uncommon and reported at similar rates with vedolizumab and placebo. In the maintenance phase haematological abnormalities were also uncommon and reported at similar rates with vedolizumab and placebo.

8.5.4.2. Other studies

In Study L297-006 four subjects were reported with anaemia: one in the 0.15 mg/kg SC group, two in the 0.15 mg/kg IV and one in the placebo.

In Study C13002 two subjects, one in the 6.0 mg/kg group and one in the placebo, were reported with anaemia.

8.5.5. Immunogenicity

8.5.5.1. Pivotal studies

In Study C13007 during the induction phase, HAHA were detected in three subjects in the vedolizumab group and three in the placebo. During the maintenance phase 33 (4%) of the vedolizumab group were positive for HAHA at some stage during the study.

In Study C13011 HAHA was reported in three (1%) subjects in the vedolizumab group and three (1%) in the placebo.

In Study C13006 at the end of the induction phase six (3%) vedolizumab subjects and three (2%) placebo were positive for HAHA. In the maintenance phase 23 (4%) subjects in the vedolizumab group were positive for HAHA and 17 (3%) had neutralizing antibodies.

8.5.5.2. Other studies

- In Study M200-021 a post-baseline HAHA titre ≥5 was reported for seven (70%) subjects in the 0.5 mg/kg group, five (42%) in the 2.0 mg/kg group and one (20%) in the placebo.
- In Study CPH-001 one subject in the 300 mg group developed HAHA.
- In Study L299-016 in subjects with CD treated with LDP-02, HAHA titre ≥5 was reported for 34 (55%) subjects in the 0.5 mg/kg group, 19 (29%) in the 2.0 mg/kg and three (5%) in the placebo. HAHA titre >125 was reported for 34% subjects in the 0.5 mg/kg group, eight (12%) in the 2.0 mg/kg and none in the placebo.
- In Study M200-022 for subjects treated with LDP-02, HAHA titre ≥5 was recorded for 35 (66%) subjects in the 0.5 mg/kg group, 13 (24%) in the 2.0 mg/kg and three (5%) in the placebo. HAHA titre >125 was recorded for 20 (38%) subjects in the 0.5 mg/kg group, six (11%) in the 2.0 mg/kg and none in the placebo.
- In Study C13004 three (4%) subjects were reported with HAHA, and one subject had neutralizing antibodies.

8.5.6. Electrocardiograph

8.5.6.1. Pivotal studies

There were no issue of concern regarding ECGs in the pivotal studies.

8.5.6.2. Other studies

In Study C13004 one subject was reported with QT prolongation..

8.5.7. Vital signs

There were no issues of concern with regard to vital signs identified in the development program.

8.6. Post-marketing experience

8.6.1. Post-marketing data

No post-marketing data were included in the submission.

The integrated summary of safety indicated similar rates for vedolizumab and placebo for the more common TEAEs in a pooled analysis of Study C13006 and Study C13007.

8.6.2. Risk minimisation plan

The Important Identified Risks are:

- Infusion-related reactions (IRRs) and hypersensitivity reactions (HSRs)

The Important Potential Risks are:

- 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)
- Malignancies

The Important Missing Information is:

- 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
- Patients with prior exposure to natalizumab, rituximab or use with concurrent biologic immunosuppressants

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Infection related adverse events

In Study C13007 during the induction phase, infection related TEAEs occurred in 161 (17%) of the subjects treated with vedolizumab and 26 (18%) in the placebo group. The pattern of infection related TEAEs was similar for the three treatment groups. During the maintenance phase, infection related TEAEs were reported in 359 (44%) subjects in the vedolizumab group and 121 (40%) in the placebo. There was one subject in the 8 weekly group and two in the 4 weekly with *Clostridium difficile* colitis.

In Study C13011 infection and infestation TEAEs were reported in 39 (19%) subjects in the vedolizumab group and 36 (17%) in the placebo. There were seven (3%) subjects with urinary tract infection in the vedolizumab group and none in the placebo.

In Study C13006 in the induction phase infection and infestation TEAEs were reported in 102 (14%) subjects in the vedolizumab group and 22 (15%) in the placebo. The pattern of infection and infestation TEAEs was similar for the two treatment s. In the maintenance phase infection and infestation TEAEs were reported in 263 (42%) subjects in the vedolizumab group and 98 (36%) in the placebo, with the increased rate in the vedolizumab group appearing to be related to an increased rate of URTI and influenza.

8.7.2. Gastrointestinal system adverse events

In Study C13007 during the induction phase, gastrointestinal related TEAEs occurred in 232 (24%) of the subjects treated with vedolizumab and 34 (23%) in the placebo group. During the maintenance phase, gastrointestinal related TEAEs occurred in 424 (52%) of the subjects treated with vedolizumab and 161 (53%) in the placebo group.

In Study C13011 gastrointestinal TEAEs were reported in 37 (18%) subjects in the vedolizumab group and 49 (24%) in the placebo.

