



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Vedolizumab (rch)

Proprietary Product Names: Entyvio/Kynteles

Sponsor: Takeda Pharmaceuticals Australia Pty
Ltd

November 2014

TGA Health Safety
Regulation

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- 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>>.

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations used commonly in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADR	Adverse drug reaction
AE	Adverse event
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index A tool used to quantify the symptoms and thereby gauge the progress or lack of progress for people with Crohn's disease
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
C _{max}	Maximum plasma concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSR	Clinical study report
CV	Coefficient of variability
EMA	European Medicines Agency
EU	European Union
GI	Gastrointestinal
h	hour/s
HAHA	Human anti-human antibodies
HBI	Harvey-Bradshaw Index Provides an index of Crohn's disease activity

Abbreviation	Meaning
HIRDS SM	HealthCore Integrated Research Database
IBD	Inflammatory bowel disease
IC ₅₀	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG ₁	Immunoglobulin G ₁
ITT	Intent-to-treat
IV	Intravenous/ly
JCV	John Cunningham virus
LDP-02	Millennium's humanized monoclonal antihuman $\alpha_4\beta_7$ integrin antibody, also known as MLN0002 (Process A) and MLN02
MAdCAM-1	Mucosal addressin cell adhesion molecule-1
min	minute/s
MLN0002	Vedolizumab, Millennium's humanized monoclonal antihuman $\alpha_4\beta_7$ integrin antibody, formerly LDP-02 and MLN02
NNT	Number needed to treat
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetic/s
PML	Progressive multifocal leukoencephalopathy
PT	Preferred term
PV	Pharmacovigilance plan
RR	Relative risk
RMP	Risk Management Plan
SE	Standard error (of the mean)
SAE	serious adverse event

Abbreviation	Meaning
$t_{1/2}$	half-life
T_{max}	Time to achieve maximal effect
TB	Tuberculosis
TEAE	Treatment emergent adverse event
$TNF\alpha$	Tumor necrosis factor-alpha
UC	Ulcerative colitis
ULN	Upper limit of normal
VCAM-1	Vascular cell adhesion molecule-1
WBC	White blood cell

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	26 June 2014
<i>Active ingredient:</i>	Vedolizumab (rch ¹)
<i>Product names:</i>	Entyvio/Kynteles
<i>Sponsor's name and address:</i>	Takeda Pharmaceuticals Australia Pty Ltd 2-4 Lyon park Road Macquarie Park NSW 2113
<i>Dose form:</i>	Powder for injection
<i>Strength:</i>	300 mg
<i>Container:</i>	Vial
<i>Pack size:</i>	1
<i>Approved therapeutic use:</i>	<i>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.</i> <i>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.</i>
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage (abbreviated):</i>	Adults (≥ 18 years): 300 mg at zero, two and six weeks and then every eight weeks thereafter (see approved Product Information at Attachment 1 for full <i>Dosage and administration</i>)
<i>ARTG numbers:</i>	210048, 210042

¹ rch = recombinant Chinese hamster and indicates production from genetically engineered Chinese hamster ovary cells.

Product background

Vedolizumab is a recombinant, humanised, immunoglobulin G type 1 (IgG₁) monoclonal antibody targeting the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to gastrointestinal (GI) mucosa and gut-associated lymphoid tissue (GALT) and is thought to have a role in increasing inflammation seen in ulcerative colitis and Crohn's disease.

This AusPAR describes the application by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register Entyvio/Kynteles, containing vedolizumab (rch) 300 mg powder for IV infusion, 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 (TNF α) 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 (TNF α) antagonist.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 27 June 2014.

At the time the TGA considered this application, a similar application was under review in the European Union (EU), the USA, Canada, and Switzerland. On 20 March 2014 the EU Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion, recommending the granting of a marketing authorisation in Europe.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

Introduction

The vedolizumab monoclonal antibody is a humanised version of the murine monoclonal antibody Act-1 targeting human $\alpha_4\beta_7$ integrin. The humanised antibody combines the antigen recognition regions of Act-1 with human immunoglobulin frameworks and constant regions of a human IgG₁ antibody. It is composed of two identical light chains of the kappa subclass and two identical heavy chains linked together by two disulfide bridges to form a Y-shaped molecule that is typical of IgG₁ immunoglobulins.

Drug substance (active ingredient)

Manufacture

The manufacturing process uses recombinant Chinese hamster ovary (CHO) cells that secrete the antibody into the culture medium. The substance is subsequently purified and processed to final filtration and bottling.

Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Information was provided on the proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life. The real time data submitted support a shelf life of 48 months when stored at $\leq -60^{\circ}\text{C}$.

Drug product

When a vial of vedolizumab drug product is reconstituted with 4.8 mL water for injection, it contains 331.2 mg antibody in 5.52 mL solution. The reconstituted drug product is hypertonic. Prior to infusion the reconstituted drug product is further diluted, resulting in an isotonic solution.

The drug product is filled into 20 mL glass vials. The vials are closed with a rubber stopper with a coating on product contact surfaces. Vials are sealed with an aluminium seal with a plastic cap. Each pack contains one vial.

Manufacture

The drug product is sterilised using filtration. The manufacturing process includes sterile filtration, aseptic filling and partial stoppering, lyophilisation, stoppering and sealing of the vials.

Specifications

Information was provided on the proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability profile of the product. The finally approved storage conditions are described in the PI (see Attachment 1).

Biopharmaceutics

Biopharmaceutic data are not required for this product as the product is for intravenous (IV) infusion.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the

Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are no Module 3 (quality) issues outstanding.

The Module 3 (quality) evaluators recommend that Entyvio vedolizumab 300 mg powder for injection vial and Kynteles vedolizumab 300 mg powder for injection vial should be approved. Should the product be approved, conditions of registration² should be applied.

III. Nonclinical findings

Introduction

The submitted nonclinical dossier was adequate and appropriate for a monoclonal antibody. Studies were generally well conducted and documented. Pivotal toxicity, cross-reactivity and immunotoxicity studies, and the cardiovascular safety pharmacology study were all compliant with Good Laboratory Practice (GLP) principles.

Pharmacology

Primary pharmacology

Crohn's disease (CD) and ulcerative colitis (UC), the main forms of inflammatory bowel disease (IBD), are chronic inflammatory disorders of the intestine and/or colon. Although the aetiology of these diseases has not been fully elucidated, the ability of the affected individual to regulate the movement of T cells into the gut-associated lymphoid tissue (GALT, which includes Peyer's patches, lymphocytes in the lamina propria and intra-epithelial lymphocytes of the intestine), gut-draining mesenteric lymph nodes and gut is increasingly recognised of importance in the induction and perpetuation of chronic intestinal inflammation (Koboziev et al., 2010³). To mount a protective immune response to pathogens entering the gut, intravascular naïve T cells must home to the GI tract (GIT) inductive sites (the GALT and gut-draining mesenteric lymph nodes) where they undergo antigen-driven priming/activation, polarisation and expansion to yield effector/memory cells which exit the lymphoid tissue via the efferent lymphatics, enter the systemic circulation, and home to the gut where they help to destroy the invading pathogens (see Koboziev et al., 2010). Several studies suggest that in the absence of appropriate regulatory mechanisms, this same sequence of events may occur in response to commensal (nonpathogenic) bacteria resulting in enteric antigen-dependent induction of chronic intestinal inflammation. The functioning of the immune system is characterised by regionalisation at multiple levels. Thus, while naïve lymphocytes recirculate primarily through secondary lymphoid organs, after infection, most antigen-specific memory T cells reside in nonlymphoid tissues and preferentially migrate through tissues in which the antigen was initially encountered such as the gut, skin, central nervous system (CNS) and lung (Sheridan and Lefrançois, 2011⁴).

Integrins are transmembrane receptors that mediate the attachment between a cell and its surroundings. They also act as cellular sensors and signalling molecules. It is now well established that the recruitment of leukocytes from the blood into virtually every tissue is regulated by sequential engagement of integrins and adhesion molecules on leukocytes

² Details of recommended conditions of registration are beyond the scope of the AusPAR.

³ Koboziev, I., Karlsson F and Grisham MB. Gut-associated lymphoid tissue, T cell trafficking, and chronic intestinal inflammation. *Ann. NY Acad. Sci.* 2010;1207: E86-E93

⁴ Sheridan, B.S. and Lefrançois, L. Regional and mucosal memory T cells. *Nature Immunol* 2011; 12:485-491.

and endothelial cells (see von Andrian and Engelhardt, 2003⁵). All integrins are composed of noncovalently linked α and β chains. The α_4 integrin chain dimerises with either the β_1 chain or the β_7 chain, while the β_7 integrin chain dimerises with the α_E chain as well as the α_4 chain.

The main ligand for $\alpha_4\beta_7$ is mucosal addressin-cell adhesion molecule 1 (MAdCAM-1), while that for $\alpha_4\beta_1$ is vascular-cell adhesion molecule 1 (VCAM-1). MAdCAM-1 is expressed selectively on high endothelial venules (HEVs) within GALT and on gut lamina propria venules (Erle et al., 1994⁶; Berlin et al., 1993⁷). Thus, the $\alpha_4\beta_7$ -MAdCAM-1 pathway is important for the homing of naïve lymphocytes, which adhere to MAdCAM-1 in HEVs within GALT and the migration of gut-homing memory cells to the intestinal lamina propria (von Andrian and Engelhardt, 2003). In contrast, the molecular interactions required for lymphocytes to enter the CNS (and some other organs) appear to be mediated mainly by $\alpha_4\beta_1$ and VCAM-1.

Vedolizumab was shown to bind to human integrin $\alpha_4\beta_7$ but not to integrins which share a subunit with $\alpha_4\beta_7$ ($\alpha_4\beta_1$ and $\alpha_E\beta_7$), since it bound to RPM18866 cells which selectively express $\alpha_4\beta_7$, and not to RAMOS cells which express $\alpha_4\beta_1$ integrin nor to $\alpha_E\beta_7$ -L1.2 cells which express $\alpha_E\beta_7$. Consistent with this, vedolizumab did not inhibit the binding of RAMOS cells to their target adhesion molecules, VCAM-1 or fibronectin.

Although MAdCAM-1 is the main ligand for $\alpha_4\beta_7$, VCAM-1 and fibronectin are also, although binding to fibronectin required activation by Mn^{2+} . While MAdCAM-1 and VCAM-1 are found on the vascular lumen and mediate diapedesis, fibronectin is a component of the extracellular matrix and does not mediate diapedesis. While vedolizumab inhibited binding to MAdCAM-1 and fibronectin (the latter only in the presence of Mn^{2+}) it did not inhibit binding to VCAM-1 (using RPM18866 cells). Thus, the effect of vedolizumab on diapedesis will be restricted to the GIT where MAdCAM-1 is selectively expressed. The effect of vedolizumab on the potential activities of $\alpha_4\beta_7$ outside of the vasculature is not clear.

The primary pharmacological target of vedolizumab is subpopulations of human leukocytes bearing the $\alpha_4\beta_7$ integrin. The expression of integrins $\alpha_4\beta_7$ and $\alpha_4\beta_1$ in human leukocyte subtypes was investigated to identify the subtypes whose function could potentially be inhibited by vedolizumab compared to antibodies that target $\alpha_4\beta_1$. The $\alpha_4\beta_1$ integrin is more widely expressed by leukocytes than the $\alpha_4\beta_7$ integrin, and the same was the case for some lymphocyte subsets, as summarised in the following table.

Table 1: Percentage of leukocyte subsets expressing $\alpha_4\beta_1$ and $\alpha_4\beta_7$

Cell type/subtype	Percentage of cells expressing $\alpha_4\beta_1$	Percentage of cells expressing $\alpha_4\beta_7$
Lymphocytes	93	61
Monocytes	99	15
Neutrophils	0	0
Eosinophils	100	89

⁵ von Andrian, U.H. and Engelhardt, B. A4 integrins as therapeutic targets in autoimmune disease. *NEJM* 2003;348: 68-72.

⁶ Erle, D.J., Briskin, M.J., Butcher, E.C., Garcia-Pardo, A., Lazarovits, A.I. and Tidswell, M. Expression and function of the MAdCAM-1 receptor, integrin $\alpha_4\beta_7$, on human leukocytes. *J Immunol* 1994; 153: 517-528.

⁷ Berlin, C., Berg, L., Briskin, M.J., et al. $\alpha_4\beta_7$ integrin mediates lymphocyte binding to mucosal vascular addressin MAdCAM-1. *Cell* 1993;74: 185-195.

Cell type/subtype	Percentage of cells expressing $\alpha_4\beta_1$	Percentage of cells expressing $\alpha_4\beta_7$
CD56+ NK cells	100	64
CD19+ B cells	100	88
CD4+CD45RO-	91	73
CD8+	99	42
CD48+CD45RO+	79	32
CD4+	90	50

Thus, an inhibitor of $\alpha_4\beta_1$ or a dual inhibitor of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ could potentially inhibit migration of a larger proportion of lymphocytes than a specific inhibitor of $\alpha_4\beta_7$. While the gut-selectivity achieved by vedolizumab (due to its selective inhibition of the $\alpha_4\beta_7$ -MAdCAM-1 pathway) would be expected to be advantageous in reducing risk associated with progressive multifocal leucoencephalopathy (PML) (see discussion below), a reduction in efficacy might be expected compared to a dual $\alpha_4\beta_1$ and $\alpha_4\beta_7$ inhibitor, since it is thought that both $\alpha_4\beta_7$ and $\alpha_4\beta_1$ are important for T cell migration to the inflamed large bowel in IBD (Koboziev et al., 2010).

Complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) are common Fc-mediated cytotoxic mechanisms for monoclonal antibodies in vivo. However, vedolizumab (at concentrations up to 10 $\mu\text{g}/\text{mL}$) did not mediate CDC or ADCC and therefore target cells were not lysed, nor did vedolizumab (at 400 $\mu\text{g}/\text{mL}$) trigger the release of cytokines (interferon gamma ($\text{INF}\gamma$), interleukin-1 β (IL-1 β), IL-2, IL-4, IL-6, IL-8, IL-12 (p70), IL-17 and $\text{TNF}\alpha$) or directly activate T cells when incubated with human whole blood. The concentration of 400 $\mu\text{g}/\text{mL}$ exceeded the C_{max} (115 $\mu\text{g}/\text{mL}$) as well as trough concentrations (about 33 μg with dosing every 4 weeks after week 6 and about 10.5 $\mu\text{g}/\text{mL}$ with dosing every 8 weeks after week 6) observed in patients given the recommended dose of vedolizumab, whereas 10 $\mu\text{g}/\text{mL}$ was comparable to trough concentrations with dosing every 8 weeks after week 6.

Data revealing internalisation of the $\alpha_4\beta_7$ integrin/vedolizumab complex on CD4+ memory T lymphocytes targeted by the drug and revealing the restoration of the integrin on these cells after removal of vedolizumab are consistent with the mechanism of action of vedolizumab being via binding to the $\alpha_4\beta_7$ integrin. These data are also consistent with the observation in nonclinical studies of the reversibility of the pharmacodynamic (PD) effects of vedolizumab. The reappearance of $\alpha_4\beta_7$ was considerably inhibited in the presence of monensin suggesting that it is a result of intracellular processes rather than the reformation of surface complexes from the individual α_4 and β_7 chains.

