Vedolizumab for the treatment of adults with moderately to severely active Crohn's disease: Critique of the evidence submitted by the company following the ACD

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ABBREVIATIONS

TNF-α antagonist	tumour necrosis factor-alpha antagonist
ASAs / 5-ASAs	Aminosalicylates
MP / 6-MP	6-mercaptopurine
AE	Adverse event
CD	Crohn's disease
c.i.	Confidence interval
CEAC	Cost-effectiveness acceptability curve
CRP	C-reactive protein
CS	Company submission
CSF	Corticosteroid-free
CSR	Clinical Study Report
ECG	Electrocardiogram
EMA	European Medicines Agency
EOW	Every other week
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
EW	Every week
FDA	Food and Drug Administration
HE	Health economics
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Incremental cost-effectiveness ratio
IPAA	Ileal pouch-anal anastomosis
ITT	Intention-to-treat
LOCF	Last observation carried forward
i.v.	Intravenous
MeSH	Medical subject heading
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ONS	Office for National Statistics
PAS	Patient Access Scheme

PbR	Payment by Results
PML	Progressive multifocal leukoencephalopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36
SG	Standard gamble
STA	Single Technology Appraisal
SmPC	Summary of product characteristics
TB	Tuberculosis
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor–alpha
UC	Ulcerative colitis
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WHO	World Health Organisation
Wk(s)	Week(s)

1. SUMMARY

1.1 Summary and critique of clinical effectiveness evidence submitted by the company

As part of the appraisal consultation document (ACD) response document the company have provided further analyses of the GEMINI II and GEMINI III trials, which were reported in the original company's submission (CS). As part of these analyses the company cite three additional references, although only one of these includes new data which have become available since the original CS. All analyses relate to the failure sub-population. For GEMINI II, this sub-population constituted 48% of the overall ITT population. In GEMINI III the failure sub-population constituted 75% of the overall ITT population.

Five analyses were presented for the induction phase. These included analyses clinical remission, and clinical response for, (1) GEMINI II and III separately in people for whom a TNF-α antagonist has failed, (2) GEMINI II and III separately based on the number of previously failed TNF-α antagonist therapies in people for whom a TNF-α antagonist has failed, (3) a pooled analysis of the GEMINI II and III trials in people for whom a TNF-α antagonist has failed, (4) of GEMINI II at Week 10 and 14 in people for whom a TNF-α antagonist has failed who did not achieve response at week 6 whilst on vedolizumab, and (5) of patient reported outcomes from GEMINI II and III separately in people for whom a TNF-α antagonist has failed. In the maintenance phase an analysis of the clinical remission and clinical response outcomes from GEMINI II in people for whom a TNF-α antagonist has failed was presented. A final analysis of longer efficacy (up to 2 years) was presented based on additional data, although, these data are based on a different scale (HBI rather than the CDAI).

The company concludes that treatment differences at 10 weeks in the induction phase, which appear to favour vedolizumab, and exploratory failure sub-group analyses up to 52 week were consistent with the overall maintenance study intention to treat (ITT) population results reported in the original CS.

The analyses presented for GEMINI II should be considered exploratory as the study was not designed to assess the failure subgroup, and should also be considered exploratory for GEMINI III as the primary endpoint of that study was not achieved. Long term efficacy at two years is presented, and does constitute new evidence compared with the original CS, however, as noted these data are based on HBI rather than the CDAI. The evidence review group (ERG) concludes that these new analyses add little to the clinical effectiveness evidence presented in the original CS.

The company also present the results of a new network meta-analysis (NMA) for a comparison between adalimumab and vedolizumab in the maintenance phase, using data from one adalimumab trial in a secondary failure population (CHARM). The analysis shows no statistically significant difference in clinical remission between vedolizumab and adalimumab, although there was a trend for greater efficacy for adalimumab. The ERG comments that the results are uncertain given the differences between the trial populations and believes a more useful comparison would have been to conduct the NMA in a similar vedolizumab population as the one included in the adalimumab trial.

1.2 Summary and critique of the cost effectiveness submitted evidence by the company

In response to the ACD, the company submitted a revised economic model. The following modifications were made to the economic analysis originally submitted to NICE:

- focusing on people for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist),
- employing a lifetime horizon,
- using an assessment time of response in line with the SmpC,
- inclusion of a revised patient access scheme (PAS) that offers vedolizumab at a new reduced price of [redacted] per 300mg vial ([redacted] discount on the list price of £2,050 per vial),
- amendment of inputs to reflect some of key concerns raised by the Appraisal Committee (AC) and evidence review group (ERG),
- amendments to the Markov trace and calculations,
- the incorporation of an exploratory analysis comparing vedolizumab against a second TNF-α antagonist in people for whom a prior TNF-α antagonist has failed.

