1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population considered by the company in this assessment (adult patients with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy and or an anti-TNF-α, or who are intolerant to either of them) matches that defined in the final NICE scope. The intervention considered in the company submission (CS), vedolizumab, also matches the final NICE scope. According to its current marketing authorisation, the recommended dose regimen of vedolizumab is 300mg administered by intravenous (i.v.) infusion at zero, two and six weeks and every eight weeks thereafter. It should be noted that the treatment regimen used in the company's model differs from the licensing and the treatment regimen described by the company in their decision problem (Section 1.10 of the CS). The final NICE scope defines comparators to be established clinical management without vedolizumab, which may include antibiotics, drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate and tumour necrosis factor-alpha antagonist (anti-TNF-α). The CS includes data on remission and response rates but did not include data on relapse rates. Data on surgery are not included in the CS but were provided following a request by the Evidence Review Group (ERG). No equity issues were highlighted in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS includes a systematic review and network meta-analysis (NMA) of the clinical effectiveness literature. The GEMINI II and GEMINI III trials form the main supporting evidence for the intervention. Both trials were Phase III, multicentre (GEMINI II 39 countries; GEMINI III 19 countries), randomised, double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of vedolizumab. The GEMINI II trial assessed vedolizumab as an induction treatment (dosing at weeks 0 and 2 with assessment at week 6) and maintenance treatment (weeks 6 to 52), and included patients who were naïve to anti-TNF-α, and patients who had an inadequate response to, loss of response to, or intolerance to immunomodulators and or anti-TNF-α. The GEMINI III trial was designed to evaluate the efficacy and safety of vedolizumab as an induction treatment with dosing at weeks 0, 2 and 6 and assessment at weeks 6 and 10. The primary analysis in the GEMINI III trial focussed on people for whom an anti-TNF-α has failed (i.e., an inadequate response to, loss of response to, or intolerance of $\geq$1 anti-TNF-α). A secondary analysis evaluated an overall population which also included patients who were naïve to anti-TNF-α, and pre-specified exploratory analyses examined the group naive to anti-TNF-α. In general, all efficacy analyses in the GEMINI II and III trials were conducted according to the intention-to-treat (ITT) principle whereby patients who withdrew prematurely were considered as treatment failures.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem as outlined in the final scope issued by NICE[8] and addressed in the company submission[1] is presented in Table 1.

Table 1 Decision problem as outlined in the final scope issued by NICE and addressed in the company's submission

	Decision problem outlined in final scope issued by NICE[8]	**Decision problem addressed in the CS[1]**
Population	Adults with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or an anti-TNF-α, or who are intolerant to either of them .	Adult patients with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy and or an anti-TNF-α, or who are intolerant to either of them (i.e. matches the population in final NICE scope)
Intervention	Vedolizumab	Vedolizumab
Comparator(s)	• Conventional treatment strategies without vedolizumab (including antibiotics, drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) • anti-TNF-α (infliximab and adalimumab)	• Conventional therapy, as defined in the GEMINI II and III study including concomitant use of glucocorticoids, immunosuppressive agents and mesalamine. • anti-TNF-α licensed for the treatment of Crohn's disease in the UK (infliximab and adalimumab)
Outcomes	disease activity surgery adverse effects of treatment health related quality of life.	The CS includes data on the remission and response rates but did not include data on the relapse rates. Data are on surgery are not included.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The submission includes a model-based cost-utility analysis of vedolizumab compared against infliximab, adalimumab and conventional non-biologic therapies. The analysis was undertaken over a 10-year time horizon from the perspective of the NHS. A Patient Access Scheme (PAS) is included for vedolizumab.

	Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators	
Subgroups to be considered	If evidence allows following subgroups will be considered: • People who have not previously received an anti-TNF-α • People for whom an anti-TNF-α has failed • People for whom anti-TNF-α are not suitable because of intolerance or contraindication.	The company present analyses for 1. anti-TNF-α naïve population 2. anti-TNF-Failure population (people for whom an anti-TNF-α has failed) 3. mixed population (includes both anti-TNF-α naïve and anti-TNF-Failure subgroups)

3.1 Population

Vedolizumab has a therapeutic indication for the treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to conventional therapy including anti-TNF-α.[9,10]

The population described in the final NICE scope[8] was adults with moderately to severely active CD in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy and or an anti-TNF-α, or who are intolerant to either of them.