In Study C13006 in the induction phase gastrointestinal TEAEs were reported in 74 (10%) subjects in the vedolizumab group and 28 (19%) in the placebo. In the maintenance phase gastrointestinal TEAEs were reported in 231 (37%) subjects in the vedolizumab group and 105 (38%) in the placebo.

8.7.3. Nervous system adverse events

In Study C13007 during the induction phase, nervous system disorders occurred in 113 (12%) of the subjects treated with vedolizumab and 14 (9%) in the placebo group. Cognitive disorders appeared to be more common in the vedolizumab group. There were no cases of PML and no positive results for JCV DNA. During the maintenance phase, nervous system disorders occurred in 180 (22%) of the subjects treated with vedolizumab and 75 (25%) in the placebo

group. During the maintenance phase, 17 (2%) subjects in the vedolizumab group and five (3%) in the placebo had one or more positive PML check list items, but no cases of PML were identified. JCV DNA was identified in four (<1%) subjects in the vedolizumab group and one (<1%) in the placebo.

In Study C13011 nervous system TEAEs were reported in 24 (11%) subjects in the vedolizumab group and 25 (12%) in the placebo. A positive PML checklist was reported for six (3%) subjects in the vedolizumab group and six (3%) in the placebo. No subjects were positive for JCV DNA.

In Study C13006 in the induction phase nervous system TEAEs were reported in 80 (11%) subjects in the vedolizumab group and 11 (7%) in the placebo. At Week 6 two vedolizumab treated subjects were positive for JCV DNA. No cases of PML were reported. In the maintenance phase nervous system TEAEs were reported in 129 (21%) subjects in the vedolizumab group and 51 (19%) in the placebo. In the maintenance phase, a positive subjective PML checklist was reported for 37 (6%) subjects in the vedolizumab group and 18 (7%) in the placebo. No subjects were persistently positive for JCV DNA.

In Study C13004 on subject was positive for JCV DNA. No subject had a positive PML checklist.

In Study C13008 a positive PML checklist was reported for 160 (7%) subjects but no subjects were diagnosed with PML by the Independent Adjudication Committee.

8.7.4. Infusion reactions

In Study C13007 during the induction phase, infusion related reactions occurred in 3% of the subjects treated with vedolizumab and seven (5%) in the placebo group. During the maintenance phase, infusion related reactions occurred in 33 (4%) of the subjects treated with vedolizumab and 14 (5%) in the placebo group.

In Study C13011 infusion related reactions were reported in four (2%) subjects in the vedolizumab group and two in the placebo. In the vedolizumab group there was one report of urticaria and one of generalized rash.

In Study C13006 in the induction phase infusion related TEAEs were reported in 17 (2%) subjects in the vedolizumab group and one (<1%) in the placebo. In the maintenance phase infusion related TEAEs were reported in 28 (5%) subjects in the vedolizumab group and three (1%) in the placebo.

In Study C13004 infusion related reactions were reported in two subjects.

In Study C13008 infusion related TEAEs were reported in 82 (4%) subjects.

8.8. Other safety issues

8.8.1. Safety in special populations

The number of elderly subjects included in the development program was limited.

8.8.2. Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not examined in the development program for vedolizumab, but would not be expected to occur with an antibody, such as vedolizumab.

8.9. Evaluator's overall conclusions on clinical safety

Overall the pattern and frequency of AEs was similar for vedolizumab and placebo. The rate of AEs did not increase with dose, and there did not appear to be any specific AEs that were more common with increasing vedolizumab dose. Treatment related TEAEs also occurred at a similar frequency and pattern with vedolizumab and placebo.

Deaths were uncommon and did not appear to be treatment related. SAEs were reported at a similar rate with vedolizumab and placebo, except for Study C13007 which had an excess of infection related SAEs in the vedolizumab group.

DAE occurred at a similar rate for vedolizumab and placebo. Infections as a reason for DAE were more common in the vedolizumab group, but AEs relating to the underlying condition were more common as reasons for DAE in the placebo group.

There appeared to be a slightly higher proportion of subjects with elevation of ALT and AST in the vedolizumab groups compared to placebo. This may require further analysis. It may represent a higher rate of infectious hepatitis with vedolizumab.

There appeared to be a slightly higher proportion of subjects with elevation of amylase and lipase in the vedolizumab groups compared to placebo. This may require further analysis. It may represent a higher rate of infectious pancreatitis with vedolizumab.

HAHA develop in approximately 4% of subjects treated with vedolizumab over a 52 week period. HAHA appeared to be related to loss of efficacy but not to AEs. HAHA were more common with the earlier versions of MLN0002, but less common with the version (vedolizumab) proposed for marketing.

There was a slightly higher rate of infections in the vedolizumab groups compared to placebo, but the difference was not clinically significant. There was no apparent difference between vedolizumab and placebo in the rate of gastrointestinal AEs. There were similar rates of nervous system disorders with vedolizumab and placebo.

Although no cases of PML were identified during the development program there were insufficient subjects treated for a sufficient duration to determine the risk for PML with vedolizumab.