Mucosal tolerance to environmental and food antigens is important for preventing exaggerated immune reactions that cause chronic inflammation, and suppression of effector T-cell function by Treg cells appears to be an important mechanism by which this is mediated. Inhibition of the activity of Treg cells may be a contributory factor in the pathogenesis of IBD (Izcue et al., 2009⁸). A study demonstrated that about 9% of the total Treg cell population in peripheral blood expressed $\alpha_4\beta_7$. Results of another study suggested that vedolizumab does not affect the suppressive activity of the total Treg cell

⁸ Izcue, A., Coombes, J.L. and Powrie, F. Regulatory lymphocytes and intestinal inflammation. *Ann Rev Immunol* 2009;27: 313-338.

population, nor the gut-homing subset of Treg cells from peripheral blood, although concentrations tested were low (up to 0.2 µg/mL), well below even trough serum concentrations (with dosing every 8 weeks after week 6) expected clinically.

The potential for vedolizumab to inhibit memory T helper 17 cells was investigated. These cells constitute a subpopulation of T helper lymphocytes that produce cytokines that augment inflammation in a number of autoimmune diseases, including IBD. In peripheral blood, vedolizumab bound to a subset (27%) of these cells that expressed $\alpha_4\beta_7$. While vedolizumab would be expected to inhibit the homing of these cells to the GIT, there remains a substantial proportion of this cell population that would be unaffected by vedolizumab.

An investigation of the species cross-reactivity of vedolizumab revealed that the drug bound to lymphocytes from rabbits and cynomolgus monkeys (as well as from humans), but not to lymphocytes from mice, rats or guinea pigs. Dogs were not tested. Vedolizumab bound to $\alpha_4\beta_7$ integrin on human, rabbit and cynomolgus monkey peripheral blood B and CD4+ cells and to human, cynomolgus and rhesus monkey CD4+ memory T cells with subnanomolar affinity. Thus, half maximal inhibitory concentration (IC₅₀) values were well below the serum C_{max} (115 µg/mL) and trough concentrations (10.5-33 µg/mL) expected at the recommended human dose of 300 mg. The trough concentration of about 10 µg/mL was about 30-40 fold the concentration needed for the saturation of binding of vedolizumab to various human whole blood lymphocyte subsets as assessed by saturation binding analysis.

IC₅₀ values for B and CD4+ T cells were broadly similar for humans, rabbits and cynomolgus monkeys. IC₅₀ values were also broadly similar for B and CD4+ cells in all these species. IC₅₀ values of vedolizumab Process A drug substance for CD8+ cells were similar in cynomolgus monkeys and humans. IC₅₀ values for CD4+ memory T cells were also broadly similar for humans and rhesus monkeys. These species similarities further confirm the validity of the animal models. IC₅₀ values for human CD4+ memory T cells were approximately an order of magnitude lower than for the other T cell types. Natalizumab showed higher IC₅₀ values (lower binding affinity) for CD4+ memory T cells in humans, and cynomolgus and rhesus monkeys than vedolizumab.

Although only submitted as a literature reference, and although Act-1 (the original murine monoclonal antibody from which vedolizumab was derived) was tested rather than vedolizumab itself, the study by Hesterberg et al., 1996⁹ was important in demonstrating efficacy in an animal model. Blocking of $\alpha_4\beta_7$ integrin by Act-1 improved stool consistency and ameliorated gut inflammatory activity in cotton-top tamarin monkeys with naturally occurring chronic colitis (these monkeys have clinical and microscopic findings similar to those of UC in humans). The density of T cells, B cells, monocytes/macrophages and neutrophils in colonic mucosal biopsies was also consistently reduced by Act-1 treatment. In the absence of pharmacokinetic (PK) data for the cotton top tamarin monkey, it is difficult to compare the doses used in this study with the human dose. The dose tested in the monkeys was 2 mg/kg which is less than the human dose of 4.3 mg/kg (assuming a 70 kg human body weight; interspecies comparisons on a mg/kg basis are probably more appropriate for this drug than comparisons on a mg/m² basis). However, the dosing frequency was much higher in the monkeys than that proposed in humans. Further, after the first IV dose, the intramuscular (IM) route was used and no bioavailability data are available for this route.

Natalizumab (Tysabri) is registered in Australia for the treatment of multiple sclerosis (MS). In the USA, it is additionally approved for the treatment of CD (under a strict risk management program). A major issue associated with natalizumab treatment is an

⁹ Hesterberg, P.E., Winsor-Hines, D., Briskin, M.J. et al. Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin $\alpha_4\beta_7$. *Gastroenterol* 1996;111:1373-1380.

increased risk of PML, an opportunistic infection of the brain that usually leads to death or severe disability, and is caused by the John Cunningham virus (JCV). Evidence from the literature suggests that PML associated with natalizumab is due to the inhibition of the $\alpha_4\beta_1$ integrin rather than the $\alpha_4\beta_7$ integrin, with the mechanism believed to be a decrease in immune surveillance of the CNS (Monaco and Major, 2012¹⁰; Steiner and Berger, 2012¹¹). It would be expected that vedolizumab would show little or no immune compromise in extra-GIT tissues such as the CNS compared to natalizumab, because of its gut selectivity (see discussion above). A study was conducted to assess this expectation using a validated rhesus monkey experimental autoimmune encephalomyelitis (EAE) model. In contrast to natalizumab, vedolizumab (30 mg/kg IV once weekly) did not affect inflammation in the CNS in this model, or decrease cerebrospinal fluid (CSF) counts of white blood cell (WBC) or lymphocyte subsets. The dose used was appropriate (it achieved an exposure ratio of 2.4 in cynomolgus monkeys (see *Repeat-dose toxicity; Relative exposure*) and would be expected to achieve a similar exposure ratio in rhesus monkeys. The results of this study are therefore consistent with the hypothesis that vedolizumab has a lower propensity to block immune surveillance in the CNS than natalizumab. Consistent with these results, vedolizumab was not found to alter CSF cellular composition (including WBC, lymphocyte or T cell subset counts (or other CSF parameters such as total protein concentrations)) in the 26 week cynomolgus monkey study. Vedolizumab is therefore likely to be associated with a lower risk of PML than natalizumab.

During product development, there have been three different products (Process A, B and C product) reflecting differences in manufacture of the drug substance and formulation of the final product. The biological activity of the Process A drug substance would be expected to be the same as that of the Process B drug substance because there were no differences in the binding regions of the two molecules. This expectation was supported by the demonstration of comparable binding affinities of vedolizumab Process A and Process B (or C) drug substances (and of Act-1) for human B lymphocytes. Further, the sponsor's quality expert report noted that Process A and Process B antibodies showed equivalent potency in inhibiting adhesion of RPMI8866 cells to an immobilised MAdCAM-muFc chimeric protein and in inhibiting the binding of soluble fluorescently-tagged MAdCAM-muFc to RPMI8866 cells. The two antibodies also showed similar binding to $\alpha_4\beta_7$ -expressing human T cell line HuT 78. There were, however, anticipated physicochemical differences between the two antibodies which were consistent with the change in expression cell line and the two amino acids, most notably, differences in glycosylation profiles (a higher level of oligosaccharide complexity with the Process A drug substance), charge profiles (the replacement of an acidic amino acid with a neutral one meant that Process A drug substance eluted earlier on cation exchange chromatography than Process B drug substance and there was an analogous shift in isoelectric focusing profile), peptide maps and molecular masses.

Secondary pharmacodynamics and safety pharmacology

Secondary PD studies are not normally required for biotechnology-derived pharmaceuticals and were not conducted on vedolizumab.

The only specialised safety pharmacology study conducted was a cardiovascular study in cynomolgus monkeys. Other core safety pharmacology studies (CNS and respiratory) were not conducted. A direct effect of vedolizumab on the CNS would not be expected as IgG molecules do not normally cross the blood-brain barrier. Observations of clinical signs in

¹⁰ Monaco, M.C. and Major, E.O. The link between VLA-4 and JC virus reactivation. *Expert Rev Clin Immunol* 2012; 8:63-72.

¹¹ Steiner, I. and Berger, J.R. Update on progressive multifocal leukoencephalopathy pathogenesis. *Curr Neurol Neurosci Rep* 2012;12: 680-686.

the repeat-dose toxicity studies gave no indication of an effect on the CNS. Respiratory rate (but no other respiratory parameters) were investigated in the two early repeat-dose toxicity studies in cynomolgus monkeys and no effect of vedolizumab was seen. Results from the repeat dose studies did not suggest any effect of vedolizumab on other organ systems such as the renal and GI (other than associated lymphoid tissue) systems, and it is acceptable that no additional safety pharmacology studies were conducted to investigate effects on other organ systems.

The cardiovascular safety study in cynomolgus monkeys did not reveal an effect of vedolizumab on mean arterial blood pressure (MAP), heart rate (HR) or quantitative electrocardiograph (ECG) parameters. Vedolizumab was tested at doses of up to 100 mg/kg IV, a dose which gave an exposure ratio of 8 on day 1 in the 26 week cynomolgus monkey toxicity study. ECGs were also investigated (qualitatively) in two repeat-dose toxicity studies in cynomolgus monkeys, the pivotal 26 week study and the 13 week study, again with negative results.

Pharmacokinetics

Available single dose and day 1 data suggested dose proportionality of exposure. While accumulation was observed following administration of vedolizumab at a high dosing frequency, the induction of anti-vedolizumab antibodies after repeated dosing in most animals often had a more profound effect on serum vedolizumab concentrations than accumulation following repeated dosing. There was no evidence, in either rabbits or cynomolgus monkeys, of a sex difference in the PK of vedolizumab.

Clearance (CL) was slow, about 0.2-0.4 mL/h/kg in cynomolgus monkeys and about 157 mL/day in humans (0.09 mL/h/kg, assuming 70 kg body weight). Volume of distribution was consistent with blood volume (4.49 L in humans (about 64 mL/kg) and 67.9 -88.3 mL/kg in cynomolgus monkeys). Serum/plasma half-life was long, about 25 days (600 h) in humans and about 15 days (350 h) in cynomolgus monkeys.

Plasma protein binding was not evaluated. This is acceptable as vedolizumab would not be expected to bind to plasma proteins. IgG molecules do not cross the blood-brain barrier (Triguero et al., 1989¹²). Standard distribution, metabolism and excretion studies were not conducted and are not required for monoclonal antibodies. The pharmacological activity of the drug in the species chosen for toxicity testing is the critical factor in the choice of species as the metabolic pathways for immunoglobulins (proteins) are generally understood and are consistent between species.

Almost all animals (rabbits and cynomolgus monkeys) dosed with vedolizumab developed antibodies by days 14 or 15. Antibodies were not detected in a single dose study but samples were only collected up to day 7 post dosing, with most animals in the studies conducted developing antibodies between about days 8-14. Although all animals developed anti-vedolizumab antibodies, there was considerable inter-animal variability in titres, with some animals developing antibodies of sustained high titre, while others only developing antibodies of very low titre. Results from a study which investigated anti-idiotypic and anti-isotypic antibodies separately suggested that the neutralising antibody effect was mediated by anti-isotypic antibodies.

Parallel with the measurement of serum vedolizumab concentrations, the PD effect was assessed by determining the percentage of CD4+ cells that stained positive for free $\alpha_4\beta_7$ (in the pivotal cynomolgus monkey study, both CD45RA+, CD45RA- and CD20+ cells were assessed for this parameter) and for bound vedolizumab (in the pivotal cynomolgus

¹² Triguero, D., Buciak, J.B., Yang, J. and Pardridge, W.M. Blood-brain barrier transport of cationized immunoglobulin G. Enhanced delivery compared to native protein. *PNAS* 1989;86:4761-4765.

monkey study, both CD45RA+ and CD45RA- cells were assessed for this parameter). These assessments revealed that in the pivotal rabbit and cynomolgus monkey studies, the percentage of cells with free $\alpha_4\beta_7$ dropped rapidly after dosing to very low levels and remained at these levels until many days after the last dose in both rabbits and cynomolgus monkeys with the exception of some increases in some of the LD cynomolgus monkeys that developed high titre antibodies, thus providing evidence of the neutralising capacity of the antibodies. Results for the percentage of cells with bound vedolizumab were more variable than those for the percentage of cells with free $\alpha_4\beta_7$, but there was a rapid increase following dosing and although values were generally sustained, some decreases from the peak were observed, mainly depending on the production of neutralising antibodies.

Pharmacokinetic drug interactions

There is a lack of any potential mechanism (for example, via the usual cytochrome (CYP) p450 enzyme interactions) for direct interaction of vedolizumab with other drugs, therefore it is acceptable that no nonclinical drug interactions studies were conducted.

Toxicology

The choice of rabbits and cynomolgus monkeys as species for toxicity studies was appropriate as they are pharmacologically responsive to vedolizumab (see *Primary Pharmacology*). Briefly, vedolizumab bound with similar affinity to human, cynomolgus monkey and rabbit $\alpha_4\beta_7$ integrins on various lymphocyte subsets. Further, in tissue cross-reactivity studies, vedolizumab showed similar cross-reactivity in human and cynomolgus monkey tissues. In both species, staining was only observed for mononuclear cells (lymphocytes and monocytes/macrophages) in lymphoid tissues and within the lumen of blood vessels, or as low-grade inflammatory infiltrates in various non-lymphoid tissues. These results are consistent with the known pattern of $\alpha_4\beta_7$ expression on the membrane of mononuclear cells in primates (Rott et al., 2000¹³).

Acute toxicity

The single dose toxicity study in cynomolgus monkeys at doses of 10 and 100 mg/kg (30 min IV infusion) revealed no adverse effects of vedolizumab (mortality, clinical signs and body weight) over an 85 day observation period and provided sufficient information for the selection of doses in the repeat-dose studies in this species.

Repeat dose toxicity

One repeat-dose toxicity study was conducted in rabbits and 4 in cynomolgus monkeys, with all being GLP compliant and including both sexes. All studies used the IV (clinical) route, although some studies used infusions of varied duration (15 min to 1 h) or injection and other studies used slow (1-10 min) injections. The 2 early studies in cynomolgus monkeys were conducted prior to the single dose toxicity study and used relatively low doses (2.5 mg/kg/dose or up to 10 mg/kg/dose, respectively), relatively high dosing frequencies and Process A vedolizumab (LDP-02). The two pivotal studies were of adequate study design (including endpoints). Animal numbers were adequate, although a higher numbers of rabbits could have been used, and interpretation is always more difficult with the low animal numbers that are typical for studies in monkeys. These studies all included recovery assessment. Although doses were not limited by toxicity, they

¹³ Rott, L.S., Briskin, M.J. and Butcher, E.C. Expression of $\alpha_4\beta_7$ and E-selectin ligand by circulating memory B cells: implications for targeted trafficking to mucosal and systemic sites. *J Leukocyte Biol* 2000;68:807-814.

achieved adequate exposure ratios (see *Relative Exposure* table below). The doses used in cynomolgus monkeys were presumably based on the negative findings at the same doses in the single dose toxicity study. While no preliminary data were available for the rabbit, the same doses were used in this species as in the cynomolgus monkey, and as might be expected for a monoclonal antibody, achieved similar exposure ratios (see *Relative Exposure* table below and *Reproductive Toxicity*). Frequency of dosing was every 2 weeks which was an appropriate dosing interval, with trough concentrations at all doses in the pivotal studies being above (generally well above) trough concentrations in humans given the recommended dose. A six month study duration (the length of the pivotal monkey study) is normally considered adequate for a biotechnology-derived pharmaceutical for chronic indications. The rabbit study was 12 weeks, but given the length of the pivotal monkey study, and the development of antibodies in many of the rabbits (which would limit the information that could be gained by a longer duration study), this was acceptable.