Although the ERG is satisfied with most changes made by the company, concerns expressed within the original ERG report regarding the model structure and parameterisation of the company's model remained. The health economic model submitted by the company is subject to a number of issues which limit the accuracy of the company's results. These include (a) potential omission of key aspects of the condition such as the relapsing-remitting nature of CD, (b) simplifying and debatable assumptions regarding surgery, (c) the difficultly associated with parameterising the company's chosen structure most notably the derivation of the transition matrices, and (d) debatable assumptions such as: the end of scheduled maintenance at one year irrespective of achievement of remission; omission of discontinuation due to lack of efficacy; derivation of the efficacy whilst on placebo and the assumptions that non-responders at the induction phase on conventional non-biologic treatment remain with moderate to severe CD (and are not able to improve). The ERG notes discrepancies

between the model prediction and observed data from the GEMINI II trial. The ERG is unclear whether the ICER would become more or less favourable following amendments of the identified issues.

Changes made by the company in the revised economic model had the effect of reducing the company's base case deterministic (probabilistic) ICER from £98,452 (not reported) to £21,620 (£27,428) per QALY gained. It should be noted that most of the changes were attributable to two amendments that are subject to uncertainty: increasing the time horizon from 10 years to a lifetime and updating the health state costs using resource use estimated through a survey conducted amongst 8 clinical experts rather than the costs reported from Bodger et al (2009).

2 BACKGROUND

The company originally submitted clinical and economic evidence of the use of vedolizumab in both patients naïve and for whom TNF-α antagonist has failed.[1] The original economic evaluation included a patient access scheme (PAS). A report detailing the evidence review group (ERG) critique of the original submission[1] is available on the NICE website.[2]

Following preliminary guidance in the appraisal consultation document (ACD),[3] the company submitted additional evidence to support the use of the vedolizumab in people for whom TNF-α antagonist has failed.[4]

This document was written in response to additional evidence submitted by the company.[4] The company's re-submission[4] included both additional clinical data and a revised Excel economic model[5] with a focus on the TNF-α antagonist failure population. The company has also agreed a further PAS, which offers a discount of [redacted] on the list price on all doses (reducing the cost per dose from £2,050 to [redacted]).

Only a critique of the additional evidence presented by the company[4] is summarised in this report. The reader is referred to the original ERG report[2] for a critique of the evidence presented for the entire population or TNF-α antagonist naïve subgroup.

3 CLINICAL EFFECTIVENESS

This section presents a critique of the additional clinical effectiveness evidence presented in the ACD response document submitted by the company to NICE.[4] This evidence relates to the clinical effectiveness of vedolizumab in adult patients with moderately to severely active CD in a sub-population of patients for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist).

3.1 Critique of the methods of review(s)

A systematic review was included in the original CS[1] and was described in an accompanying 498 page document[6] submitted alongside the CS[1] (referred as the Takeda on file document[6]). The systematic review was critiqued as part of the original ERG document,[2] and it was concluded that the systematic review process followed by the company was adequate.

Although the company states that the ACD response document[4] is a submission of new evidence, in terms of clinical effectiveness the majority of the data relates to trials outlined in the original submission.[1] This new submission[4] focuses on one sub-population, rather than three as presented in the original submission.[1] This population is of moderately to severely active CD in a sub-population of people for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist).

Three new citations[7-9] which have been published since the original CS[1] was submitted have been included in the ACD response document.[4] In response to clarification (see clarification response[10] question 2) the company confirmed that full updated searches and an update to the systematic review were not performed. The three new citations[7-9] were identified from an updated search of the UEGW (United European Gastroenterology: Week) and ECCO (European Crohn's and Colitis Organisation) conference websites. Therefore, it is possible that further new references relating the intervention or the comparators may have been missed. A further issue relating to the three new citations is that two relate to conference abstracts [7,8] and one to a conference poster.[9] It should be noted that abstracts reported in conference proceedings may be limited in the information that they provide, and there may also be differences between data presented in an abstract and those presented in a final report. For these reasons caution should be taken when interpreting the evidence from such sources[11,12]

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

3.2.1 Summary of the evidence included in the original CS[1] (reproduced from the ERG report[2])

Both trials[13,14] 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[13] 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 people who were naïve to TNF-α antagonist, and people who had an inadequate response to, loss of response to, or intolerance to immunomodulators or TNF-α antagonist.