Infusion related reactions occurred at a higher rate with vedolizumab in the longer term studies. These appear to occur in 5% of subjects over one year.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

9.1.1. Benefits in CD

Efficacy was demonstrated for induction of remission for subjects with moderate to severe CD for the 300 mg dose level of vedolizumab. In Study C13007, at Week 6 there were significantly more subjects in the vedolizumab group achieving clinical remission but not enhanced clinical response. Clinical remission was achieved by 32 (14.5%) subjects in the vedolizumab group and 10 (6.8%) in the placebo, RR (95% CI) 2.1 (1.1 to 4.2), p = 0.0206. Enhanced clinical response was achieved by 69 (31.4%) subjects in the vedolizumab group and 38 (25.7%) in the placebo, RR (95% CI) 1.2 (0.9 to 1.7), p = 0.2322. There was less efficacy in subjects with greater disease severity (CDAI >330).

Efficacy at Week 10 was better demonstrated than for Week 6. This supports the Sponsor's proposed regimen for induction of remission, i.e. 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. In Study C13011, the proportion of subjects in clinical remission at Week 10 was greater for vedolizumab in the TNFα Antagonist Failure ITT Subpopulation and in the Overall ITT Population. For the TNFα Antagonist Failure ITT subpopulation, Clinical remission at Week 10 was reported for 42 (26.6%) subjects in the vedolizumab group and 19 (12.1%) in the placebo, RR (95% CI) 2.2 (1.3 to 3.6), p = 0.0012; and for the Overall ITT population 60 (28.7%) subjects in the vedolizumab group and 27 (13.0%) in the placebo, RR (95% CI) 2.2 (1.4 to 3.3), p <0.0001.

In Study C13007, at Week 6 clinical remission rates were lower for both placebo and vedolizumab in subjects with prior TNFα antagonist failure. In those subjects with intolerance or lack of response to TNFα inhibitors there was a significant benefit for vedolizumab. However, in subjects that had previously lost response to TNFα antagonist treatment, there did not appear to be efficacy for vedolizumab. In Study C13011, in the population of subjects with previous TNFα antagonist treatment failure there was no significant difference in efficacy between vedolizumab and placebo. Hence, in subjects that had initially responded to TNFα antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.

In both Study C13007 and Study C13011, clinical remission rates were higher for vedolizumab in subjects with concomitant corticosteroid treatment. However, clinical remission rates were not affected by concomitant immunomodulator use.

The pooled analysis of efficacy of data from Study L299-016, Study C13007 and Study C13011 indicated a mean (95% CI) difference, vedolizumab-placebo in remission rate of 7.4 (2.6 to 12.2) %, p = 0.0027.

Maintenance of remission was demonstrated for up to 52 weeks. Clinical remission was achieved by 60 (39.0%) subjects in the vedolizumab group 8 weekly group (RR [95% CI] 1.8 [1.3 to 2.6], p = 0.0007), 56 (36.4%) in the 4 weekly (RR [95% CI] 1.7 [1.2 to 2.4], p = 0.0042), and 33 (21.6%) in the placebo.

The secondary efficacy outcome measures were supportive of the primary efficacy outcome measures.

There was little difference in efficacy between the 4 weekly administration regimen for maintenance and the 8 weekly regimen. Hence the recommendation to increase dosing frequency from 8 weekly to 4 weekly in patients who do not respond requires further justification.

The choice of a 14 week time period from initiation of treatment to determine response, and therefore initiation of maintenance treatment, does make sense given the proposed dosing regimen. Were there a 10 week assessment, patients would be making an additional visit to their health provider that would not influence the likelihood of ongoing treatment.

There were too few subjects that were positive for HAHA to make meaningful conclusions about the effect of HAHA on efficacy.

There were no comparator controlled studies conducted in subjects with CD. Hence the studies did not comply with CHMP guidance for first line or single agent therapy, but did comply with guidance for second line and add-on therapy. The clinical endpoints and inclusion criteria did comply with CHMP guidance. Duration of assessment was sufficient for demonstration of maintenance of remission. The inclusion and exclusion criteria for the study populations in the pivotal studies were consistent with the indication sought.

9.1.2. Benefits in UC

Efficacy was demonstrated for induction of clinical response and maintenance of remission in subjects with moderate to severe UC. The treatment benefit was clinically significant. At Week 6 there were significantly more subjects in the vedolizumab group achieving clinical response. Clinical response was achieved by 106 (47.1%) subjects in the vedolizumab group and 38 (25.5%) in the placebo, RR (95% CI) 1.8 (1.4 to 2.5), p <0.0001. At Week 52 there were significantly more subjects in both of the vedolizumab groups achieving clinical remission. Clinical remission was achieved by 51 (41.8%) subjects in the vedolizumab group 8 weekly group (RR [95% CI] 2.7 [1.7 to 4.2], p <0.0001), 56 (44.8%) in the 4 weekly (RR [95% CI] 2.8 [1.8 to 4.4], p <0.0001), and 20 (15.9%) in the placebo.