Relative exposure

Exposure ratios have been calculated based on animal:human serum are under the concentration-time curve (AUC) values. Human reference values are from clinical Study C13009. Exposure ratios achieved were acceptable.

Table 2: Relative exposure in repeat-dose toxicity studies

Species	Study duration (sampling day)	Dose mg/kg/dose	AUC period	AUC [^] (µg·h/mL)	Exposure ratio#
Rabbit	12 weeks (day 84)	30	AUC _{0-337 h}	81,350	1.7
		100		1,192,500	25
Cynomolgus monkey	26 weeks (day 1)	10	AUC _{0-336 h}	38,200	0.8
		30		113,000	2.4
		100		376,000	8
Human (healthy volunteers)	single dose	300 mg	AUC _{0-t}	47,760*	-

[^] combined sexes; # = animal:human plasma AUC; * 1990 x 24 to convert from µg.day/mL to µg.h/mL

AUC values used for the calculation of exposure ratios for the rabbit were for day 84 as these were the only data available. At the HD, one female out of 9 animals (5/sex minus one unscheduled death) had persistent high titre antibodies that resulted in reduced serum vedolizumab concentrations. For cynomolgus monkeys, day 1 AUC values were used because of the variability of the data at the end of the study associated with the impact of anti-vedolizumab antibodies in some of the animals. AUC values for humans were for a single dose, so correspond with the day 1 values for monkeys. In cynomolgus monkeys, day 1 levels were not maintained for the full duration of the study in a number of animals at the low dose and mid dose, but at the high dose, serum concentrations were maintained throughout the study in all animals as no animal developed persistent high titre antibodies, and mean C_{max} and AUC values were about two times higher on day 169 than on day 1.

The exposure ratios are likely to be underestimates because the AUC measurement period in the animal studies (336-337 h) was shorter than that in humans which was to the last time point at which concentrations were measurable, (this value in humans was only slightly lower than the value extrapolated to infinity). Toxicokinetic data (on gestation day 132) for the pre-/postnatal study in cynomolgus monkeys illustrate this, as two AUC values were available, $AUC_{0-336\text{ h}}$ and $AUC_{0-3480\text{ h}}$ (the latter value, a calculation based on sampling to day 277 post coitus). In animals that did not develop high titre antibodies, these two values were 62,200 and 105,000 $\mu\text{g}\cdot\text{h}/\text{mL}$ at the low dose (10 mg/kg/dose) and 692,000 and 1,140,000 $\mu\text{g}\cdot\text{h}/\text{mL}$ at the high dose (100 mg/kg/dose); the lower value was 59% and 61% of the higher value at the low dose and high dose, respectively.

Data for two studies have not been included in the above table as AUC values were not calculated in the former and only $AUC_{0-24\text{ h}}$ was calculated for the latter. Data for a further study have also not been included since the dose levels and dosing regimen were the same as for the pivotal 26 week study; C_{max} values (day 1) for these two studies were comparable at all dose levels, but AUC values were higher in one, presumably in part reflecting the longer period over which they were calculated (336 h compared with 168 h, with the former being closer to the AUC_{0-t} calculated for humans), although trough values were also higher in one study. Exposure ratios based on C_{max} values (6 and 83 in rabbits and 2.6, 8 and 24 in cynomolgus monkeys at the ascending doses) were higher than those based on AUC values.

Major toxicities

There was no indication from the repeat dose toxicity studies of any target organ toxicity, with the exception of low level changes in lymphoid tissue. Lymphoid hyperplasia in the spleen was observed in the rabbit study and the 2 week cynomolgus monkey study. In the monkey study, lymphoid hyperplasia was additionally observed in the stomach, duodenum and mandibular lymph node. These studies used high frequency dosing and there were no similar findings in the 13 or 26 week monkey studies. In lymphoid tissue, it is also difficult to distinguish between changes that might be due directly to vedolizumab and changes that might be due to chronic stimulation of the immune system associated with anti-vedolizumab antibodies.

In rabbits, at the both doses tested, decreased lymphoid follicle size was observed in the sacculus rotundus (a spherical, thick-walled enlargement at the distal end of the ileum in rabbits which contains lymphoid tissue that functions similarly to other GALT). Minimal to mild lymphoid depletion in Peyer's patches was also observed in 0, 1, 2 and 2 main study males (n=4) in the ascending dose groups in the 26 week monkey study and in 1 of 2 high dose recovery females. These findings are considered to be associated with the primary pharmacological activity of the drug and are consistent with the impaired formation of GALT in mice lacking functional $\alpha_4\beta_7$ and $\alpha_E\beta_7$ integrins ($\beta_7^{-/-}$) mice (Wagner et al., 1996¹⁴).

Leukocytes migrating out of the vasculature into the tissues eventually return to the vasculature via the draining lymphatics. When the movement of leukocytes into tissues from the vasculature is blocked by antibodies, but not the movement back into the vasculature, accumulation of leukocytes in blood can be observed, as for example, following the administration of natalizumab. This effect would be expected to be less for vedolizumab since it blocks only $\alpha_4\beta_7$ rather than both $\alpha_4\beta_7$ and $\alpha_4\beta_1$. This was borne out by the general lack of haematological changes in the repeat-dose toxicity studies. Further, in the rhesus monkey EAE model study and in the comparative immunotoxicity study, vedolizumab at the same dose as natalizumab, was without effect on blood leukocyte or lymphocyte numbers. However, in the repeat-dose rabbit toxicity study, although not

¹⁴ Wagner, N., Lohler, J., Kunkel, E.J., et al. Critical role for β_7 integrins in formation of the gut-associated lymphoid tissue. *Nature* 1996;382:366-370.

statistically significant, increases in leukocyte and lymphocyte numbers were observed in males at both doses (30 and 100 mg/kg/dose) (lymphocyte numbers were also increased in high dose females).

Genotoxicity and carcinogenicity

No genotoxicity studies were submitted and this is appropriate as routine genotoxicity studies are generally not applicable to biotechnology-derived pharmaceuticals (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topic S6(R1¹⁵)). Further, a monoclonal antibody would not be expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material.

No carcinogenicity studies were submitted and this is acceptable given that vedolizumab was not pharmacologically active in mice or rats, and also elicited a significant antibody response.

The effect of Act-1 on the in vitro growth of a relevant tumour type, a human B cell lymphoma cell line expressing $\alpha_4\beta_7$ was investigated. Growth was not stimulated by Act-1.

The cross-reactivity of Act-1 with cryosections of 10 human colon adenocarcinomas was also investigated. As this is a malignant tumour and the GIT is the primary pharmacological target organ for vedolizumab, this was an appropriate tumour to investigate. There was no evidence that Act-1 bound to the tumour tissue, as staining was restricted to mononuclear cells which would represent the resident or infiltrating lymphocytes. Although the study was conducted with Act-1, as noted above, Act-1 and vedolizumab showed similar staining patterns in tissue cross-reactivity studies.

These two studies thus provided no suggestion of carcinogenic potential for Act-1 (and therefore, vedolizumab).

Reproductive toxicity

Fertility studies were not conducted, although such studies are relevant to the patient population. There was no evidence of cross reactivity of vedolizumab with human reproductive tissues and no evidence from the repeat-dose toxicity studies in rabbits or cynomolgus monkeys of an effect of vedolizumab on the reproductive organs of either males or females. Fertility studies are normally conducted in rats or mice, although guinea pigs have sometimes been used (for example, the effects of natalizumab on fertility were studied in guinea pigs (see Tysabri PI)). Vedolizumab was not pharmacologically active in any of these species. However, it is disappointing that some additional fertility endpoints (such as reproductive hormones, menstrual cycling and sperm analysis) were not included in the repeat-dose toxicity studies in cynomolgus monkeys. The sponsor's nonclinical expert noted that normal fertility was observed in β_7 -/- mice (Wagner et al., 1996), although the paper itself does not mention any fertility testing or continuation of the line of mice by breeding. In response to a TGA request for further information on this issue, the sponsor indicated that the Wagner paper had been incorrectly cited, but noted other relevant literature about the model: "Litter size and frequency of pregnancy are the same in β_7 integrin null females and C57Bl/6 females at the source colony" (Croy et al., 1997¹⁶). The sponsor further referred to another mouse strain with a homozygous knock-in mutation of the β_7 gene, which increases leukocyte-endothelial stickiness and prevents leukocyte migration out of the vasculature: "These mice were born under normal

¹⁵ EMA/CHMP/ICH/731268/1998. ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals

¹⁶ Croy, B.A., Ashkar, A.A., Foster, R.A., et al. Histological studies of gene-ablated mice support important functional roles for natural killer cells in the uterus during pregnancy. *J Reprod Immunol* 1997;35(2):111-133.

Mendelian ratios, were fertile, and did not exhibit gross abnormalities” (Park et al., 2007¹⁷). This mouse model can be purchased from Jackson Laboratories, Bar Harbor, Maine; the website indicates: “Mice homozygous for this β_7 (D146A) targeted mutation are viable and fertile” (Jackson Laboratory Mice Database).

Embryofetal development studies (pilot and main) were conducted in rabbits, an appropriate species. The studies were adequate with respect to study design, including animal numbers, dose levels and parameters measured. The rabbits were given a single dose of vedolizumab on gestation day (GD) 7. Although dosing with standard low molecular weight drugs in embryofetal development studies in rabbits is usually over GD6/7 to GD18, the vedolizumab-treated rabbits were exposed to the drug at least over GD7-GD20 as serum vedolizumab concentrations on GD20 were 2.97, 79.0 and 236 $\mu\text{g/mL}$, respectively, at the ascending doses.

Some acute mortalities and acute clinical signs were observed in the vedolizumab treated groups in the pilot study and the types of reactions and the results of an investigative anaphylactic testing phase suggested that these were the result of anaphylactoid reactions, possibly associated with the relatively rapid infusion (15 min), as these reactions were not observed in the main study or the repeat-dose toxicity study in rabbits. Vedolizumab did not adversely affect embryofetal development in rabbits. There was no clear evidence of a teratogenic effect (external, skeletal and visceral malformations or variations), including no effects on early cardiac development, a process known to involve α_4 integrins (Yang et al., 1995¹⁸). Fetal incidences of mal-aligned sternbrae were 0, 0, 0.5 and 1.9% in the ascending dose groups in the main study, with the incidence at the high dose being outside the historical control range for the laboratory (0-1.1%), but in the absence of any other developmental changes, this finding was probably incidental. The no observed adverse effect level (NOAEL) was therefore 100 mg/kg IV given on GD7. The exposure ratio at this dose was 8 (see below).

A pre-/postnatal development study was conducted in cynomolgus monkeys. Dosing was every 2 weeks from GD20-GD132. With standard low molecular weight drugs, dosing is generally over the period from implantation until weaning. Thus, if a drug crosses the placenta and is excreted in milk, the embryo/fetus/offspring would normally be exposed to drug throughout pregnancy and lactation. In the current cynomolgus monkey pre-/postnatal study, exposure also began at implantation, and although dosing only continued until GD132 (gestation length is normally approximately 160 days in cynomolgus monkeys), exposure continued until about post natal day (PND) 117 at the high dose (vedolizumab was still detectable, albeit at a low level, at day 277 post coitus (about PND 117) at the high dose). PND0-117 represents about half the lactation period (normally 230-240 days) in cynomolgus monkeys. This study demonstrated a lack of any adverse effect of vedolizumab on either the dams or offspring when the dams were exposed to drug over the period of gestation from implantation to parturition, and at least at the high dose, in early lactation. There was no evidence of teratogenicity, although the number of offspring was limited, and offspring were examined for external malformations/variations only. The NOAEL was 100 mg/kg/dose which achieved an exposure ratio of 24.

¹⁷ Park, E.J., Mora, J.R., Carman, C.V., et al. Aberrant activation of integrin $\alpha_4\beta_7$ suppresses lymphocyte migration to the gut. *J Clin Invest* 2007;117(9):2526-2538.

¹⁸ Yang, J.T., Rayburn, H. and Hynes, R.O. Cell adhesion events mediated by α_4 integrins are essential in placental and cardiac development. *Development* 1995;121:549-560.

Table 3: Relative exposure in reproductive toxicity studies

Species	Study (sampling day)	Dose mg/kg/dose	AUC period	AUC (µg·h/mL)	Exposure ratio#
Rabbit	Embryofetal development (GD7)	10	AUC _{0-337 h}	28,300	0.6
		30		102,000	2.1
		100		366,000	8
Cynomolgus monkey	Pre-/postnatal development (GD132)	10	AUC _{0-3480 h}	105,000	2.2
		100		1,140,000	24
Human (healthy volunteers)	single dose	300 mg	AUC _{0-t}	47,760*	-

= animal:human plasma AUC; * 1990x24 to convert from µg.day/mL to µg.h/mL

Exposures in pregnant rabbits were very similar to those in cynomolgus monkeys at the same doses (sexes combined) in the repeat-dose toxicity study (no toxicokinetic data were available on day 1 in rabbits in the 12 week repeat-dose toxicity study), consistent with the choice of mg/kg as the basis for interspecies comparisons. Achieved exposure ratios in rabbits were adequate and those achieved in cynomolgus monkeys were high. At the high dose in cynomolgus monkeys, although several females developed high titre antibodies, serum vedolizumab concentrations were not affected, so all high dose animals remained exposed throughout the study.

Although the specific placental transfer of vedolizumab was not investigated, IgG antibodies are known to cross the placenta. Vedolizumab was detected at low concentrations in the milk of cynomolgus monkeys, but only at the high dose (exposure ratio 24, although dosing was not done during the lactation period). Maternal serum:milk ratios could not be calculated because serum concentrations were not measured on the day of milk collection (PND28). In infants born to the high dose dams, serum vedolizumab concentrations were generally in the range 10-100 µg/mL on PND28.

Pregnancy classification

The sponsor has proposed pregnancy Category B2¹⁹. There were no treatment related adverse findings in fetuses in the rabbit embryofetal development studies or in cynomolgus monkey infants, and the pharmacological effects of vedolizumab (binding to α₄β₇ sites on relevant leukocytes and a consequent reduction in gut immunosurveillance) are unlikely to be detrimental to fetuses. There was also no evidence from the cynomolgus monkey study that this pharmacological effect of the drug caused adverse effects in newborns, which is relevant when considering use in pregnancy. Given the long half-life of vedolizumab (25 days in humans), consideration needs to be given to the newborn when this drug is administered during pregnancy. Although there was no evidence from the monkey study that gestational exposure had an adverse effect on the infants, animal

¹⁹ Category B2 for use of medicines in pregnancy is defined: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

numbers were low and offspring were examined only externally. Consequently, the choice of Category B2 is appropriate.