The GEMINI III trial[14] 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[14] focussed on people for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist).

A secondary analysis evaluated an overall population which also included people who were naïve to TNF-α antagonist, and pre-specified exploratory analyses examined the group naïve to TNF-α antagonist.

In general, all efficacy analyses in the GEMINI II[13] and III[14] trials were conducted according to the intention-to-treat (ITT) principle whereby people who withdrew prematurely were considered as treatment failures.

3.2.2 Additional analyses presented in the ACD response document[4]

As part of the ACD response document[4] the company have provided further analyses of the same evidence reported in the original CS[1] together with data from three new citations.[7-9] All data relate to the failure sub-population.

For GEMINI II,[13] the failure sub-population constituted 48% of the overall ITT population. This trial was designed to assess efficacy and safety of the entire population (both failure and naïve subgroups) and therefore it is unclear whether it is powered to assess the failure sub-group as a primary analysis.

Table 1 Characteristics of included studies (reproduced from pg. 79-82 from the original CS[1])

Study	Location (sites)	Design	Population	Interventions (n=randomised)	Comparator	Primary outcome measures	Duration
GEMINI II[13] CSR13007[15]	285 medical centres in 39 countries	Phase III randomised, double-blind, placebo-controlled, induction and maintenance trial	People aged 18 to 80 years with moderate to severe active CD (defined as; CD for ≥3 months CDAI score 220-450), inadequate response to, loss of response to, or intolerance of at least 1 of conventional therapy or TNF-α antagonist .	Induction phase Vedolizumab (IV) 300 mg week 0 and 2 Cohort 1 (n=220), Cohort 2 (n=747) Maintenance phase Vedolizumab (IV) 300mg every 8 weeks (n=154) , every 4 weeks (n=154)	Induction phase Placebo (IV) at week 0 and 2 (n = 148) Maintenance phase Placebo (IV) every 4 weeks (n=153)	Induction Phase Clinical remission at week 6 (CDAI score of <150) Clinical response at week 6 (>100 decrease in CDAI score) Maintenance Phase Clinical remission at week 52	Induction phase 6 weeks Maintenance phase 52 weeks
GEMINI III[14] CSR 13011[16]	107 medical centres in 19 countries	Phase III randomised, double-blind, placebo-controlled, induction trial	People aged 18 to 80 years with moderate to severe active CD (defined as; CD for ≥3 months CDAI scores 220-400.	Vedolizumab (IV) 300 mg at 0, 2, and 6 weeks (n = 416)	Placebo (IV) at 0, 2 and 6 weeks (n = 207)	Clinical remission at week 6 (CDAI score of <150) in people with prior TNF-α antagonist failure.	10 weeks

GEMINI III[14] was designed to assess clinical remission at both Week 6 and Week 10 in people who had failed prior TNF-α antagonist therapy. The failure sub-population (primary analysis) constituted 75% of the overall ITT population. Table 2 shows the proportion of people who failure a TNF-α antagonist in the GEMINI II[13] and GEMINI III[14] studies.

Table 2 Proportion of TNF-α antagonist failure patients in the GEMINI II and GEMINI III studies (reproduced from Table 1, p.15, ACD response document[4])

	GEMINI II		GEMINI III	
	Induction cohort 1 population		Overall ITT population	
	PLA N=148	VDZ N=220	PLA N=207	VDZ N=209
Medication Use/Failure category				
Prior TNF-α antagonist use,a n (%)	72 (48.6)	111 (50.5)	157 (75.8)	158 (75.6)
Third-line indication				
Any prior TNF-α antagonist failure, n (%)	70 (47.3)	105 (47.7)	156 (75.4)	155 (74.2)
Inadequate response,b n (%)	41 (58.6)	56 (53.3)	69 (44.2)	66 (42.6)
Loss of response,c n (%)	22 (31.4)	40 (38.1)	69 (44.2)	71 (45.8)
Intolerance,d n (%)	7 (10.0)	9 (8.6)	18 (11.5)	18 (11.6)
1 prior TNF-α antagonist failure, n (%)e	28 (18.9)	49 (22.3)	45 (21.7)	59 (28.2)
2 prior TNF-α antagonist failures, n (%)e	31 (20.9)	48 (21.8)	90 (43.5)	82 (39.2)
3 prior TNF-α antagonist failures, n (%)e	11 (7.4)	8 (3.6)	21 (10.1)	14 (6.7)

a Data for prior TNF-α antagonist use at randomisation were obtained from the IVRS

b Inadequate response to TNF-α antagonists was defined as persistent active disease despite Induction treatment with specified medications

c Loss of response to TNF-α antagonists was defined as recurrence of symptoms during Maintenance dosing following prior clinical benefit

d Intolerance was defined as occurrence of treatment-related toxicities

e Multiple failures are counted once per patient

Source: Sandborn et al., 2013;[13] Sands et al., 2014.[14]

The analyses presented in the ACD response document[4] are outlined below for the induction and maintenance phases respectively.