The secondary efficacy outcome measures were supportive of the primary analyses.

Although the primary efficacy outcome measure for Study C13006 was clinical response, the study did show significant benefit for clinical remission (a secondary efficacy outcome measure). In the opinion of the Evaluator, this justifies the inclusion of clinical remission in the indication.

A higher proportion of subjects were able to discontinue oral corticosteroids with vedolizumab. This was significantly greater than placebo for both vedolizumab regimens, but there was a greater, though not statistically significant, proportion of subjects able to discontinue oral corticosteroids in the 4 weekly regimen than the 8 weekly. The proportion of subjects using oral corticosteroids at baseline (Week 0) who discontinued corticosteroids and were in clinical remission at Week 52 was 33 (45.2%) subjects in the vedolizumab 4 weekly group ($p = 0.0120$ compared to placebo), 22 (31.4%) in the 8 weekly ($p < 0.0001$) and 10 (13.9%) in the placebo. The mean (SE) change in oral corticosteroid use was -9.5 (1.46) mg/day for vedolizumab 8 weekly, -11.6 (1.33) mg/day for 4 weekly and -4.6 (1.49) mg/day for placebo. The adjusted mean (95% CI) difference compared with placebo was Mean (SE) -4.7 (-7.9 to -1.4) mg/day for vedolizumab 8 weekly and -7.1 (-10.3 to -3.8) mg/day for 4 weekly. The proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 180 days was greatest for the vedolizumab 4 weekly group: 42.5% for 4 weekly, 28.6% for 8 weekly and 11.1% for placebo.

When comparing key endpoints in the subgroup of patients with previous exposure to TNFα antagonist therapy and in the subgroup of patients defined as having failed TNFα antagonist therapy, there was better response in the vedolizumab treated groups compared with placebo, but for all groups there was better response in those subjects that had not previously failed TNFα antagonist treatments. However, efficacy was still demonstrated in the subgroup of patients that had failed previous TNF-α antagonist treatment, therefore vedolizumab treatment is justified in this subgroup.

For key endpoints in the subgroups of patients on concomitant therapies, responses were better for subjects without concomitant immunomodulator use for all treatment groups, but treatment effect for vedolizumab was preserved. Concomitant corticosteroid use did not affect response.

The results supported decreased resource utilisation and improved quality of life with both vedolizumab regimens.

There was little difference in efficacy between the 4 weekly administration regimen for maintenance and the 8 weekly regimen. Hence the recommendation to increase dosing frequency from 8 weekly to 4 weekly in patients who do not respond requires further justification.

The choice of a 14 week time period from initiation of treatment to determine response, and therefore initiation of maintenance treatment, does make sense given the proposed dosing regimen. Were there a 10 week assessment, patients would be making an additional visit to their health provider that would not influence the likelihood of ongoing treatment.

There were too few subjects that were positive for HAHA to make meaningful conclusions about the effect of HAHA on efficacy.

There were no comparator controlled studies conducted in subjects with UC. Hence the studies did not comply with CHMP guidance for first line or single agent therapy, but did comply with guidance for second line and add-on therapy. The clinical endpoints and inclusion criteria did comply with CHMP guidance. Duration of assessment was sufficient for demonstration of maintenance of remission. The inclusion and exclusion criteria for the study populations in the pivotal study were consistent with the indication sought.

9.2. First round assessment of risks

Overall the pattern and frequency of AEs was similar for vedolizumab and placebo. The rate of AEs did not increase with dose, and there did not appear to be any specific AEs that were more common with increasing vedolizumab dose. Treatment related TEAEs also occurred at a similar frequency and pattern with vedolizumab and placebo.

Deaths were uncommon and did not appear to be treatment related. SAEs were reported at a similar rate with vedolizumab and placebo, except for Study C13007 which had an excess of infection related SAEs in the vedolizumab group.

DAE occurred at a similar rate for vedolizumab and placebo. Infections as a reason for DAE were more common in the vedolizumab group, but AEs relating to the underlying condition were more common as reasons for DAE in the placebo group.

There appeared to be a slightly higher proportion of subjects with elevation of ALT and AST in the vedolizumab groups compared to placebo. This may require further analysis. It may represent a higher rate of infectious hepatitis with vedolizumab.

There appeared to be a slightly higher proportion of subjects with elevation of amylase and lipase in the vedolizumab groups compared to placebo. This may require further analysis. It may represent a higher rate of infectious pancreatitis with vedolizumab.

HAHA develop in approximately 4% of subjects treated with vedolizumab over a 52 week period. HAHA appeared to be related to loss of efficacy but not to AEs. HAHA were more common with the earlier versions of MLN0002, but less common with the version (vedolizumab) proposed for marketing.

There was a slightly higher rate of infections in the vedolizumab groups compared to placebo, but the difference was not clinically significant. There was no apparent difference between vedolizumab and placebo in the rate of gastrointestinal AEs. There were similar rates of nervous system disorders with vedolizumab and placebo.