Immunotoxicity

The potential immunotoxicity of vedolizumab was investigated as part of the 13 week study in cynomolgus monkeys with fortnightly dosing at up to 100 mg/kg/dose IV and in dedicated immunotoxicity studies. In the 13 week monkey study, vedolizumab had no effects on lymphocyte subsets (absolute numbers and relative proportions) or natural killer (NK) cell activity, nor did it impair the systemic adaptive immune system, as measured by a T-cell dependent antibody response (TDAR). Lymphocyte subset phenotyping was also conducted in another study (earlier 13 week study with IV LDP-02 at up to 10 mg/kg/dose) in cynomolgus monkeys, again with negative results. Two dedicated immunotoxicity studies were conducted in cynomolgus monkeys, the first involving single doses of natalizumab at 10 and 30 mg/kg IV and the second involving 3 doses of vedolizumab and natalizumab, each at 30 mg/kg IV given at weekly intervals, with only the former study including a positive control compound. In the latter study, the results for vedolizumab were consistent with those from the repeat dose study, with no changes in immunophenotyping results or TDAR. The 30 mg/kg dose is an appropriate dose (it achieved an exposure ratio of 2.4 on day 1 in the 26 week toxicity study in cynomolgus monkeys). The results for natalizumab were not consistent between the two studies, with an effect on TDAR in the single dose study but not in the multi-dose study. The reason for this is not clear, although there were some small differences in experimental conditions.

There was no evidence that Act-1 had an immunosuppressive effect based on the results of a study which investigated humoral antibody response and cutaneous delayed-type hypersensitivity (effector stage) in rhesus monkeys immunised with tetanus toxoid.

In summary, relevant endpoints were investigated in a number of studies and the weight of evidence suggests that vedolizumab lacks any immunotoxic effects.

Tissue cross-reactivity

The results for these studies have been discussed under relevant sections above.

Local tolerance

There was no evidence of any local irritation in a local tolerance study in rabbits, but the routes investigated were subcutaneous (SC) and IM which are not relevant for the current application for which the proposed clinical route is IV. While there was no dedicated study investigating IV or paravenous irritation, there was generally no evidence of injection site irritation in the single dose or repeat-dose toxicity studies. There were some findings (intimal hyperplasia, acute haemorrhage and inflammation) at the injection site in the 2 week cynomolgus monkey study, possibly associated with the high frequency of dosing (daily).

Paediatric use

Vedolizumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Manufacturing process

Several nonclinical studies were also conducted to support process changes in manufacturing.

Other studies

Other studies such as phototoxicity studies are not required for vedolizumab and were not conducted.

Nonclinical summary and conclusions

- The overall quality of the nonclinical dossier was good and relevant studies were GLP compliant.
- Vedolizumab binds to the $\alpha_4\beta_7$ integrin on various leukocytes and prevents the binding of lymphocytes bearing this receptor to adhesion molecule, MAdCAM-1. Vedolizumab does not bind to $\alpha_4\beta_1$ or $\alpha_E\beta_7$ integrins, does not inhibit the binding of $\alpha_4\beta_7$ integrin to VCAM-1, and is gut selective since MAdCAM-1 is expressed selectively in the gut. Vedolizumab appears to ameliorate intestinal inflammatory conditions by preventing the gut-homing of memory T helper lymphocytes. It showed efficacy in an animal model (naturally-occurring chronic colitis in cotton-top tamarin monkeys), although the exposure achieved in this study was not determined.
- A study in an EAE model in rhesus monkeys provided no evidence that vedolizumab at an adequate dose inhibits immunosurveillance in the CNS. Vedolizumab is therefore not expected to be associated with PML. Further, CSF analyses in the 26 week cynomolgus monkey study did not reveal any effect of vedolizumab on infiltration of leukocytes into the CSF. No secondary PD studies were submitted which is acceptable.
- A single safety pharmacology study, an in vivo cardiovascular study in cynomolgus monkeys, revealed no effects of vedolizumab at an adequate dose (up to 100 mg/kg IV infusion) on MAP, HR or ECG parameters. Results of qualitative ECGs in several repeat dose toxicity studies were also negative. There were no findings in repeat-dose studies which suggested the need for further safety pharmacology studies.
- Vedolizumab was cleared slowly, volume of distribution was consistent with blood volume and half-life was very long (about 15 days in cynomolgus monkeys and 25 days in humans).
- A single dose toxicity study in cynomolgus monkeys did not reveal any toxicity (mortality, clinical signs or body weight) at doses up to 100 mg/kg IV infusion.
- Repeat dose IV toxicity studies were conducted in rabbits and cynomolgus monkeys, both pharmacologically responsive species. Pivotal studies were a 13 week study in rabbits and a 26 week study in cynomolgus monkeys with twice weekly dosing (0, 10 (monkeys only), 30 and 100 mg/kg/dose by IV infusion in both species). There were no toxic effects that were clearly associated with vedolizumab treatment. Lymphoid depletion was observed in Peyer's patches in all male dose groups in the cynomolgus monkey study and a decrease in lymphoid follicle size in the sacculus rotundus was observed in mid dose and high dose rabbits, findings considered to be related to the primary pharmacological activity. Lymphoid hyperplasia in the spleen was observed at the mid dose and high dose in rabbits, possibly associated with chronic antigenic stimulation due to anti-vedolizumab antibodies rather than a direct effect of vedolizumab. Animal to human exposure ratios at the high were 25 in rabbits (day 84 data) and 8 in cynomolgus monkeys (day 1 data), and these may be underestimates.
- Almost all rabbits and cynomolgus monkeys treated with vedolizumab developed anti-vedolizumab antibodies, generally after about 8-14 days. Titres varied among animals, and were generally higher at the lower doses. In some animals, with consistently high titres, serum vedolizumab concentrations were reduced.

- Genotoxicity studies are not required for monoclonal antibodies and were not conducted. No standard carcinogenicity studies were conducted. Vedolizumab was not pharmacologically active in mice or rats. Two in vitro studies with Act-1 (the murine antibody from which vedolizumab was derived) did not provide any signal of carcinogenic potential of vedolizumab. Thus, Act-1 inhibited rather than stimulated the growth of a human B-cell lymphoma cell line and did not show any tissue cross-reactivity with tumour tissue from 10 human colon adenocarcinomas.
- Placental transfer of vedolizumab was not investigated but IgG is known to cross the placenta. No fertility studies were conducted. Vedolizumab did not show a toxic effect on reproductive tissues in the repeat-dose toxicity studies and did not cross-react with reproductive tissues in tissue cross-reactivity studies. In embryofetal development studies in rabbits, vedolizumab showed no evidence of teratogenicity and did not affect embryofetal development at doses up to 100 mg/kg IV (infusion) given on GD7.
- A pre-/postnatal development study was conducted in cynomolgus monkeys with IV (infusion) dosing fortnightly at 10 and 100 mg/kg/dose from GD20 to GD132. No adverse effects were observed in dams or infants (the latter were observed for 6 months after birth). On PND28, a low concentration of vedolizumab was detected in milk at the high dose only.
- Vedolizumab showed no evidence of immunotoxic potential in repeat dose toxicity studies in cynomolgus monkeys or in a dedicated comparative (vedolizumab versus natalizumab) immunotoxicity study. No effect of vedolizumab was observed on immunophenotyping of lymphocyte subsets, NK cell activity or T-cell dependent antibody responses. Vedolizumab also showed no immunosuppressive activity in a model of cutaneous delayed type hypersensitivity in rhesus monkeys.
- In tissue cross-reactivity studies, vedolizumab was tested for binding to cryosections of 37 human and monkey tissues. In both species, staining was only observed for mononuclear cells (lymphocytes and monocytes/macrophages) in lymphoid tissues and within the lumen of blood vessels, or as low-grade inflammatory infiltrates in various non-lymphoid tissues.
- Local tolerance was investigated using the SC and IM routes (not relevant for the current IV submission). Injection site irritation was generally not observed in the repeat-dose toxicity studies which all used the IV route.
- The manufacturing process used to produce vedolizumab, and the formulation of the medicinal product, have been changed twice during development (giving Process A, B and C products). For the change from Process A to B: no differences in binding affinity or cross-reactivity for human tissues were observed, but CL appeared somewhat more rapid with one than the other. No differences in toxicity between Process B and C vedolizumab (at 10 and 30 mg/kg IV infusion) were seen in a single dose study in cynomolgus monkeys.

Conclusions and recommendation

- The nonclinical data provided were satisfactory.
- Primary pharmacology studies adequately demonstrated the mechanism of action of vedolizumab (inhibition of binding of $\alpha_4\beta_7$ integrin to MAdCAM-1) and vedolizumab was shown to be efficacious in a cotton-top tamarin monkey model of naturally occurring chronic colitis, although the exposure achieved in this study was not determined. Evidence was provided that vedolizumab is unlikely to inhibit immune surveillance in the CNS and therefore is unlikely to be associated with a risk of PML. Rabbits and monkeys, but not rats and mice, were shown to be pharmacologically responsive species.

- A safety pharmacology study (cardiovascular study in cynomolgus monkeys) at appropriate doses did not reveal any effects of vedolizumab on MAP, HR or ECG parameters.
- Adequate repeat-dose toxicity studies in rabbits did not identify any target organs. Adequate or high exposure ratios were achieved (up to 25 in rabbits and 8 in cynomolgus monkeys).
- Genotoxicity studies were not conducted and are not required. Carcinogenicity studies were not conducted but there was no evidence of carcinogenic potential from in vitro studies examining the effect of the vedolizumab predecessor antibody (Act-1) on the growth of a human B-cell lymphoma cell line and the cross-reactivity of vedolizumab with tumour tissue from human colon adenocarcinomas.
- No fertility studies were conducted. Embryofetal development studies in rabbits (at exposure ratios up to 8) did not reveal any evidence of teratogenicity or embryofetal toxicity. There were no effects on infants when vedolizumab (at exposure ratios up to 24) was administered to cynomolgus monkeys throughout most of the gestation period.
- Vedolizumab showed no evidence of immunotoxic potential in repeat-dose toxicity studies or a dedicated immunotoxicity study.
- In cross-reactivity studies with human and cynomolgus monkey tissues, staining was only observed for mononuclear cells (lymphocytes and monocytes/macrophages) in lymphoid tissues and within the lumen of blood vessels, or as low-grade inflammatory infiltrates in various non-lymphoid tissues.

There are no nonclinical objections to registration of vedolizumab for the proposed indications.

Amendments to nonclinical statements in the draft PI were recommended; details of these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in the extract from the clinical evaluation report (CER) at Attachment 2.

Introduction

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 TNF α antagonists, there is a need for new targeted therapies, particularly one that reduces the gastrointestinal inflammatory process without increasing the risk for toxicities commonly seen with the currently available agents. Vedolizumab is a gut-selective anti-inflammatory agent that was developed to help fulfil this important unmet medical need.*

Guidance

Relevant guidelines include:

- 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)

The sponsor provided justification with regard to deviations from the above.

Contents of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 14 clinical pharmacology studies, including 14 that provided PK data and 12 that provided PD data.
- 2 population PK 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.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The studies submitted in the dossier are stated to have been conducted according to good clinical practice (GCP). It is the evaluator's belief that the sponsor has adhered to GCP when conducting these studies.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 shows the studies relating to each PK topic.

Table 4: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Study C13001
		Study L297-007
		Study C13012

PK topic	Subtopic	Study ID
		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.

Evaluator's summary and conclusions on pharmacokinetics

- The PK of vedolizumab have been adequately characterised.
- Vedolizumab has a half-life of around 26 days, CL of around 0.16 L/day and (from Study C13009) volume of distribution around 4.5 L. The PK conformed to a two compartment model. The typical value of volume of distribution from the Metrum Research Group population PK study was 3.19 L for the central volume and 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% (coefficient of variability, 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 (0), 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 weeks 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 Research Group population PK study, the covariate modelling indicated that prior treatment with TNF α inhibitors increased CL, as did the presence of human anti-human antibodies (HAHA). Azathioprine, methotrexate, 6-mercaptopurine and aminosalicylates did not have a clinically significant effect on CL. Clearance was decreased in subjects with low serum albumin at baseline. Age and gender did not have a significant effect upon clearance.
- 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 (see *Clinical questions* below).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each PD topic.

Table 5: 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
Secondary Pharmacology	Effect on CSF CD4+/CD8+	Study C13012
	Effect on immunogenicity	Study C13013
Population PD and PK-PD	Target population	Projections Research Population PK-PD Report

PD Topic	Subtopic	Study ID
analyses		Metrum Research Group Population PK-PD Report

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

Evaluator's summary and conclusions on pharmacodynamics

- The PD 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 h (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.

Dosage selection for the pivotal studies

The dosage selection for the pivotal studies appears to have been based on the PD 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.

Efficacy

Studies providing efficacy data in Crohn's disease

Efficacy was examined in two Phase III 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 treatment²⁰. In addition to these studies there was a Phase II study (Study L299-016) 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*: Crohn's Disease Activity Index (CDAI) score \leq 150 points
- *Clinical response*: a \geq 70 point decrease in CDAI score from baseline (Week 0)

²⁰ 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 TNF α antagonist therapy (TNF α antagonist failure subpopulation)

- *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 $\geq 80\%$ of study visits including final visit (Week 52)
- *Durable clinical response*: clinical response at $\geq 80\%$ of study visits including final visit (Week 52)
- *Durable enhanced clinical response*: enhanced clinical response at $\geq 80\%$ 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 Harvey-Bradshaw Index (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 CHMP *Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease* (CPMP/EWP/2284/99 Rev. 1).

A pooled analysis of efficacy was performed using data from Study C13007 and Study C13011.

Evaluator's summary and conclusions on efficacy in 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 group, relative risk (RR) (95% confidence interval (CI)) was 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 group, RR (95% CI) 1.2 (0.9 to 1.7), $p = 0.2322$. The clinical response was less effective 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, that is, 300 mg administered by IV infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. In Study C13011, the proportion of subjects in clinical remission at Week 10 was greater for vedolizumab in the TNF α Antagonist Failure intent to treat (ITT) subpopulation and in the Overall ITT Population. For the TNF α 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 group, 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 TNF α antagonist failure. In those subjects with intolerance or lack of response to TNF α inhibitors there was a significant benefit for vedolizumab. However, in subjects that had previously lost response to TNF α antagonist treatment, there did not appear to be efficacy for vedolizumab. In Study C13011, in the population of subjects with previous TNF α antagonist treatment failure there was no significant difference in efficacy between vedolizumab and placebo. Hence, in subjects that

had initially responded to TNF α 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 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 group (RR [95% CI] 1.7 [1.2 to 2.4], $p = 0.0042$), and 33 (21.6%) in the placebo group.

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.

Studies providing efficacy data in ulcerative colitis

Efficacy was examined in one Phase III 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, TNF α antagonists and corticosteroids. In addition to these studies there were two Phase II studies (Study C13002 and Study M200-022) 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 score²¹ of ≤ 2 points and no individual subscore > 1 point
- *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 $\geq 30\%$ 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 $\geq 25\%$ from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point

²¹ The method for calculating the Mayo score is displayed in Table 3 of the CER (see AusPAR Attachment 2).

- *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 $\geq 25\%$ 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 CHMP *Guideline on the Development of New Medicinal Products for Ulcerative Colitis* (CHMP/EWP/18463/2006).

There were no pooled results of efficacy for UC.

Evaluator's conclusions on efficacy in 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 group, 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 group. The mean (standard error, 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 TNF α antagonist therapy and in the subgroup of patients defined as having failed TNF α 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 TNF α 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.

Safety

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, GI, 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 (vedolizumab) 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.

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 (patient numbers) by study is summarised in Table 6.

Table 6: Summary of patient exposure in safety studies

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 III 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. Details of exposure by dose level in studies conducted in subjects with CD or UC are summarised in the CER (Attachment 2 of this AusPAR).

Safety issues with the potential for major regulatory impact

Infection related adverse events

In Study C13007 during the induction phase, infection related treatment emergent AEs (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.