The company does not provide a clear statement of the population included in the submission, but states that *"the patient population considered within this appraisal is in line with the final scope population"* (see CS[1] pg. 63).

The patient population included in the submission reflects patients included in both the GEMINI II and GEMINI III trials.[11,12] The company states that the eligibility criteria of the GEMINI II and III trials are identical (see CS[1] pg. 83). The ERG noted some differences in the inclusion criteria between the GEMINI II[11] and III[12] studies (see Section 4.2).

Demographic, baseline disease characteristics and medication history of patients in the GEMINI II (see CS[1] Table 6.3.4.1 pg. 84) and III (see CS[1] Table 6.3.4.2 pg. 86). In the GEMINI II trial,[11] patients had an overall mean age of 36.1 (standard deviation [SD] =12.1) years, were predominantly white (89.2%) as a cohort, and 46.6% were male with a mean body weight of 69.8 kg (SD=19.4). Mean duration of disease was 9.0 (SD=7.8) years and patients had a mean CDAI score of 324 (SD=69). The site of the disease was in the ileum only, colon only or both in 16.2%, 28.3% and 55.4% of patients respectively. Concomitant medications for CD included glucocorticoids only (34.2%),

"severe", "very severe" or even "extremely severe" elsewhere in the literature.[13] The current NICE clinical guidelines[7] defines "severe active Crohn's" as "very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease". The guidelines[7] also state that *"this clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more"*. As such, it is likely that patients with the most severe disease have not been included in the GEMINI trials, and generalisation to this population may not be possible.

3.2 Intervention

The intervention described in the CS[1] matches the intervention described in the final scope issued by NICE.[8]

Vedolizumab (brand name Entyvio®) is a humanized monoclonal antibody that binds exclusively to the α4β7 integrin on gut-homing T helper lymphocytes and selectively inhibits adhesion of these cells to mucosal addressing cell adhesion molecule-1 (MAdCAM-1) and fibronectin, but not vascular cell adhesion molecule-1 (VCAM-1).[1] The gut-selective mechanism of action of vedolizumab is described in the CS[1] as being novel, with the potential to reduce adverse effects beyond the gut seen with current anti-TNF-α inhibitors (see CS[1] pg. 58).

Vedolizumab has a therapeutic indication for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy and or an anti-TNF-α.[9,10]

Vedolizumab is available as a powder for concentrate for solution for infusion. Each pack contains one vial containing 300mg of vedolizumab. Based on correspondence between the company and NICE (21st August 2014), the basic NHS list price of vedolizumab is £2,050 per 300mg vial, although at the time of writing the product was not listed on the British National Formulary (BNF). The company's model includes a lower drug acquisition cost to reflect the agreed Patient Access Scheme (PAS) for vedolizumab; the price used in the model is [redacted] per 300mg vial. The agreed PAS takes the form of a simple price discount (a reduction of [redacted] of the NHS list price) for the NHS.

In adherence with the licensing of the drug,[9,10] the company[1] states the treatment regimen for vedolizumab to be the following (see CS[1] Table 1.10.1 pg. 35):