Although no cases of PML were identified during the development program there were insufficient subjects treated for a sufficient duration to determine the risk for PML with vedolizumab.

Infusion related reactions occurred at a higher rate with vedolizumab in the longer term studies. These appear to occur in 5% of subjects over one year.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of vedolizumab (ENTYVIO / VEDOLIZUMAB TAKEDA) 300 mg powder for injection, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

The Evaluator is unable to recommend the approval of vedolizumab (ENTYVIO / VEDOLIZUMAB TAKEDA), 300 mg powder for injection, for the following indication:

Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

The reason for this decision is that vedolizumab did not appear to offer benefit for those patients with CD who had initially responded to TNFα antagonist treatment, and subsequently lost response.

However, the Evaluator would have no objection to the approval of vedolizumab (ENTYVIO / VEDOLIZUMAB TAKEDA), 300 mg powder for injection, for the following indication:

> *Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.*
>
> *Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to a conventional therapy or had an inadequate response with, or are intolerant to a tumour necrosis factor-alpha (TNFα) antagonist. In subjects with Crohn's disease who had initially responded to TNFα antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.*

11. Clinical questions

11.1. Pharmacokinetics

Question 1: The numbers of elderly subjects in the PK studies requires clarification.

11.2. Pharmacodynamics

The Evaluator does not have any questions relating to pharmacodynamics.

11.3. Efficacy

The Evaluator does not have any questions relating to efficacy.

11.4. Safety

Question 2: There appeared to be a slightly higher proportion of subjects with elevation of ALT and AST in the vedolizumab groups compared to placebo. This may represent a higher rate of infectious hepatitis with vedolizumab. Can the Sponsor please provide further analysis of these subjects, including a listing of all subjects satisfying the criteria of Hy's Law?

Question 3: There appeared to be a slightly higher proportion of subjects with elevation of amylase and lipase in the vedolizumab groups compared to placebo. This may represent a higher rate of infectious pancreatitis with vedolizumab. Can the Sponsor please provide further analysis of these subjects?

12. Second round evaluation of clinical data submitted in response to questions

Question 1: The numbers of elderly subjects in the PK studies requires clarification.

The Sponsor has responded that there were 1885 subjects aged ≤65 years, 69 subjects aged 65 to 74 years, and 15 aged 75 to 84 years that were included in the PK and PD studies. In the opinion of the Evaluator, as the covariate "Age" appears to have been coded as a continuous covariate in the population PKPD studies, the covariate models would not have been able to

detect a change in clearance, or volumes of distribution, in subjects >65 years. This is because the data from subjects >65 years age is a small proportion of the total data. Had age >65 years been coded as a categorical variable it might have been possible to perform an exploratory analysis of its effect on PK parameters. However, use in the elderly is currently listed as Important Missing Information in the RMP and the absence of this information should not preclude approval of the current application. The Sponsor should be encouraged to include PKPD modelling studies, conducted in the elderly population, in any future application to extend the use of vedolizumab to the elderly population.

Question 2: There appeared to be a slightly higher proportion of subjects with elevation of ALT and AST in the vedolizumab groups compared to placebo. This may represent a higher rate of infectious hepatitis with vedolizumab. Can the Sponsor please provide further analysis of these subjects, including a listing of all subjects satisfying the criteria of Hy's Law?

The Sponsor has based their response on the Subjects in Study C13006 and Study C13007 who only received VDZ in comparison with those who only received placebo. There were 22 (1.5%) subjects who only received VDZ and 3 (1.0%) who only received placebo who had ALT >3xULN; and 16 (1.1%) subjects who only received VDZ and none (0.0%) who only received placebo who had AST >3xULN. None of the subjects with elevated ALT or AST were reported with a liver infection adverse event, a SAE due to liver infection or DAE due to liver infection. In Study C13008, there were 55 (2.5%) subjects with ALT >3xULN and 45 (2.0%) with AST >3xULN. In the full safety population there was one subject with Hepatitis A and one subject with Hepatitis E. There were two subjects who satisfied the criteria of Hy's Law:

- One [redacted] female subject with ALT 952 U/L, total bilirubin 48 µmol/L and ALP of 158 U/L who was diagnosed with hepatitis of unclear origin. Her condition improved even though the vedolizumab was continued.
- One [redacted] female subject with ALT up to 1593 IU/L, AST up to 932 IU/L and bilirubin up to 13.85 mg/dL. She was diagnosed with autoimmune hepatitis because of an elevated ANA, and later with SLE. She improved with topical steroids.

Overall there were 22 subjects with hepatic parenchymal events while being treated with VDZ, compared with none during placebo treatment. Four of these subjects had hepatic parenchymal SAEs and three had hepatic parenchymal AEs that led to discontinuation. There were 16 subjects that were reported with hepatocellular damage or hepatitis, giving an event rate of 0.334 per 100 patient-years, and the most common of these events were: hepatic steatosis (9 subjects), cytolytic hepatitis (3 subjects) and hepatitis (2 subjects).