Gastrointestinal system adverse events

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

In Study C13011 GI TEAEs were reported in 37 (18%) subjects in the vedolizumab group and 49 (24%) in the placebo. In Study C13006 in the induction phase GI TEAEs were reported in 74 (10%) subjects in the vedolizumab group and 28 (19%) in the placebo. In the maintenance phase GI TEAEs were reported in 231 (37%) subjects in the vedolizumab group and 105 (38%) in the placebo.

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 study's Independent Adjudication Committee.

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 generalised 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.

Postmarketing data

No post-marketing data were included in the submission.

Integrated summary of safety

The Integrated Summary of Safety indicated similar rates for vedolizumab and placebo for the more common TEAEs in a pooled analysis of Studies C13006 and C13007 (Table 7).

Table 7: Frequency and Incidence Density of AEs Occurring in ≥ 3% of Patients in the Combined Vedolizumab Group by Preferred Term – UC and CD Combined Induction/Maintenance Safety Population (C13006 and C13007)

Preferred Term, n (%)	ITT Placebo ^a		Non-ITT Placebo ^b		Combined Vedolizumab ^c	
	Patients n (%) N = 279	Events (Density ^d) TPY = 192.9	Patients n (%) N = 297	Events (Density ^d) TPY = 156.3	Patients n (%) N = 1434	Events (Density ^d) TPY = 988.8
Patients with at least 1 AE / Total number of events	234 (84)	1180 (6.117)	232 (78)	1082 (6.923)	1203 (84)	6161 (6.231)
Nasopharyngitis	29 (10)	38 (0.197)	21 (7)	23 (0.147)	180 (13)	232 (0.235)
Headache	43 (15)	76 (0.394)	32 (11)	55 (0.352)	177 (12)	287 (0.290)
Arthralgia	36 (13)	45 (0.233)	29 (10)	36 (0.230)	166 (12)	210 (0.212)
Crohn's disease	29 (10)	32 (0.166)	36 (12)	41 (0.262)	164 (11)	194 (0.196)
Nausea	26 (9)	33 (0.171)	23 (8)	31 (0.198)	128 (9)	175 (0.177)
Pyrexia	30 (11)	33 (0.171)	22 (7)	29 (0.186)	127 (9)	156 (0.158)
Abdominal pain	20 (7)	29 (0.150)	29 (10)	36 (0.230)	114 (8)	148 (0.150)
Upper respiratory tract infection	19 (7)	25 (0.130)	19 (6)	23 (0.147)	106 (7)	134 (0.136)
Colitis ulcerative	29 (10)	29 (0.150)	29 (10)	33 (0.211)	97 (7)	119 (0.120)
Fatigue	14 (5)	16 (0.083)	10 (3)	14 (0.090)	86 (6)	104 (0.105)
Vomiting	14 (5)	17 (0.088)	16 (5)	21 (0.134)	75 (5)	97 (0.098)
Anaemia	10 (4)	10 (0.052)	20 (7)	20 (0.128)	70 (5)	80 (0.081)
Cough	10 (4)	13 (0.067)	10 (3)	11 (0.070)	70 (5)	73 (0.074)
Back pain	7 (3)	7 (0.036)	10 (3)	10 (0.064)	62 (4)	65 (0.066)
Bronchitis	11 (4)	12 (0.062)	10 (3)	11 (0.070)	57 (4)	63 (0.064)
Influenza	10 (4)	11 (0.057)	5 (2)	5 (0.032)	51 (4)	54 (0.055)
Urinary tract infection	10 (4)	12 (0.062)	8 (3)	9 (0.058)	49 (3)	60 (0.061)
Dizziness	9 (3)	11 (0.057)	8 (3)	8 (0.051)	48 (3)	56 (0.057)
Diarrhoea	19 (7)	20 (0.104)	10 (3)	13 (0.083)	44 (3)	49 (0.050)
Sinusitis	10 (4)	10 (0.052)	3 (1)	3 (0.019)	44 (3)	52 (0.053)
Influenza like illness	11 (4)	14 (0.073)	9 (3)	9 (0.058)	43 (3)	51 (0.052)
Rash	7 (3)	8 (0.041)	6 (2)	6 (0.038)	42 (3)	48 (0.049)
Oropharyngeal pain	6 (2)	9 (0.047)	4 (1)	4 (0.026)	42 (3)	46 (0.047)
Pruritus	3 (1)	3 (0.016)	4 (1)	4 (0.026)	39 (3)	58 (0.059)
Oedema peripheral	8 (3)	8 (0.041)	12 (4)	17 (0.109)	38 (3)	44 (0.044)
Pain in extremity	7 (3)	7 (0.036)	4 (1)	7 (0.045)	38 (3)	41 (0.041)

Source: Table 18.2.2.5A, Table 18.2.2.3B.

Abbreviations: AE = adverse event; CD = Crohn's disease; ITT = intent-to-treat; TPY = total person time in years; UC = ulcerative colitis.

- a Patients received vedolizumab during Induction Phase and were randomized to placebo for the Maintenance Phase.
- b Patients received placebo during the Induction Phase and continued to receive placebo during Maintenance Phase.
- c Includes the ITT vedolizumab Q8W, ITT vedolizumab Q4W, and non-ITT vedolizumab Q4W groups.
- d Density = number of events divided by total person time in years, with end of study defined as last scheduled dosing date + 16 weeks if not continuing into Study C13008; otherwise, as last scheduled dosing date.

Evaluator's summary and conclusions on 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.

Discontinuation due to AEs (DAEs) 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 the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (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.

Human anti-human antibodies 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 vedolizumab but less common with the version of 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 GI 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.

First round benefit-risk assessment

First round assessment of benefits

Benefits in 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), $p = 0.2322$. The clinical response was less effective 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, that is, 300 mg administered by IV infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. In Study C13011, the proportion of subjects in clinical remission at Week 10 was greater for vedolizumab in the TNF α Antagonist Failure ITT Subpopulation and in the Overall ITT Population. For the TNF α 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 TNF α antagonist failure. In those subjects with intolerance or lack of response to TNF α inhibitors there was a significant benefit for vedolizumab. However, in subjects that had previously lost response to TNF α antagonist treatment, there did not appear to be efficacy for vedolizumab. In Study C13011, in the population of subjects with previous TNF α antagonist treatment failure there was no

significant difference in efficacy between vedolizumab and placebo. Hence, in subjects that had initially responded to TNF α 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 *Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease* (CPMP/EWP/2284/99 Rev. 1) 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.

Benefits in 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 group, 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 group.

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 group. 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 TNF α antagonist therapy and in the subgroup of patients defined as having failed TNF α 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 TNF α 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 *Guideline on the Development of New Medicinal Products for Ulcerative Colitis* (CHMP/EWP/18463/2006) 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.

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. Serious AEs 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.

Discontinuation due to AE 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.

Human anti-human antibodies 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 vedolizumab but less common with the version of 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 GI 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.

First round assessment of benefit-risk balance

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

First round recommendation regarding authorisation

The evaluator is unable to recommend the approval of vedolizumab (Entyvio/Kynteles), 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 (TNF α) 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 (TNF α) antagonist.

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

However, the evaluator had no objection to the approval of vedolizumab (Entyvio/Kynteles), 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 (TNF α) 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 (TNF α) antagonist. In subjects with Crohn's disease who had initially responded to TNF α antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.

Clinical questions

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

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 Law²²?

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?

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 \leq 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 PK-PD 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 risk management plan (RMP) and the absence of this information should not preclude approval of the current application.

- 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?

²² Model used to predict risk of serious liver toxicity

The sponsor has based their response on the subjects in Study C13006 and Study C13007 who only received vedolizumab in comparison with those who only received placebo. There were 22 (1.5%) subjects who only received vedolizumab and 3 (1.0%) who only received placebo who had ALT > 3 x upper limit of normal (ULN); and 16 (1.1%) subjects who only received vedolizumab and none (0.0%) who only received placebo who had AST > 3 x ULN. None of the subjects with elevated ALT or AST were reported with a liver infection AE, a SAE due to liver infection or DAE due to liver infection. In Study C13008, there were 55 (2.5%) subjects with ALT > 3 x ULN and 45 (2.0%) with AST > 3 x ULN. 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 female subject with ALT 952 U/L, total bilirubin 48 µmol/L and alkaline phosphatase (ALP) of 158 U/L who was diagnosed with hepatitis of unclear origin. Her condition improved even though the vedolizumab was continued.
- One 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 elevated antinuclear antibodies (ANA) and later with systemic lupus erythematosus (SLE). She improved with topical steroids.

Overall there were 22 subjects with hepatic parenchymal events while being treated with vedolizumab, 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 vedolizumab 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 RMP 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 elevated amylase and lipase. In Study C13006 and Study C13007, in the population of subject only treated with vedolizumab there were 20 (1.4%) subjects with amylase > 2 x ULN and 28 (2.0%) with lipase > 2 x ULN, 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 > 2 x ULN and 44 (2.0%) with lipase > 2 x ULN. Acute pancreatitis was reported for ten subjects treated with vedolizumab 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 vedolizumab 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.*"

Sponsor's response to comments in the clinical evaluation report

In addition to providing information against each of the questions raised by the clinical evaluator, the sponsor addressed several comments made by the evaluator in the CER. The clinical evaluator's evaluation of these is below.

Evaluator comment: Vedolizumab did not appear to offer benefit for those patients with CD who had initially responded to TNF α antagonist treatment, and subsequently lost response.

The sponsor 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 randomisation was not stratified by type of prior TNF α antagonist failure. Therefore, small sample sizes for patients with each type of failure to TNF α 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 TNF α and consistent treatment benefit was observed in all groups administered vedolizumab versus 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 TNF α inhibitors, there were the following results:

- At Week 6 clinical remission was reported in 15 (15.0%) subjects in the vedolizumab population and 13 (12.6%) of the placebo, difference (95% CI) vedolizumab-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 vedolizumab population and 22 (21.4%) of the placebo, difference (95% CI) vedolizumab-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 vedolizumab population and 14 (13.6%) of the placebo, difference (95% CI) vedolizumab-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 vedolizumab population and 10 (9.7%) of the placebo, difference (95% CI) vedolizumab-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 TNF α 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 group 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 vedolizumab population and 0 (0.0%) of the placebo, difference (95% CI) vedolizumab-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 vedolizumab population and 7 (18.4%) in the placebo, difference (95% CI) vedolizumab-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 sponsor's response are different to those reported in the Clinical Study Report for Study

C13007. This is confusing but appears to be because the sponsor's 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 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 dosing 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 comment: Subgroup Analyses of Patients Who Were Taking Concomitant Medication and were not able to take TNF α antagonists

The sponsor provided additional tabulations and graphical presentations of subgroup analyses for subjects taking concomitant medications and who were not able to take TNF α antagonists. These tabulations indicate that concomitant corticosteroid and/or immunomodulator treatment does not affect response to vedolizumab

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 TNF α antagonist did not have a sustained response to vedolizumab. For the 8 weekly dosing regimen the difference in response rate (95% CI) at Week 52, vedolizumab-placebo, was 8.1 (-27.9 to 42.0) % for subjects with loss of response to TNF α antagonists, 37.5 (4.5 to 65.2) % for subjects with inadequate response to TNF α antagonists and 48.3 (7.2 to 78.8) % in subjects with intolerance to TNF α antagonists. Hence this provides further evidence of lack of long term efficacy of vedolizumab for subjects with loss of response to TNF α antagonists for both UC and CD.

Evaluator's additional comments on the data submitted in the overall application***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 4 weekly and eight weekly vedolizumab 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 vedolizumab were in clinical remission at Week 52 than those who received placebo. A similar difference occurred for enhanced clinical response where the difference was around 15% (favouring vedolizumab). No statistical comparisons of efficacy between the vedolizumab 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 TNF α antagonist naïve and those who had experienced failure both had statistically significant benefit from treatment at the Week 10 assessment. An additional 14.5% of patients who had previously failed TNF α 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 TNF α 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 TNF α antagonist failure.

Taking the results of the two Phase II studies together the data support the proposed induction regimen for patients with moderate to severe CD, including patients with prior TNF α 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.

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 vedolizumab 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 8 weekly and 4 weekly 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 every 8 weeks 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 patients with MS had been exposed to natalizumab for more than 2 years. Long term safety data for vedolizumab 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 UC 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.

Second round benefit-risk assessment

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 UC 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 TNF α antagonist.
- Efficacy has been demonstrated for vedolizumab in the treatment of adult patients with moderate to severe CD 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 TNF α antagonist.

However, the evaluator is unable to conclude sustained efficacy for subjects with UC or CD who had initially responded to TNF α antagonists and subsequently lost response.

Increasing the frequency of dosing from every 8 weeks to every 4 weeks in subjects that lose response to vedolizumab has not been demonstrated to be beneficial in an appropriately designed study.

Second round assessment of risks

After consideration of the responses to clinical questions, the evaluator concludes that in addition to the risks identified in the *First round assessment of risks*, above:

- There is a higher rate of elevation of transaminases and of hepatic parenchymal damage in subjects treated with vedolizumab 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.

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.

Second round recommendation regarding authorisation

The evaluator is unable to recommend the approval of vedolizumab (Entyvio/Kynteles), 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 (TNF α) 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 (TNF α) antagonist.

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

However, the evaluator has no objection to the approval of vedolizumab (Entyvio/Kynteles), 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 (TNF α) 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 (TNF α) antagonist.

In subjects with ulcerative colitis or Crohn's disease who had initially responded to TNF α antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Vedolizumab EU-RMP version 1.0, dated 5 February 2013 (data lock point 16 July 2012) + Australian-specific Annex (ASA) version 1.0 dated June 2013) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

Table 8: Summary of ongoing safety concerns

Ongoing safety concerns	
Important identified risks	Infusion-related reactions (IRRs), including hypersensitivity reactions (HSRs)
Important potential risks	<ul style="list-style-type: none"> • Infections <ul style="list-style-type: none"> – Gastrointestinal infections and systemic infections (serious and non-serious) against which the gut constitutes a defensive barrier – Other serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML) • Malignancies
Important missing information	<ul style="list-style-type: none"> • Use in Pregnancy and lactation • Use in Paediatric patients • Use in Elderly patients • Use in Hepatic Impairment • Use in Renal Impairment • Use in Cardiac Impairment • Long-term safety • Patients with prior exposure to natalizumab or Rituximab or use with concurrent biologic immunosuppressants

Pharmacovigilance plan

The sponsor's proposed pharmacovigilance activities are summarised in Table 9.