"…300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of Vedolizumab at Week 10. Continue therapy every 8 weeks from Week 14 in responding patients.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The company[1] presented a systematic review of the clinical effectiveness and safety of vedolizumab for the treatment of moderately to severely active CD in adults who were naïve to anti-TNF-α and those who are intolerant of, or whose disease has an inadequate response or loss of response to conventional therapy and or anti-TNF-α. The systematic review aimed to assess the best available evidence to evaluate the efficacy and safety of all biologics in patients with moderate to severe CD to inform a NMA. A review of vedolizumab only was not performed. The CS[1] included a description of a separate search for surgery, although this is not relevant to this appraisal as it is not listed as a comparator. The CS[1] documents that an initial search was undertaken in April 2013, with update searches performed on February 12th 2014 and limited to publications from April 1st 2013. These searches had a global remit to assess vedolizumab against certolizumab and natalizumab in countries where they are licensed for use, as these biologics are not licensed for use in the UK they are not relevant to this assessment and were therefore excluded at sifting stage. The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (formerly QUOROM) flow diagram[1] relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/statement.htm). Despite minor discrepancies, the flow diagram (see CS[1] pg. 71) represents the identification and selection of relevant biologic therapies for the treatment of CD (i.e. for the systematic review of vedolizumab and for the systematic review/ potential NMAs incorporating infliximab and adalimumab indicated for the treatment of moderate to severe CD using indirect comparisons) and appears to be an adequate record of the literature searching and screening process. For clarity, a separate PRISMA flow diagram for each of the reviews would have been beneficial as it would aid the transparency of the identification and selection process for each of the reviews. A separate flow diagram relating to a review of surgery is presented in the CS[1] (page 72) but is not presented here as it is outside the scope of the evaluation.

The PRISMA flow diagram indicates of a total of 1,648 potentially relevant records were identified, 1,491 were excluded at title/abstract sift (level 1) and 81 articles were excluded at full paper (level 2). Subsequently, according to the CS[1]18 studies were included in the NMA, of which 10 were relevant to this appraisal. However, this includes all biologics and citations from both the original and update searches. These 81 exclusions are separated into categories indicating broad reasons for exclusion for the original and update searches respectively. These categories included study design (original search n=15; updated search n=34), population (original search n=4; updated search n=0), intervention (original search n=5, updated search n=6), and outcomes (original search n=12, updated search n=5). Excluded studies relating to the systematic review of vedolizumab are not documented in the CS[1]. However, reasons for excluding studies from the network meta-analysis are provided in Takeda data

Main evidence for vedolizumab: GEMINI II[11] and GEMINI III trials[12]

The CS[1] included two Phase III, multicentre, randomised, double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of vedolizumab as induction therapy (dosing at weeks 0 and 2 with assessment at week 6 in GEMINI II,[11] and dosing at weeks 0, 2 and 6 with assessment at weeks 6 and 10 in GEMINI III[12]) and maintenance therapy (weeks 6 to 52 in GEMINI II[11] only) in adults with moderately to severely active CD who had an inadequate response to, loss of response to, or intolerance to immunomodulators and or anti-TNF-α. It is noteworthy that although the studies were designed against placebo, conventional therapies (5-ASAs, corticosteroids, immunomodulators, antibiotics, probiotics, and antidiarrheal) were concomitantly administered to patients in both treatment arms. However, as noted in the European Public Assessment Report (EPAR),[10] the lack of an anti-TNF-α compound comparator arm represents a limitation of the studies.

The GEMINI II trial[11] included patients who were naïve to anti-TNF-α, and patients who had an inadequate response to, loss of response to, or intolerance to immunomodulators or anti-TNF-α.

The primary analysis in the GEMINI III trial[12] focussed on people for whom an anti-TNF-α has failed (i.e., an inadequate response to, loss of response to, or intolerance of ≥1 anti-TNF-α). A secondary analysis evaluated an overall population which included patients who were naïve to anti-TNF-α, and pre-specified exploratory analyses examined the group naïve to anti-TNF-α.

<u>GEMINI II Trial[11]</u>

An overview of the induction and maintenance phases in the GEMINI II trial[11] is provided in Figure 2. Although the study was designed to compare vedolizumab with placebo, conventional therapies (5-ASAs, corticosteroids, immunomodulators, antibiotics, probiotics, and antidiarrheal) were concomitantly administered to patients in both treatment arms.

The GEMINI II trial[11] was conducted at 285 medical centres in 39 countries from 2008 to 2012. Of the 285 sites, enrolment at 9 sites was discontinued because of concerns about the ability to fully comply with good clinical practice. At 6 of these sites, enrolment was later resumed. Enrolment was also permanently discontinued at country level in India due to concern for patient safety affecting 8 sites. This arose as serious adverse events (SAEs) led to 2 deaths at sites in India. The cause of death attributed by the principle investigators at each site, were study-related 'septic shock', and study-related 'sepsis' (further details are provided in the supplementary appendix to Sandborn et al.[11]).