In the opinion of the Evaluator these data confirm that there is a higher rate of elevation of transaminases and of hepatic parenchymal damage in subjects treated with VDZ compared to placebo. Most of these events are not serious and there is no clear indication of the aetiology. The Evaluator recommends including hepatic adverse events in the Safety Specification as an Important Potential Risk. The Evaluator also notes that the Sponsor has stated: "Takeda plans to continue monitoring for evidence of liver dysfunction as part of the standard post-marketing safety surveillance."

Question 3: There appeared to be a slightly higher proportion of subjects with elevation of amylase and lipase in the vedolizumab groups compared to placebo. This may represent a higher rate of infectious pancreatitis with vedolizumab. Can the Sponsor please provide further analysis of these subjects?

The Sponsor has provided additional data with regard subjects with elevate amylase and lipase. In Study C13006 and Study C13007, in the population of subject only treated with VDZ there were 20 (1.4%) subjects with amylase >2xULN and 28 (2.0%) with lipase >2xULN, compared to in the placebo treated only group 8 (2.7%) and 8 (2.7%) respectively. In Study C13008 there

were 34 (1.5%) subjects with amylase >2xULN and 44 (2.0%) with lipase >2xULN. Acute pancreatitis was reported for ten subjects treated with VDZ and one with placebo, giving incidence rate for acute pancreatitis of 0.21 per 100 patient years and 0.47 per 100 patient years respectively.

In the opinion of the Evaluator these data are reassuring and do not indicate an increased risk for pancreatitis following treatment with VDZ, in comparison with placebo. The Evaluator also notes that the Sponsor has stated: "Takeda plans to continue monitoring pancreatitis as part of the standard post-marketing safety surveillance."

Evaluator's Question/comment: Vedolizumab did not appear to offer benefit for those patients with CD who had initially responded to TNFα antagonist treatment, and subsequently lost response.

The Sponsor has responded with the following arguments:

- It should be noted that Studies C13007 and C13011 were not powered to establish efficacy in any specific subgroup and randomization was not stratified by type of prior TNFα antagonist failure. Therefore, small sample sizes for patients with each type of failure to TNFα antagonist treatment limits interpretation.
- In the Induction Phase of Study C13007, numerically higher rates were observed in both primary endpoints including clinical remission at Week 6 and enhanced clinical response at Week 6 in patients who have had loss of response to TNFα and consistent treatment benefit was observed in all groups administered vedolizumab vs placebo in both Study C13007 and Study C13011.

The Sponsor provided tabulations of data from Study C13011. In the subgroup of subjects who had lost response to TNFα inhibitors, there were the following results:

- At Week 6 clinical remission was reported in 15 (15.0%) subjects in the VDZ population and 13 (12.6%) of the placebo, difference (95% CI) VDZ-placebo in remission rates 2.4 (-7.0 to 11.9) %
- At Week 6 enhanced clinical response was reported in 34 (34.0%) subjects in the VDZ population and 22 (21.4%) of the placebo, difference (95% CI) VDZ-placebo in remission rates 12.6 (0.4 to 24.8) %.
- At Week 10 clinical remission was reported in 25 (25.0%) subjects in the VDZ population and 14 (13.6%) of the placebo, difference (95% CI) VDZ-placebo in remission rates 11.4 (0.6 to 22.2) %
- At Week 10 sustained clinical remission was reported in 11 (11.0%) subjects in the VDZ population and 10 (9.7%) of the placebo, difference (95% CI) VDZ-placebo in remission rates 1.3 (-7.1 to 9.7) %.

The Evaluator notes that in Study C13011, the primary efficacy endpoint (clinical remission in the population of subjects with previous TNFα antagonist treatment failure) there was no significant difference in efficacy between vedolizumab and placebo. There were 24 (15.2%) subjects in the vedolizumab group and 19 (12.1%) in the placebo who achieved clinical remission: RR (95% CI) 1.2 (0.7 to 2.2), p = 0.4332. Hence overall this study did not demonstrate efficacy, and therefore could not be taken to demonstrate efficacy in a subpopulation.

The Sponsor provided tabulations of data from Study C13007:

- In the induction phase, at Week 6 clinical remission was reported in 8 (13.3%) subjects in the VDZ population and 0 (0.0%) of the placebo, difference (95% CI) VDZ-placebo in remission rates 13.3 (-7.1 to 33.0) %

- In the induction phase, at Week 6 enhanced clinical response was reported in 16 (26.7%) subjects in the VDZ population and 7 (18.4%) in the placebo, difference (95% CI) VDZ-placebo in remission rates 8.2 (-8.4 to 24.9) %.

The Evaluator notes that the numbers of subjects and the results presented in the Section 31 Response are different to those reported in the Clinical Study Report for Study C13007. This is confusing but appears to be because the Section 31 response is based upon whether the subject had been reported as having loss of response at all, whereas the Clinical Study Report based the post-hoc analysis on "worst failure type". The Evaluator places more emphasis on the analysis presented in the Clinical Study Report, in the belief that this analysis was originally considered more significant by the Sponsor when the protocol was written. The Evaluator interprets these results as indicating that if treatment failure was primarily because of loss of response, then sustained benefit in subjects with CD is unlikely.