Table 9: Proposed pharmacovigilance activities

Proposed pharmacovigilance activities	
Important identified risks	
<p>Infusion-related reactions (IRRs), including hypersensitivity reactions (HSRs)</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance: signal detection, Periodic Safety Update Reports (PSURs), adverse event (AE) surveillance and reporting, literature surveillance • Additional Pharmacovigilance: MLN-0002_401: A postmarketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease C13008: Ongoing long-term safety extension study of patients from Studies C13004, C13006, C13007, and C13011
Important potential risks	
<p>Infections: Gastrointestinal infections and systemic infections against which the gut constitute a defensive barrier</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance: signal detection, PSURs, AE surveillance and reporting, literature surveillance • Additional Pharmacovigilance: MLN-0002_401: A postmarketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease. C13008: Ongoing long-term safety extension study of patients from Studies C13004, C13006, C13007, and C13011
<p>Other serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML)</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance: signal detection, PSURs, AE surveillance and reporting, literature surveillance • Event-specific follow-up form for cases of suspected neurologic symptoms/PML (annex 7) • Additional Pharmacovigilance: MLN-0002_401: A postmarketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease C13008: Ongoing long-term safety extension study of patients from Studies C13004, C13006, C13007, and C13011
<p>Malignancies</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance: signal detection, PSURs, AE surveillance and reporting, literature surveillance • Additional Pharmacovigilance: MLN-0002_401: A postmarketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease C13008: Ongoing long-term safety extension study of

Proposed pharmacovigilance activities	
	patients from Studies C13004, C13006, C13007, and C13011
Missing information	
<ul style="list-style-type: none"> · Pregnancy and lactation · Paediatric · Elderly · Use in patients with hepatic impairment · Use in patients with renal impairment · Use in patients with cardiac impairment · Prior exposure to natalizumab and rituximab and use with concurrent biologic immunosuppressants 	<ul style="list-style-type: none"> · Routine Pharmacovigilance: signal detection, PSURs, AE surveillance and reporting, literature surveillance · Additional Pharmacovigilance: MLN-0002_401: A postmarketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease

Risk minimisation activities

Sponsor's conclusion regarding the need for risk minimisation activities

The sponsor commits to report cases of overdose through the future Periodic Safety Update Reports (PSURs). The sponsor recognises the potential off-label use of vedolizumab in other indications and in paediatric population. It is planned to manage these issues through information provided by product labelling.

Planned actions

The sponsor proposes routine risk minimisation activities for all the safety concerns addressed in the plan. A physician educational brochure is also proposed for the safety concern of other serious infections, including opportunistic infections such as progressive PML.

Reconciliation of issues outlined in the RMP report

Table 10 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 10: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for	Takeda acknowledged that further changes to the RMP may be requested and committed to responding to any requests	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
information and/or the nonclinical and clinical evaluation reports. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP.	received as they occur.	
The sponsor should undertake to inform the TGA if its application is rejected by other overseas regulatory agencies.	The sponsor provided assurance that the TGA will be informed of any changes to the overseas regulatory status for applications currently under review.	The sponsor's response is satisfactory.
The sponsor did not address the safety issue of 'long-term safety' in the pharmacovigilance and the risk minimisation plan.	Long-term Safety is addressed in version 2 of the RMP submitted with the sponsor's response (see below). The RMP ASA, section has been updated to list 'Long-term safety' under 'Missing Information'.	The sponsor's response is satisfactory.
The sponsor should clarify whether, pending the approval of the product by the TGA, Australia will be one of the participating countries in study MLN-0002_401. In addition, the sponsor should provide its alternative plan in case its applications to overseas regulatory agencies in the EU and the USA are rejected or deferred.	Study MLN-0002_401 is a prospective, observational, international, multi-centre, cohort study, to be conducted in North America and Europe. The sponsor committed to reassessing the plan and working with the [OPR] in order to reach a mutually acceptable alternative should applications to overseas regulatory agencies in the EU and USA are rejected or deferred.	It is satisfactory that if applications in the EU and the USA are rejected or deferred, the sponsor reassesses the plan and work with the TGA to reach a mutually acceptable alternative.
It is expected that updates and findings of the ongoing and planned studies will be communicated to the TGA and included in PSURs when available. It is recommended that results of these studies are communicated to the TGA at the same time as they are communicated to other	An assurance was granted that updates and findings of the ongoing and planned studies will also be communicated to the TGA when they are communicated to other recognised regulatory agencies.	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
regulatory agencies.		
The table in section 3 of the ASA is titled 'Summary of Planned Pharmacovigilance Actions' whilst the content is risk minimisation activities. The sponsor should note the difference between the two terms and change the title of the table to 'Summary of Planned Risk Minimisation Activities'.	The table in section 3 of the ASA has been revised.	The sponsor's response is satisfactory.
It is noted that a Patient Alert Card is proposed in the EU-RMP to address the safety concern of infections. This activity is deemed not applicable in the ASA and the issues will be managed by information in the PI and CMI. As both the specific objectives of the alert card and the safety concerns apply to the Australian context, the sponsor should include the Patient Alert Card in the Australian risk minimisation plan.	The sponsor agreed to the inclusion of the Patient Alert Card in the Australian Specific Annex.	The sponsor's response is satisfactory.
The sponsor should provide a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI as currently stated in the 'Summary of Planned Pharmacovigilance Actions' should be included in the table.	The sponsor agreed with the evaluator's recommendation and the table in section 3 of ASA was revised.	The sponsor's response is satisfactory.

Key changes to the updated RMP

In response to the TGA request for information, the sponsor provided an updated EU-RMP, version 2.0, dated 27 September 2013 (data lock point 14 March 2013), with the ASA version 2.0, dated January 2014. Key changes from the versions evaluated at Round 1 are summarised in Table 11:

Table 11: Key changes from RMP version 1 to version 2

RMP Updates	
Safety specification	<p>'Upper respiratory tract infections' have been added as important identified risk;</p> <p>'Off label use' including mild UC and CD; use in children and adolescents; and use with concomitant anti-tumour necrosis factor drugs has been added as important potential risk;</p> <p>'Use with concurrent biologic immunosuppressant' has been removed from missing information.</p>
Pharmacovigilance activities	<p>Routine pharmacovigilance have been added for the safety risks including 'upper respiratory tract infections', 'off label use' and 'long-term safety';</p> <p>Additional pharmacovigilance including study MLN-0002_401 and C13008 has been added for 'upper respiratory tract infections'.</p>
Risk minimisation activities	<p>Routine risk minimisation has been added for the safety risks including 'upper respiratory tract infections', 'off label use' and 'long-term safety';</p> <p>Additional risk minimisation in the form of a patient alert card has been added for infections.</p>

The evaluator has no objection to the above changes.

Summary and recommendations

Issues in relation to the RMP

The sponsor has adequately addressed all of the issues identified in the round one RMP evaluation report.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

Advice on the pharmacovigilance aspects of this application were sought from ACSOM and passed onto the Delegate (see *Overall conclusion and risk/benefit assessment*, below).

Comments on the Safety Specification of the RMP

The clinical evaluator, TGA Office of Medicines Authorisation (OMA), has provided the following comments in the clinical evaluation report:

The sponsor provided new clinical information after the first round but did not revise the Safety Specification in the draft RMP. After consideration of the new clinical information, the comments on the Safety Specification made ... are revised as follows:

Elevation of transaminases and hepatic parenchymal damage should be included as an Important Potential Risk.

The Sponsor needs to address the long-term risk of PML in the RMP through a long-term surveillance study.

The OPR evaluator supports the comments made by the clinical evaluator and adopts the following recommendations regarding the RMP:

- Elevation of transaminases and hepatic parenchymal damage should be included as an 'Important Potential Risk'.
- The sponsor needs to address the long-term risk of PML in the RMP through a long-term surveillance study.'
- Relevant sections of the EU-RMP and the ASA, including the ongoing safety concerns, pharmacovigilance and risk minimisation plan, should be updated accordingly to include plans to mitigate the risks.

The nonclinical evaluator, TGA Office of Scientific Evaluation (OSE), has provided the following comments in the nonclinical evaluation report:

Results and conclusions drawn from the nonclinical program for vedolizumab detailed in the sponsor's draft Risk Management Plan are in general concordance with those of the nonclinical evaluator.

Recommendation

The OPR evaluators recommend to the Delegate that the updated version of the RMP is implemented as follows:

- Implement EU-RMP version 2.0, dated 27 September 2013 (data lock point 14 March 2013) with Australian-specific Annex version 2.0, dated January 2014 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Vedolizumab is a recombinant humanised IgG₁ monoclonal antibody to selectively target human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interactions with MAdCAM-1. Vedolizumab is intended to be gut-selective having anti-inflammatory activity without generalised immunosuppression. This is a novel mechanism of action. Infliximab and adalimumab are TNF α antagonist monoclonal antibody therapies registered currently in Australia with indications that include UC and CD.

Ulcerative colitis is a chronic, relapsing, immune-mediated, inflammatory disease of the colon that always affects the rectum, extends proximally to a variable extent, and is characterised by a relapsing and remitting course. As noted in *Therapeutic Guidelines (Gastroenterology)*, the aims of treatment are to change the natural history of the disease and its long-term outcomes, rather than simply to achieve symptomatic control. Currently treatments for severe UC include: cyclosporine, azathioprine, 6-mercaptopurine, methotrexate and TNF α antagonists.

Crohn's disease is a chronic, relapsing, immune-mediated, inflammatory bowel disease. Current therapies include: 5-aminosalicylic acid, immunosuppressive agents such as azathioprine and 6-mercaptopurine, corticosteroids, antibiotics and TNF α antagonists.

Quality

There are no objections to approval from the biological chemistry evaluators. Consent has been given to use the existing EU English label via S14 exemption, by overstickering to

ensure compliance with the Australian specific requirements for a period of 12 months after approval.

Conditions of registration recommended by the quality evaluators were noted.

Nonclinical

There are no objections to approval from the nonclinical evaluator.

The nonclinical evaluator noted that the primary mechanism of action of vedolizumab is inhibition of binding of $\alpha_4\beta_7$ integrin to MAdCAM-1. Evidence was provided that vedolizumab is unlikely to inhibit immune surveillance in the CNS and therefore is unlikely to be associated with a risk of PML. Rabbits and monkeys, but not rats and mice, were shown to be pharmacologically responsive species.

A safety pharmacology study (cardiovascular study in cynomolgus monkeys) at appropriate doses did not reveal any effects of vedolizumab on MAP, HR or ECG parameters.

Adequate repeat dose toxicity studies in rabbits did not identify any target organs. Adequate to high exposure ratios were achieved (up to 25 in rabbits and 8 in cynomolgus monkeys).

Genotoxicity studies were not conducted and are not required. Carcinogenicity studies were not conducted but there was no evidence of carcinogenic potential from in vitro studies examining the effect of the vedolizumab predecessor antibody (Act-1) on the growth of a human B-cell lymphoma cell line and the cross-reactivity of vedolizumab with tumour tissue from human colon adenocarcinomas.

No fertility studies were conducted. Embryofetal development studies in rabbits (at exposure ratios up to 8) did not reveal any evidence of teratogenicity or embryofetal toxicity. There were no effects on infants when vedolizumab (at exposure ratios up to 24) was administered to cynomolgus monkeys throughout most of the gestation period.

Vedolizumab showed no evidence of immunotoxic potential in repeat-dose toxicity studies or a dedicated immunotoxicity study.

In cross-reactivity studies with human and cynomolgus monkey tissues, staining was only observed for mononuclear cells (lymphocytes and monocytes/macrophages) in lymphoid tissues and within the lumen of blood vessels, or as low-grade inflammatory infiltrates in various non-lymphoid tissues.

Clinical

Pharmacology

Pharmacokinetics

In initial studies vedolizumab was given on a body weight-adjusted (mg/kg) basis. Fixed doses were given in the Phase III studies. Population PK modelling was performed on the Phase III data (see CER extract at Attachment 2).

Vedolizumab has a half-life of around 26 days, CL of around 0.16 L/day and volume of distribution around 5 L. At the 300 mg dose level, CV% for CL was 12.2%, for $t_{1/2}$ it was 22.1% and for volume of distribution at steady state (V_{ss}) it was 18.9%. The PK of vedolizumab was dose proportional within the range 2.0 to 10.0 mg/kg. The PK in patients with UC and CD were similar to those in healthy volunteers using the formulation intended for marketing.

Covariate modelling was conducted and evaluated by TGA. Weight based dosing resulted in higher exposure in high body weight patients and has not been proposed by the sponsor. Statistically significant but not clinically significant increases in CL of vedolizumab were associated with TNF α inhibitors and presence of HAHA. Azathioprine, methotrexate, mercaptopurine and aminosalicylates did not have statistically significant effects on the clearance of vedolizumab. Age, gender, body weight and baseline serum albumin were also predicted to not significantly affect the PK of vedolizumab.

As vedolizumab is not a cytokine modulator and is gut selective, the potential for P450-mediated drug interactions with vedolizumab acting as perpetrator was considered to be lower than that of drugs that systemically and directly affect the cytokines. Interaction studies were not performed. There were no studies in patients with impaired hepatic or renal function.

Pharmacodynamics

Two flow cytometric assays: (1) Act-1 Binding Interference Assay, and (2) MAdCAM-1-Fc binding interference assay, were used to examine the effect of vedolizumab on $\alpha_4\beta_7$ integrin. These assays were used to demonstrate the presence of vedolizumab on the surface of cells bearing $\alpha_4\beta_7$ integrin and to assess the time course of $\alpha_4\beta_7$ receptor saturation. Vedolizumab given as single doses from 0.2 to 10 mg /kg inhibited Act-1 and MAdCAM nearly maximally at all time points where vedolizumab was measurable and the time of the maximal effect was generally the first sample time.

In clinical trials the 300 mg and 600 mg doses achieved similar initial maximal inhibition of Act-1 and MAdCAM-1-Fc within 24 h of dosing. 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 was decreased by the presence of HAHA.

Vedolizumab had no apparent effect on CD4+: CD8+ ratio in the CSF or the total concentration of CD4+ and CD8+ expressing lymphocytes in the CSF. There was no change in lymphocyte expression in peripheral blood.

Efficacy

Crohn's disease

Efficacy was examined in two randomised, placebo-controlled, double-blind Phase III studies: C13007 and C13011. Just over half the patients enrolled in C1007 had prior TNF α antagonist experience (ceased due to treatment failure or intolerance) and in C13011 enrolment was restricted such that 75% of the population were TNF α antagonist failure. In addition to these studies there was a Phase II study and two long-term studies with exploratory efficacy endpoints. Efficacy endpoints were generally the same across the clinical study program (see *Studies providing efficacy data in Crohn's disease*, above for details).

Study C13007 was conducted in two phases. There were also two cohorts in the induction phase. Patients in Cohort 1 were initially randomised to vedolizumab 300 mg IV infusion at Weeks 0 and 2 or placebo for the induction phase. Additional patients received open label induction with vedolizumab (Cohort 2). Patients given vedolizumab in the induction phase who responded were combined with additional patients that had responded to open label vedolizumab, and the combined group of responder patients were re-randomised to: vedolizumab 300 mg IV infusion every 4 weeks; vedolizumab 300 mg IV infusion every 8 weeks; or placebo for the maintenance phase. The total duration of treatment was 52 weeks. Non-responders at Week 4 in the randomised part of the induction study were followed separately in a non-ITT analysis.

Notable inclusion criteria were: a CDAI score of 220 to 450; inadequate response to, loss of response to, or intolerance of therapeutic doses of at least one of the following agents:

immunomodulators (6-mercaptopurine; methotrexate; TNF α antagonists: infliximab, adalimumab, certolizumab pegol), or corticosteroids. Patients could continue to receive oral 5-aminosalicylate compounds, oral corticosteroid therapy, probiotics, anti-diarrhoeal agents, azathioprine or 6-MP, methotrexate, and antibiotics used for the treatment of CD during the study. Notable exclusion criteria were: history of extensive colonic resection; ileostomy/colostomy or known stenosis of the intestine; receipt of non-biologic therapies (for example cyclosporine, thalidomide), a non-biologic investigational therapy, adalimumab within 30 days of enrolment; receipt of infliximab or certolizumab pegol within 60 days prior to enrolment; topical rectal treatment with 5-aminosalicylate or corticosteroids within 2 weeks of enrolment.