Patients eligible for inclusion in GEMINI II[11] were required to be aged between 18 to 80 years with moderate to severely active CD as determined by having;

- CD for ≥3 months,

4.2.4 Summary and critique of results

This section presents the results (as reported by the company[1]) from the GEMINI II[11] and III trials,[12] which forms the pivotal evidence in the CS[1] for the efficacy and safety of vedolizumab in the induction and maintenance treatment of patients with moderate to severe active CD. Additional information, not reported in the CS,[1] was provided by the company in their response to the clarification questions[2] raised by the ERG, and in a supplementary document – Takeda data on file document.[16] Where applicable, data have been re-tabulated by the ERG to ensure clarity.

<u>GEMINI II Trial[11]</u>

In the GEMINI II trial,[11] at induction phase, patients were predominantly white (89.2%) with a mean age of 36.1 years. The mean body weight was 69.8kg and 46.6% were male. The mean duration of disease was 9 years, patients had a mean CDAI score of 324, and the mean faecal calprotectin score was 1,254. Concomitant medications for CD included glucocorticoids only (34.2%), immunosuppressant only (16.2%), glucocorticoids and immunosuppressant (17%) and neither glucocorticoids nor immunosuppressant (32.6%). 61.8% of patients had received prior anti-TNF-α treatment. The CS[1] (page 84), suggests that no relevant differences in baseline demographic or clinical characteristics were observed between the treatment groups (*p*-values were not provided). In the US, patients were required to have failed either an immunomodulator (6-MP or azathioprine) and or an anti-TNF-α agent, whilst outside of the US, failing corticosteroids alone was sufficient for study entry. It is unclear to the ERG how the different criteria might have impacted on the study results.

All study withdrawals were adequately described in the CSR[22] and all patients were accounted for, this included 9% (105/1115) of the total population in the induction phase who prematurely discontinued from the study (vedolizumab Cohort 1, 10% [21/220], placebo Cohort 1, 7% [11/148], and vedolizumab Cohort 2, 10% [73/747]). The primary reason for discontinuation in the induction phase was due to adverse events 5% (7/148) in the placebo arm, and 3% (33/968) in the combined vedolizumab arm, followed by lack of efficacy 1% (1/148) in the placebo arm, and 3% (31/968) in the combined vedolizumab arm. In general, the validity of a study may be threatened if attrition is more than 20%.[43] As such, the ERG acknowledges that attrition bias should be considered low in the induction phase of the GEMINI II trial.[11] The maintenance phase ITT population only includes vedolizumab patients who had a clinical response at week 6. At the start of the maintenance phase, these patients were randomised to one of two vedolizumab dosing regimens (300 mg every 4 weeks or every 8 weeks) or placebo. During the maintenance phase, of the ITT population, 58% (89/153) discontinued in the placebo arm, 53% (81/154), and 47% (72/154) discontinued in the vedolizumab Q8W and Q4W arms respectively. The main reason for discontinuation in the maintenance phase was due to lack of efficacy, 42% (64/153) in the placebo arm, and 38% (58/154) and 31% (48/154) in the vedolizumab every 8 weeks (Q8W) and the vedolizumab every 4 weeks (Q4W) arms respectively. As

noted earlier it has been argued that loss to follow-up of 20% or greater means that the validity of the study may be threatened.[43] The ERG acknowledges that in a study of this length, whereby patients are continued on placebo for an extended period of time, greater discontinuations may be expected. However, attrition rates as these levels have the potential to impact on the maintenance study results, posing a serious threat to external validity. As withdrawals were counted as treatment failures for the efficacy outcomes, the ERG believes that the estimates of efficacy are problematic more in terms of generalizability rather than estimation of the treatment effect within the trial. However, the ERG believes that the loss of patients may be problematic for the assessment of adverse events.