Evaluator's comment: There was little difference in efficacy between the 4 weekly administration regimen for maintenance and the 8 weekly regimen. Hence the recommendation to increase dosing frequency from 8 weekly to 4 weekly in patients who do not respond requires further justification.

The Sponsor responded that the recommendation to increase the dosing frequency from 8 weekly to 4 weekly in patients who do not respond is based upon the analysis of subjects who terminated early from Study C13006 and Study C13007. These subjects were entered into Study C13008 and were treated with the 4 weekly dosing regimen. However, the numbers of subjects treated at this doing frequency decreased with increasing time: 31 with UC at Week 0, 19 at Week 24 and 15 at Week 52; and 57 with CD at Week 0, 40 at Week 28 and 30 at Week 52. Hence, the improvement in mean Mayo scores may have been due to a flawed study design for the following reasons:

- The mean partial Mayo scores may have improved over time because the subjects with the worst scores dropped out completely from the study
- The natural history of the condition, with natural remissions and exacerbations, may have resulted in apparent improvement
- Concomitant medications may have resulted in improvement

Study C13008 did not have a comparison group and was not suitable for determining the efficacy of an alternative dosing regimen.

In the opinion of the Evaluator Study C13008 was not designed to be able to demonstrate the efficacy of an alternative dosing strategy. Increasing the dosing frequency to 4 weekly in subjects that do not respond to the 8 weekly regimen would increase exposure with no demonstrated benefit. The risk benefit for this dosing recommendation is unfavourable.

Evaluator's comment: Subgroup Analyses of Patients Who Were Taking Concomitant Medication and were not able to take TNFa antagonists

The Sponsor has provided additional tabulations and graphical presentations of subgroup analyses for subjects taking concomitant medications and were not able to take TNFα antagonists. These tabulations indicate that concomitant corticosteroid and/or immunomodulator treatment does not affect response to VDZ

However, in these tabulations the Sponsor also provided another table from the Study C13006 report. The table indicates that the subgroup of subjects who had lost response to a TNFα antagonist did not have a sustained response to VDZ. For the 8 weekly dosing regimen the difference in response rate (95% CI) at Week 52, VDZ-placebo, was 8.1 (-27.9 to 42.0) % for subjects with loss of response to TNFα antagonists, 37.5 (4.5 to 65.2) % for subjects with inadequate response to TNFα antagonists and 48.3 (7.2 to 78.8) % in subjects with intolerance

to TNFα antagonists. Hence this provides further evidence of lack of long term efficacy of VDZ for subjects with loss of response to TNFα antagonists for both UC and CD.

12.1. Evaluator's additional comments on the data submitted in the overall application

12.1.1. Crohn's disease

The measures of disease severity, the efficacy endpoints and the subgroup analyses undertaken in the CD study program were appropriate. The use of enhanced clinical response as an efficacy endpoint differs from that of more recently examined agents in the treatment of CD. There were deviations from the EU Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease that has been adopted in Australia. To address these deviations the sponsor carried out supplementary analyses.

Study C13007, the pivotal study for this indication, did not use the proposed induction regimen. The proposed Q4W and Q8W VDZ maintenance regimens were compared with placebo but not with each other. This study also had design features which made determination of the extent of long term benefit for a patient commencing induction treatment complex. The induction phase of the study had a co-primary efficacy measure (clinical remission or enhanced clinical response). Neither of these efficacy measures was the basis for subsequent selection of patients into the maintenance phase of the study. The maintenance phase selected patients to continue therapy only if they had achieved a clinical response. Clinical response was not an efficacy endpoint in the induction phase and was not reported in the induction phase study results. Thus the proportion of patients randomised to commence induction and who would go on to receive long term benefit from maintenance treatment could not be calculated from the data presented in the body of the study report.

Supplemental analyses of maintenance results by induction study cohorts (Cohort 1 was randomised and Cohort 2 open) were performed. Among patients who had an initial clinical response at Week 6 approximately 17% more patients who continued on either dose of VDZ were in clinical remission more at Week 52 than those who received placebo. A similar difference occurred for enhanced clinical response where the difference was around 15% (favouring VDZ). No statistical comparisons of efficacy between the VDZ maintenance dose regimens were performed but no clinically significant difference was apparent.

Results from the induction study using the proposed regimen were reassuring. Patients who were TNFα antagonist naïve and those who had experienced failure both had statistically significant benefit from treatment at the Wk 10 assessment. An additional 14.5% of patients who had previously failed TNFα antagonist treatment and 19.1% who overall achieved clinical remission over those receiving placebo in addition to their concomitant treatments for CD. This is a reasonable clinical gain in a group who have a condition that is difficult to treat, particularly those who have failed prior TNFα antagonist therapy. The proportion of patients likely to benefit from maintenance therapy is a subgroup of those who initially responded and, based on the maintenance study results, is likely to be around 1 in 6 patients overall and somewhat fewer patients with prior TNFα antagonist failure.