The primary efficacy outcome measure for the induction phase was the proportion of patients in clinical remission at Week 6 and the proportion that had achieved enhanced clinical response at Week 6. The primary efficacy outcome measure for the maintenance phase was the proportion of patients in clinical remission at Week 52.

A total of 220 patients were randomised to vedolizumab and 148 to placebo and a further 747 patients were included in the open label vedolizumab group. All patients in the randomised groups had received prior treatment for CD, with 287 (78%) having received immunomodulators, 192 (52%) received TNF α antagonists and 54 (15%) received only systemic corticosteroids. In the randomised groups, 177 (80%) patients in the vedolizumab group and 123 (83%) in the placebo had extra-intestinal manifestations of CD.

For randomised patients, clinical remission at Week 6 was achieved by 32 (14.5%) patients given vedolizumab and 10 (6.8%) given placebo, RR (95% CI) 2.1 (1.1 to 4.2), $p = 0.0206$ and number needed to treat (NNT) to achieve an additional subject in clinical remission at Week 6 = 13. Enhanced clinical response was achieved by 69 (31.4%) patients given vedolizumab and 38 (25.7%) given placebo, RR (95% CI) 1.2 (0.9 to 1.7), $p = 0.2322$.

This difference was not clinically significant however the statistical plan allowed for failure to demonstrate superiority of one primary endpoint and the criteria for superiority of vedolizumab for clinical remission were satisfied.

A subgroup analysis was conducted by prior TNF α antagonist exposure. Patients with prior TNF α antagonist exposure had lower clinical remission and response rates compared to those without prior exposure. The clinical remission rate at Week 6 for patients with prior TNF α antagonist exposure was 4.3% for patients given placebo and 10.5% for patients given vedolizumab, a non-statistically significant difference.

In the maintenance study, at Week 52 there were significantly more patients in both vedolizumab dose groups achieving clinical remission compared with placebo. Clinical remission was achieved by 60 (39.0%) patients given vedolizumab every 8 weeks (RR [95% CI] 1.8 [1.3 to 2.6], $p = 0.0007$), 56 (36.4%) given vedolizumab every 4 weeks (RR [95% CI] 1.7 [1.2 to 2.4], $p = 0.0042$), and 33 (21.6%) given placebo (ITT population).

An exploratory analysis of patients (ITT population) with prior TNF α antagonist exposure was presented. There were only small differences in remission and enhanced response rates between the two vedolizumab dose groups and no statistical comparison between these groups was provided. TNF α antagonist naïve patients had higher remission and response rates than those with prior exposure. Both experienced and naïve subgroups had statistically significant higher clinical remission rates at Week 52 than patients randomised to placebo. The differences in enhanced clinical response were statistically significant for the naïve patients given vedolizumab every 8 weeks and the experienced patients given vedolizumab every 4 weeks.

Patients given vedolizumab in the induction phase (randomised and open cohorts) who failed to achieve reduction in CDAI score of ≥ 70 points at Week 6 were followed separately from the randomised maintenance study. These patients received vedolizumab 300 mg IV infusion every 4 weeks. Post hoc analyses were performed to examine efficacy over time in these patients. The clinical remission rate at Week 52 was 18.8% (95% CI 14.9, 23.3) compared with 7.2% (95% CI: 2.4, 16.1) for patients given placebo. The enhanced clinical response rate in this population at Week 52 was 25.4% (95% CI 20.9, 30.2) for patients given vedolizumab and 7.2% (95% CI 2.4, 16.1) for patients given placebo. However analysis was based on few patients and no statistical comparison between placebo and active treatment groups was provided. Results for enhanced clinical response in this group summarised in Table 12 and Table 13.

Table 12: Enhanced clinical response for patients who did not achieve clinical response at Week 6. Delayed response population (Study 007)

Enhanced Clinical Response ^a	PLA N=69	Week 6 Non-Responders		VDZ (Combined) N=351
		VDZ q4 wks (Cohort 1) N=86	VDZ q4 wks (Cohort 2) N=265	
Number (%) Achieving Enhanced Clinical Response at Week 52	5 (7.2)	21 (24.4)	68 (25.7)	89 (25.4)
95% CI	(2.4, 16.1)	(15.8, 34.9)	(20.5, 31.4)	(20.9, 30.2)

Table 13: Clinical Remission at Week 52 by Induction Phase Cohort –Maintenance Study (007) ITT Population

Clinical Remission, ^a n (%)	Cohort 1			Cohort 2		
	PLA N = 32	VDZ Q8W N = 32	VDZ Q4W N = 32	PLA N = 121	VDZ Q8W N = 122	VDZ Q4W N = 122
Number (%) achieving clinical remission	6 (18.8)	8 (25.0)	13 (40.6)	27 (22.3)	52 (42.6)	43 (35.2)
95% CI	(5.2, 32.3)	(10.0, 40.0)	(23.6, 57.6)	(14.9, 29.7)	(33.8, 51.4)	(26.8, 43.7)
Difference from placebo ^b		6.3	22.0		20.3	12.8
95% CI for difference from placebo		(-12.9, 25.4)	(-0.3, 44.3)		(8.6, 32.0)	(1.5, 24.0)
P-value for difference from placebo ^c		0.5220	0.0535		0.0007	0.0262
Relative risk ^d		1.3	2.1		1.9	1.6
95% CI for relative risk		(0.5, 3.3)	(0.9, 5.0)		(1.3, 2.8)	(1.0, 2.4)

Source: Table 14.3.1.32AM (post hoc).

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

a Clinical remission defined as CDAI score ≤ 150 points.

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

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

d Adjusted relative risk and its 95% CI.

Supplementary analyses of this study were conducted. In the overall analysis of Cohorts 1 and 2 combined statistically significantly greater proportions of patients in the vedolizumab treatment groups achieved clinical remission at Week 52 compared with placebo ($p = 0.0007$ for 8 weekly dosing; $p = 0.0042$ for 4 weekly dosing). The difference from placebo was 17.4% (95% CI: 7.3, 27.5) in the vedolizumab 8 weekly dosing group and 14.7% (95% CI: 4.6, 24.7) in the vedolizumab 4 weekly dosing group. The proportion of patients in Cohort 1 and 2 combined analysis for enhanced clinical response in the maintenance population was 13.4% (95% CI: 2.8, 24.0) in the vedolizumab 8 weekly group and 15.3% (95% CI: 4.6, 26.0) in the vedolizumab 4 weekly group.

A statistically significant difference in rates of durable clinical remission at Week 52 (defined as CDAI score ≤ 150 points at $\geq 80\%$ of study visits including final visit [Week 52]) was not demonstrated for the combined Cohorts 1 and 2 analysis ITT maintenance population.

The second Phase III study, Study C13011 assessed efficacy of the proposed induction regimen of vedolizumab 300 mg IV infusion at Weeks 0, 2 and 6. This study used similar efficacy measures and inclusion and exclusion criteria as Study C13007 with the primary assessments at Week 6 and further assessments at Week 10.

The primary objective was to determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the subgroup of patients defined as having failed TNF α antagonist therapy. The primary efficacy endpoint was the proportion of patients in clinical remission at Week 6 in the TNF α antagonist failure ITT subpopulation.

A total of 416 patients were randomised to treatment: 209 to vedolizumab and 207 to placebo. Of these 315 (76%) had previously failed TNF α antagonist treatment. This study failed to demonstrate a statistically significant increase in clinical remission rates compared with placebo at Week 6 in patients who had failed previous TNF α antagonist treatment. For that population, clinical remission rates at Week 6 were: 15.2% in the vedolizumab group and 12.1% in the placebo group; RR (95% CI) 1.2 (0.7 to 2.2), $p = 0.4332$. The Week 10 results for clinical remission were statistically significant for the TNF α Antagonist Failure ITT subpopulation 26.6% in the vedolizumab group versus 12.1% in the placebo group, RR (95% CI) 2.2 (1.3 to 3.6), $p = 0.0012$; and for the Overall ITT population 60 (28.7%).

A statistically significant difference was demonstrated for enhanced clinical response at Week 6 in the TNF α Antagonist Failure Subpopulation: 39.2% in the vedolizumab group versus 22.3% in the placebo group, RR (95% CI) 1.8 (1.2 to 2.5), $p = 0.0011$. For the TNF α Antagonist naïve sub-population at Week 10, 35.3% of patients given vedolizumab versus 16.0% given placebo had achieved clinical remission; the treatment difference from placebo was 19.1% (95% CI 2.4, 35.8). Further efficacy results for this sub-population are in the CER (Attachment 2).

Ulcerative colitis

The pivotal study for UC was Study C13006, a randomised, placebo-controlled, double-blind study to evaluate the efficacy and safety of vedolizumab as induction and maintenance treatments in patients with moderately to severely active UC who had an inadequate response to, loss of response to, or intolerance to one or more of the following therapies: immunomodulators, corticosteroids, or TNF α antagonists.

Study C13006 had many of the design features of Study C13007. The induction phase included a randomised, placebo-controlled, double-blind group (for ITT analysis) and a group receiving open label vedolizumab. Responders to either randomised treatment or open label vedolizumab were re-randomised after the induction phase into the maintenance phase where they received vedolizumab 300 mg IV infusion either every 4 weeks or every 8 weeks or placebo to Week 52.

Inclusion criteria of note were: 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 and an inadequate response to, loss of response to, or intolerance of at least one of the following agents: immunomodulators: 6-mercaptopurine (≥ 0.75 mg/kg), methotrexate (≥ 12.5 mg/week); TNF α antagonists: infliximab, adalimumab, and certolizumab pegol; and corticosteroids. Patients were permitted to receive concomitant therapeutic doses of oral 5-aminosalicylate compounds, oral corticosteroid therapy, probiotics, anti-diarrhoeal agents, and azathioprine or 6-mercaptopurine. Exclusion criteria of note were: receipt of non-biologic therapies (for example, cyclosporine,

thalidomide) within 30 days prior to enrolment, infliximab within 60 days prior to enrolment and any prior exposure to natalizumab, efalizumab, or rituximab.

The primary efficacy outcome measure for the induction phase was the proportion of patients with clinical response at Week 6. Clinical response was defined as a reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point. The primary efficacy outcome measure for the maintenance phase was the proportion of patients in clinical remission at Week 52. Clinical remission was defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point.

In both the induction and maintenance phases, groups were stratified by corticosteroid use and prior TNF α antagonist or concomitant immunomodulator use. In the induction phase, 374 patients were randomised: 225 to vedolizumab and 149 to placebo. A further 521 patients were included in the open label vedolizumab group. In the randomised groups clinical response was achieved by 106 (47.1%) patients given vedolizumab and 38 (25.5%) given placebo, RR (95% CI) 1.8 (1.4 to 2.5), $p < 0.0001$. The difference from placebo was 21.6%, NNT 4.6. There was no apparent difference in clinical response if the disease was extensive colitis.

In the maintenance phase 373 patients were randomised: 122 to vedolizumab every 8 weeks; 125 to vedolizumab every 4 weeks; and 126 to placebo. As in Study C13007 patients who did not have an initial clinical response continued treatment outside of the randomised maintenance phase of the study. An additional 373 non-responder patients were treated with vedolizumab every 4 weeks ($n=373$) or placebo ($n= 135$). For the ITT population clinical remission at Week 52 was achieved by 51 (41.8%) patients given vedolizumab every 8 weeks (RR [95% CI] 2.7 [1.7 to 4.2], $p < 0.0001$) by 56 (44.8%) given vedolizumab every 4 weeks (RR [95% CI] 2.8 [1.8 to 4.4], $p < 0.0001$), and by 20 (15.9%) given placebo. Durable clinical remission, defined as clinical remission at both Weeks 6 and 52 was achieved by 30 (24.0%) patients given vedolizumab every 4 weeks ($p = 0.0009$ compared to placebo); 25 (20.0%) given vedolizumab every 8 weeks ($p = 0.0079$) and 11 (8.7%) in the placebo group.

Supplemental analyses were conducted for patients who achieved clinical response at Week 6 (Maintenance Study ITT population) and for patients who achieved clinical remission at Week 6. The purpose of these analyses was to examine the durability of response in more detail than was provided by the protocol defined durability (that is, clinical remission at Week 6 and Week 52). The proportion of patients with clinical remission at $\geq 80\%$ of Maintenance Study visits; proportion of patients with clinical remission at the last 11 (of 13) Maintenance Study visits and the proportion of patients with clinical remission at 100% of Maintenance Study visits were examined. These supplemental analyses confirmed durable remission over the course of study treatment. Clinical remission at 100% of study visits during maintenance was present for 11.1%, 23.0%, and 18.4% of the placebo, vedolizumab every 8 weeks, and vedolizumab every 4 weeks groups, respectively in the ITT population. Both vedolizumab regimens were statistically significantly superior to placebo for clinical remission at 100% of maintenance visits.

Clinical response and clinical remission were assessed at Week 6 only; there was no additional assessment to confirm maintenance of remission around 4 weeks later as recommended in the CHMP *Guideline on the Development of New Medicinal Products for Ulcerative Colitis* (CHMP/EWP/18463/2006). To address this deviation from the Guideline, supplemental analyses were performed to evaluate sustained clinical remission (defined as clinical remission at both Week 6 and Week 10. Clinical remission was sustained in 53.2% (95% CI: 44.5, 61.9) of patients who received vedolizumab during induction and 30.0% (95% CI: 17.3, 42.7) who received placebo during induction. All the patients in this analysis had been evaluated as achieving clinical response at Week 6, and

all received placebo starting at Week 6 in the maintenance phase (that is, no patient received an additional dose of vedolizumab after Week-2 induction dosing).

Safety

A total of 3326 subjects received at least one dose of vedolizumab in the clinical development program. 621 patients with either UC or CD received ≥ 24 infusions, and 125 received ≥ 36 infusions. This extent of exposure is consistent with the recommendations in the ICH guideline on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions²³. It is not sufficient to identify rare AEs such as PML.

The placebo control groups were smaller and patients randomised to placebo generally had shorter treatment durations than those randomised to vedolizumab. Consequently it would be anticipated that AE occurrences would be higher in the vedolizumab treatment groups. This was the case. The most frequently reported adverse events were those consistent with underlying disease e.g. abdominal pain, nausea, and diarrhoea and these occurred with similar frequencies across the placebo and active treatment groups.

No increase in the proportion of serious AEs or in study discontinuation due to AEs was apparent with decreased dose interval from every 8 weeks to every 4 weeks. There were 12 deaths in the study program however only 2 of these were considered related to study treatment (CD with sepsis and septic shock). In both the UC and CD patient groups, infections occurred more frequently in the patients given vedolizumab compared with the placebo group (non-ITT).

Infection was more frequently reported in the vedolizumab treatment groups than the placebo groups with nasopharyngitis, fatigue, cough, sinusitis, bronchitis, influenza, oropharyngeal pain, and pruritus, all having higher incidence rates in the combined vedolizumab groups versus placebo groups for both UC and CD patients. A combined analysis was provided of the more frequent AEs with a calculation of incidence density to account for the reduced duration of exposure in the placebo treated groups. Fungal infections and herpes infections were not more frequently associated with vedolizumab than with placebo treatment.