GEMINI III Trial[12]

In the GEMINI III trial,[12] most patients were white (90%). The mean age was 37.9 years, mean body weight was 70.4kg and 43% were male. Other baseline characteristics were reported only for each treatment group (vedolizumab vs. placebo). Median duration of disease was 8.4 years in the vedolizumab group and 8 years in the placebo group. Patients in the vedolizumab group had a mean CDAI score of 301.3, and 313.9 in the placebo group. Median faecal calprotectin score was 1148.1 in the vedolizumab group, and 1426.5 in the placebo group. Concomitant medications for CD included corticosteroid use (53% in the vedolizumab group and 52% in the placebo group), immunosuppressant use (34% in the vedolizumab group and 33% in the placebo group), and 5-ASA use (33% in the vedolizumab group and 29% in the placebo group). In each group 76% of patients had had a prior anti-TNF-α failure. The CS[1] (see CS[1] pg. 84), suggests that most baseline demographics were similar between the treatment groups with the exception of the vedolizumab-treated patients who had a slightly higher baseline CDAI compared to the placebo group (313.9 vs 301.3, p=0.015), and more placebo-treated patients (51%) were <35 years of age compared to vedolizumab-treated patients (42%) (*p*-values were not provided).[12,23] In the US, patients were required to have failed either an immunomodulator (6-MP or azathioprine) and or an anti-TNF-α agent, whilst outside of the US, failing corticosteroids alone was sufficient for study entry. It is unclear to the ERG how these different criteria might have impacted on the study results.

All study withdrawals were adequately described and all patients were accounted for; this included 7% (28/416) of the total population who prematurely discontinued from the study (vedolizumab anti-TNF-α failures, n=7; vedolizumab anti-TNF-α naïve, n=6; placebo anti-TNF-α failures, n =12; placebo anti-TNF-α naïve, n = 3). The primary reason for discontinuation was not provided in the CS[1], Takeda data on file[16] or the CSR[23]. Discontinuation due to AEs was reported in 2% (4/209) of placebo patients and in 4%

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainties in the clinical evidence primarily relate to duration of treatment and generalizability to the UK population. Further details are provided below.

Duration of treatment

The duration of treatment of vedolizumab in the GEMINI II trial was 52 weeks, followed by enrolment in the ongoing GEMINI LTS study. As a result, the long-term efficacy and safety of vedolizumab is unknown and the optimum duration of therapy remains unclear. There are no data on strategies for withdrawal of the drug in those on maintenance therapies or with respect to how to predict instances in which this can be successfully achieved. The SmPC for vedolizumab[9,10] recommends monitoring and reporting of any suspected adverse reactions after authorisation especially for new onset or worsening of neurological signs and symptoms.

Generalizability to the population of England and Wales

In GEMINI II,[11] at induction phase, patients were predominantly white (89.2%) with a mean age of 36.1 years. The mean body weight was 69.8kg and 46.6% were male. The mean duration of disease was 9 years, patients had a mean CDAI score of 324, and the mean faecal calprotectin score was 1,254. In GEMINI IIIl,[12] most patients were white (90%). The mean age was 37.9 years, mean body weight was 70.4kg and 43% were male. Median duration of disease was 8.4 years in the vedolizumab group and 8 years in the placebo group. Patients in the vedolizumab group had a mean CDAI score of 301.3, and 313.9 in the placebo group. Median faecal calprotectin score was 1148.1 in the vedolizumab group, and 1426.5 in the placebo group. It should be noted that the faecal calprotectin in the GEMINI trials was deemed to be high, indicating that patients may had had significant active inflammation. Although information on the number of UK-based study sites was not available, it appears that very few were used and very few UK patients included in either GEMINI II[11] or GEMINI III.[12] In comparison, a large number of study sites were US-based. In the US, patients were required to have failed either an immunomodulator (6-MP or azathioprine) and or an anti-TNF-α agent, whilst outside of the US, failing corticosteroids alone was sufficient for study entry. It is unclear to the ERG how the different criteria might have impacted on the study results. The trials also assess response in the induction phase earlier than would be done in the UK, at six weeks. As such, the population entering the maintenance phase in GEMINI II is not fully representative of the UK spectrum, as patients who take longer to respond are excluded. This could conceivably lead to an overestimation of maintenance treatment effect, if these patients are also less likely to maintain a response when in remission.