Taking the results of the two Phase 2 studies together the data support the proposed induction regimen for patients with moderate to severe CD, including patients with prior TNFα antagonist failure. If maintenance treatment were to be given it is not clear when an assessment of clinical response to determine whether treatment should continue should occur at Week 6 or Week 10 given that maintenance data in non-responders at Week 6 were not obtained from a randomised, double-blind study. The sponsor has proposed clinical benefit be assessed at Week 14.

12.1.2. Ulcerative colitis

The primary efficacy parameter of interest in UC is the proportion of study patients maintaining remission throughout the study period. This was not one of the secondary endpoints in the pivotal study plan but was assessed as a supplemental analysis. An additional 22% of patients given VDZ achieved a clinical response at Week 6 compared to patients given placebo. Of patients who had achieved a clinical response with maintenance treatment clinical remission at Week 52 was achieved by an additional 26% to 29% of patients compared with those who were maintained on placebo. However only an additional 11.3% more patients above than those given placebo achieved a durable clinical remission to Week 52. While a statistically significant benefit has been demonstrated only a minority of patients had clinically significant benefits from ongoing treatment.

The proposed induction regimen has not been examined in patients with UC. The response in patients with UC was assessed primary at 6 weeks after commencing a two dose induction regimen. At Week 6 only patients with a clinical response were selected to continue into the controlled, randomised maintenance study.

The sponsor has also proposed that treatment response be assessed at Week 14 after commencing treatment. It is not clear why this time point was selected as it was not a major efficacy assessment time point in the pivotal clinical study. Only patients with a clinical response at Week 6 continued randomised treatment.

Another issue with the proposed maintenance regimens for both indications was that there was no consistent difference in outcome between the Q8W and Q4W dose regimens, though no formal statistical comparison was made. There were insufficient efficacy data to justify reducing the dose interval in patients who do not respond to initial treatment at Q8W or who become unresponsive after an initial response.

The main safety issue that has not been resolved is whether PML will be associated with vedolizumab as it is with natalizumab. The risk with natalizumab did not become apparent until a considerable time after first approval when increasing numbers of MS patients had been exposed to natalizumab for more than 2 years. Long term safety data for VDZ are quite limited. In addition, patients in the clinical trial program were intensively screened to reduce the probability of PML infection developing. No such plan is in place for patients post-approval and the proposed patient alert card does not specifically warn of the possibility of PML. Crohn's disease and ulcerative colitis are managed by gastroenterologists who are likely to have less awareness of the signs and symptoms of PML than is the case for neurologists who manage natalizumab treatment in patients with MS.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of vedolizumab in the proposed usage are:

- Efficacy has been demonstrated for vedolizumab in the treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to a conventional therapy or had an inadequate response with, or are intolerant to a tumour necrosis factor-alpha (TNFα) antagonist.
- Efficacy has been demonstrated for vedolizumab in the treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to a conventional therapy or had an inadequate response with, or are intolerant to a tumour necrosis factor-alpha (TNFα) antagonist.

However, the Evaluator is unable to conclude sustained efficacy for subjects with Ulcerative Colitis or Crohn's disease who had initially responded to TNFα antagonists, and subsequently lost response. Increasing the frequency of dosing from 8 weekly to 4 weekly in subjects that lose response to vedolizumab has not been demonstrated to be beneficial in an appropriately designed study.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the Evaluator concludes that in addition to the risks identified in Section 9.2:

- There is a higher rate of elevation of transaminases and of hepatic parenchymal damage in subjects treated with VDZ compared to placebo. Most of these events are not serious and there is no clear indication of the aetiology.
- The data submitted by the Sponsor do not indicate an increased risk of pancreatitis.

13.3. Second round benefit-risk assessment

The benefit-risk balance of vedolizumab is unfavourable given the proposed usage, but would become favourable if the changes recommended under *Second round recommendation regarding authorisation*, below, are adopted.

14. Second round recommendation regarding authorisation

The Evaluator is unable to recommend the approval of vedolizumab (ENTYVIO / VEDOLIZUMAB TAKEDA), 300 mg powder for injection, for the following indication:

Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

The reason for this decision is that vedolizumab did not appear to offer benefit for those patients with UC or CD who had initially responded to TNFα antagonist treatment, and subsequently lost response.

However, the Evaluator would have no objection to the approval of vedolizumab (ENTYVIO / VEDOLIZUMAB TAKEDA), 300 mg powder for injection, for the following indication:

> *Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to a conventional therapy or had an inadequate response with, or are intolerant to a tumour necrosis factor-alpha (TNFα) antagonist.*
>
> *Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to a conventional therapy or had an inadequate response with, or are intolerant to a tumour necrosis factor-alpha (TNFα) antagonist.*
>
> *In subjects with Ulcerative Colitis or Crohn's disease who had initially responded to TNFα antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.*

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au