Across the clinical studies, there were 10 reports of serious sepsis cases (4 with UC, 6 with CD and 2 with placebo). There were 2 serious systemic bacterial Infections: listeria meningitis in the first 3 months of vedolizumab treatment in a CD patient taking concomitant immunomodulators and corticosteroids; and salmonella sepsis in a CD patient who had received up to 18 months of vedolizumab. Tuberculosis (TB) was reported in 4 patients receiving up to 18 months of vedolizumab in the extension safety study C13008. All were from TB endemic countries and none were confirmed by culture.

Vedolizumab is an integrin antagonist. When an increased incidence of PML was associated with natalizumab (another integrin antagonist) the FDA had placed a clinical hold on the US Investigational New Drug application for vedolizumab. This was lifted in July 2007 with the implementation of an active screening and monitoring program for PML that required each subject/patient to be screened (using checklists), prior to each dose of study drug, for early signs and symptoms associated with PML. This program was implemented during the remainder of the development process. Before entering the study, a questionnaire inquiring about the presence of specific neurologic signs and symptoms (Subjective Checklist) was to be administered to each patient. One or more positive responses at baseline would exclude a patient from the study. While on study, the Subjective Checklist was to be administered at each visit before study drug administration

²³ CPMP/ICH/375/95. ICH Topic E 1 *Population Exposure: The Extent of Population Exposure to Assess Clinical Safety* (June 1995).

and at the Final Safety visit. In addition, patients, all of whom were educated on the risks and symptoms of PML, were asked to contact the study doctor immediately if they noticed any new neurological symptoms between visits.

Patients with PML may present with cognitive or behavioural symptoms which have been most commonly observed either alone or in association with motor, language, or visual symptoms. No cases of PML, pneumocystis carinii pneumonia (PCP), disseminated fungal infections, or mycobacterium avium complex infections were reported during the development program.

Eleven non-squamous/non-basal cell dermatological malignancies were reported in the Phase III studies: colorectal cancer (n = 4), melanoma (n = 2), breast cancer (n = 2) and 1 each of transitional cell carcinoma, carcinoid tumour of the appendix and B-cell lymphoma. Comparison of the incidence rates for these malignancies with rates in patients with moderate to severe IBD in the HealthCore Integrated Research Database (HIRD) database did not suggest a signal for increased risk of malignancy with vedolizumab.

Infusion reactions are associated with vedolizumab and were reported with an incidence of 4% of patients in the randomised, controlled population in Studies C13006 and C1007. The most frequently observed AEs that were consistent with an infusion reaction in the vedolizumab treated patients were: nausea, headache, pruritus, dizziness, fatigue, infusion related reaction, pyrexia, urticaria, and vomiting. Only one of these events was considered serious: a patient in Study C13007 who developed dyspnoea, bronchospasm, urticaria, flushing, rash, and increased heart rate and blood pressure 13 min after the start of the second vedolizumab infusion.

In Phase III controlled studies, 4% (56/1434) of patients given continuous vedolizumab were HAHA positive at any time during treatment. Of these 9 (1%) were persistently positive.

Clinical evaluator's recommendation

The evaluator was unable to recommend the approval of vedolizumab 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 (TNF α) 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 (TNF α) antagonist.

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

However, the evaluator had no objection to the approval of vedolizumab 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 (TNF α) 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 (TNF α) antagonist.

In subjects with ulcerative colitis or Crohn's disease who had initially responded to TNF α antagonists, and subsequently lost response, treatment with vedolizumab may not be justified.

Risk management plan

The RMP evaluator is satisfied with the RMP and has recommended that EU-RMP version 2.0, dated 27 September 2013 (data lock point 14 March 2013) with Australian-specific Annex version 2.0, dated January 2014 and any future updates be implemented as a condition of registration.

The proposed risk minimisation plan in Australia includes routine risk minimisation activities, a physician educational brochure, and a patient alert card. The patient alert card is proposed to contain the following information:

- *Infections*

Entyvio increases the risk of getting infections.

Infections may progress more rapidly and be more severe. This may include serious brain and nervous system infections.

You should not be treated with Entyvio if you have a severe infection.

If you develop symptoms suggestive of infections for example fever, persistent cough, weight loss, listlessness, or nervous system problems for example confusion, difficulties with vision or movement then you should seek medical attention immediately.

This submission was presented to the ACSOM on 7 March 2014. At that time ACSOM was aware that, based on previous experience and the very limited safety data being provided for vedolizumab, the TGA Delegate was considering restricting the indication of vedolizumab to 'induction of remission' and excluding maintenance treatment.

ACSOM noted the proposal to restrict the indication to 'induction of remission' and to exclude maintenance treatment and commented that the indication needs to be considered in the context of chronic, relapsing conditions. ACSOM considered that it was not appropriate to restrict the indication to induction of remission. The indication should focus on those who respond to vedolizumab therapy as this is the patient group in which the risk benefit profile is most favourable.

The Delegate noted that ACSOM did not have access to the clinical evaluation report at the time it considered the application. At this stage the Delegate did not intend to accept the ACSOM recommendation regarding the indication.

Risk-benefit analysis

Delegate's considerations

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 4 weekly and 8 weekly vedolizumab 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.

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 vedolizumab were in clinical remission at Week 52 than those who received placebo. A similar difference occurred for enhanced clinical response where the difference was around 15% (favouring vedolizumab). No statistical comparisons of efficacy between the vedolizumab 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 TNF α antagonist naïve and those who had experienced failure both had statistically significant benefit from treatment at the Week 10 assessment. An additional 14.5% of patients who had previously failed TNF α 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 TNF α 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 TNF α antagonist failure.

Taking the results of the two Phase II studies together the data support the proposed induction regimen for patients with moderate to severe CD, including patients with prior TNF α 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. In any case the clinical benefit from maintenance treatment is quite modest.

Given the limited efficacy of maintenance treatment, the limited data on safety of long term use and the theoretical concern that vedolizumab could be associated with an increased incidence of PML, particularly if used long term, the Delegate considered the indication should be for induction therapy only. Maintenance therapy could be re-considered once more data on the safety of long term use are available.

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 vedolizumab 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. As with vedolizumab in patients with CD, its use in patients with UC will require periodic review and patients who do not show ongoing clinically significant benefits from treatment should not continue.

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 2 dose induction regimen. At Week 6 only patients with a clinical response were selected to continue into the controlled, randomised maintenance study. Because the only available data are for a 2 dose regimen with assessment at Week 6 the Delegate proposed that this be the induction regimen for UC.

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. Given the limited efficacy of maintenance treatment, the limited data on safety of long term use and the theoretical concern that vedolizumab could be associated with PML, particularly if used long term, the Delegate considered at this stage the indications should be for induction therapy only. Maintenance therapy could be re-considered once more data on the safety of long term use are available.

Another issue with the proposed maintenance regimens for both indications was that there was no consistent difference in outcome between the 8 weekly and 4 weekly 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 every 8 weeks or who become unresponsive after an initial response. Given that the Delegate did not propose at this stage to approve maintenance treatment for either indication this point was not further discussed.

The main safety issue that had not been resolved at the time of the Delegate's overview was 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 patients with MS had been exposed to natalizumab for more than 2 years. Long term safety data for vedolizumab 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 UC 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.

Proposed action

The Delegate was not in a position to say, at this time, that the application for vedolizumab should be approved for registration. If the indications are amended to induction therapy for CD and UC this position would be reconsidered. Satisfactory completion of negotiations for the RMP was also required.

Product Information

Under *Dosage and Administration*, the Delegate recommended removal of reference to the maintenance dose regimens as they are inconsistent with the indication proposed for approval.

Under the CD subheading the induction dose regimen should be 0, 2 and 6 weeks and readers should be referred to the *Clinical Trials* section. The statement that “*Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit by Week 14*” should be deleted because it implied therapy will continue beyond the induction period. Under the Ulcerative Colitis subheading the induction dose regime should be 0 and 2 weeks (see *Clinical Trials*).

Other revisions to the draft PI recommended by the Delegate are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the Advisory Committee on Prescription Medicines (ACPM) and to request the committee provide advice on the following specific issues:

1. Does the committee consider the proposed induction regimen for CD and UC of 300 mg IV infusion at 0, 2 and 6 weeks to be adequately justified by the data presented?
2. Does the committee consider that there are sufficient data to permit maintenance treatment for either CD or UC?
3. Should the committee recommend maintenance treatment be approved, does the committee consider that a decision on continuing treatment should be made at Week 6 or at Week 14 as proposed by the sponsor?
4. Does the committee consider that patients with prior TNF α antagonist experience should be eligible to receive vedolizumab?

Response from Sponsor

The sponsor addressed the following items raised during the TGA evaluation:

- The clinical evaluation report recommended approval, albeit for a revised indication; it did not recommend rejection of maintenance treatment for either UC or CD.
- The efficacy of vedolizumab has been robustly demonstrated for both induction and maintenance treatment and the product has demonstrated a positive benefit-risk profile. A detailed discussion of the supporting scientific evidence on maintenance treatment was provided.
- Episodic treatment with biologics can make patients immunogenic and potentially resistant to future treatment. In addition, for patients who fail conventional and TNF α antagonist therapy, it is unclear what the pharmacological options would be after induction with vedolizumab.
- There is substantial long-term vedolizumab exposure data in UC and CD in the clinical development program. Vedolizumab’s safety profile has been shown to be consistent with its gut-selective mechanism of action, as well as with AEs typically seen in patients with IBD.
- The risk of progressive PML has been thoroughly assessed in the development program, both from a nonclinical and clinical perspective. To date no cases of PML have been reported. If the risk of PML with vedolizumab were similar to that of natalizumab, based on data through 14 March 2013, 6 to 7 cases of PML would be expected to have occurred in the vedolizumab clinical program. Further, if vedolizumab shared the same risk estimates for PML as natalizumab, the probability of observing zero cases of PML with vedolizumab would be less than 0.5%.

- The Delegate expressed concern that patients had been intensely screened for PML. Although the Risk Assessment and Minimization for PML (RAMP) was applied as a screening tool for symptoms, it did not screen for the actual virus that causes PML, JCV and no patients were excluded based upon the JCV deoxyribonucleic acid screening for the Phase III trials.
- Information contained in the PI, Consumer Medicine Information (CMI) and the proposed RMP, adequately addresses the vedolizumab safety aspects.
- ACSOM recommended that it is not appropriate to restrict vedolizumab's indications to 'induction of remission'.
- Importantly, given the toxicities associated with chronic immunosuppression of the immune system associated with corticosteroids, immunomodulators and TNF α antagonists, there is a need for new targeted therapies, particularly one that reduces the GI inflammatory process, without increasing the risk for toxicities commonly seen with currently available agents. Vedolizumab provides a therapeutic option with a gut-selective mechanism of action, for patients in whom there is an exceptionally high unmet clinical need, in particular patients with UC and CD who have failed TNF α antagonists and for whom no other pharmacological treatment alternatives exist.

The remainder of the sponsor's response has not been included in this AusPAR.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Kynteles/Entyvio powder for injection containing 300 mg of vedolizumab to have an overall positive benefit–risk profile for the proposed 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 (TNF α) 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 (TNF α) antagonist.

Proposed conditions of registration:

The ACPM advised that the RMP should be finalised to the satisfaction of the TGA prior to registration of vedolizumab.

Proposed PI and CMI amendments:

The ACPM agreed with the Delegate on the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- there should be a clear statement in the *Precautions* section on the potential risk of PML.
- reference in the Patient Alert card to PML should be a stronger statement.

Specific advice:

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the committee consider the proposed induction regimen for CD and UC of 300 mg IV infusion at 0, 2 and 6 weeks to be adequately justified by the data presented?

The ACPM advised that in CD: There was evidence for efficacy for the induction regimen but it was not particularly impressive in that the number needed to treat (NNT) was 13 and the assessment only at 6 weeks does not comply with the EMA guideline.

The ACPM advised in UC: An adequate response was demonstrated in the trial at both 6 and 10 weeks and the NNT was better at 4-5.

2. Does the committee consider that there are sufficient data to permit maintenance treatment for either CD or UC?

The ACPM advised that in CD: Remission and steroid free remission was adequately demonstrated at 52 weeks, supporting maintenance treatment in patients who achieved clinical response with the induction regimen, but (i) durable remission was not shown (ii) steroid-free remission was not shown in subgroup analyses by anti-TNF α experience (except for every 8 weeks treatment group with prior anti-TNF α failure).

The ACPM advised in UC: The evidence from the trials show that remission at 52 weeks, supporting maintenance treatment in patients who achieved clinical response with the induction regimen with a NNT of 3.4-4; durable remission with a NNT of 6-9 and corticosteroid-free remission with a NNT of 3-6 were all adequately demonstrated. However, the ACPM noted that UC can be reliably treated with surgery, without the adverse events inherent in long-term drug treatment.

3. Should the committee recommend maintenance treatment be approved, does the committee consider that a decision on continuing treatment should be made at Week 6 or at Week 14 as proposed by the sponsor?

The ACPM advised that, although the evidence for predicting continued efficacy was better at 6 weeks for both CD and UC, the 14 week cut-off was not unreasonable, as there was a small cohort of patients who did show efficacy in the intervening period. In addition assessment of clinical response at Week 6 would not allow for completion of the proposed induction regimen of 300 mg IV infusion at 0, 2 and 6 weeks.

4. Does the committee consider that patients with prior TNF α antagonist experience should be eligible to receive vedolizumab?

The ACPM advised that in CD: There were two Phase III studies in induction and remission, C13007 and C13011. In C13007, just over half the patients enrolled had prior TNF α antagonist experience and in C13011 75% of the population enrolled had prior treatment with a TNF α antagonist.

At Week 6 patients with prior TNF α antagonist exposure had a lower clinical remission rate and response rates compared to those without prior exposure, which were non-statistically significant differences compared to placebo.

Both experienced and naïve subgroups (in Study C13007) had statistically significant higher clinical remission rates at Week 52 than patients randomised to placebo.

Study C13011 failed to demonstrate a statistically significant increase in clinical remission rates compared with placebo at Week 6 in patients who were TNF α antagonist experienced. However, the Week 10 results for clinical remission were statistically significant for the TNF α antagonist failure ITT subpopulation. In total, these results support the use of vedolizumab in patients with prior TNF α antagonist experience. There is sufficient evidence to support the use of vedolizumab as maintenance treatment for both CD and UC, provided clinical response is demonstrated around 6 to 8 weeks after completion of the induction regimen has been administered. The definition of clinical response used to determine whether treatment should continue into a maintenance phase should be the same as was applied in the pivotal clinical trials.

The ACPM advised that in UC: In the pivotal study in both induction and remission in UC, when comparing patients defined as having failed TNF α antagonist therapy, there was

better response in the vedolizumab treated groups compared with placebo but less in this group than those who were TNF α antagonist-naïve.

Thus while the efficacy rates were lower for patients with prior TNF α antagonist experience, there was some efficacy.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Entyvio/Kynteles, containing vedolizumab (rch) 300 mg powder for injection vial, indicated for:

- *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 (TNF α) 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 (TNF α) antagonist.*

Specific conditions of registration applying to these goods

- The vedolizumab EU-RMP version 2.0, dated 27 September 2013 (data lock point 14 March 2013) with Australian Specific Annex version 20, dated January 2014 and any future Risk Management Plan updates included with submission PM-2013-01102-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The physician education brochure and patient alert card must be supplied following the launch of vedolizumab in Australia.

Attachment 1. Product Information

The Product Information approved for Entyvio at the time this AusPAR was published is at Attachment 1. The PI for Kynteles is identical except for the product name. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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