Induction:

1. Outcomes (clinical remission, sustained clinical remission, clinical response and enhanced clinical response) from GEMINI II and III separately in people for whom a TNF-α antagonist has failed,
2. Outcomes (clinical remission, clinical response and enhanced clinical response) from GEMINI II and III separately based on the number of previously failed TNF-α antagonist therapies in people for whom a TNF-α antagonist has failed. Of note, this analysis is not used in the updated cost-effectiveness model.
3. Outcomes (clinical remission and enhanced clinical response) from a pooled analysis of the GEMINI II and III trials in people for whom a TNF-α antagonist has failed.[14]
4. Outcomes (clinical remission, enhanced clinical response) at Week 10 and 14 in people for whom a TNF-α antagonist has failed who did not achieve response at week 6 whilst on vedolizumab from GEMINI II only.[9] Of note, this analysis is not used in the updated cost-effectiveness model.
5. Patient reported outcomes from GEMINI II and III separately in people for whom a TNF-α antagonist has failed. Of note, this analysis is not used in the updated cost-effectiveness model.

Maintenance:

1. Outcomes (clinical remission, clinical response and enhanced clinical response) from GEMINI II in people for whom a TNF-α antagonist has failed.

Long-term efficacy:

1. Updated long-term efficacy analyses for up to 2 years.[7] Although these data are based on a different scale (HBI rather than the CDAI).

The results of these analyses are detailed in the text in the subsequent sections

3.2.3 Results of the additional analyses together with ERG comment

3.2.3.1 Induction

1 - Efficacy of vedolizumab in clinical remission, clinical response, and enhanced clinical response in CD people who previously failed a TNF-α antagonist therapy (third-line indication)

Summary of the analyses and ERG comments:

- The company present analyses of the failure subgroup from GEMINI II and III for three outcome measures, clinical remission (CDAI< 150), clinical response (CDAI-70) and enhanced clinical response (CDAI-100), and at two time points, week 6 and week 10, together with sustained clinical remission (≥150-point reduction in CDAI at both Week 6 and Week 10) in GEMINI III.
- Some of these analyses are repeated from the original CS[1] with the addition of the outcome measure clinical response (CDAI-70) which although was not reported in the clinical section of the original CS,[1] was used in the original economic model[17] and these data were available at the time of the original CS (in the CSR).
- Furthermore, week 10 data are presented for GEMINI II,[13] in addition to week 6 data in some cases and as an alternative to in other cases, and again these data were available for inclusion in the original CS[1] (in the CSR[15]). These should be considered as exploratory only, as indicated by the company.
- Further analyses of the GEMINI III data are presented despite the fact that the primary endpoint was not met, as indicated in the original CS,[1] therefore, all analyses relating to GEMINI III[14] should be considered exploratory.
- An additional reference has been cited[8], representing data previously reported in the CSR, not newly collected data.
- The results for each outcome are presented below and relate to the failure sub-population only.

Clinical remission at Week 6 in the failure sub-population

GEMINI II

Clinical remission at Week 6 in the TNF-α antagonist failure sub-population of Cohort 1 was achieved by 10.5% of vedolizumab patients and 4.3% of placebo patients (95% CI for difference from placebo: -9.1, 21.3; P value reported as 'not tested' by the company) (Table 3 below). In the exploratory analysis of people who had failed TNF-α antagonist treatment in the safety population, clinical remission at Week 10 was achieved by a greater percentage of people than at Week 6 for both the vedolizumab (16.0%) and placebo (8.6%) groups (95% CI for difference from placebo: 0.2, 14.6; P value reported as 'not tested' by the company).

The company has confirmed during clarification (see clarification response[10] question 5) where the safety population was used in the analysis and have clarified the definition of this as follows;

The Induction Phase Safety Population are all patients enrolled in Cohort 1.. randomised to blinded induction treatment and all patients enrolled in Cohort 2... open-label treatment. The Maintenance Phase Safety population are all patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomised to the Maintenance Study ITT Population at Week 6, all patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase, and all patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

GEMINI III

As reported in the original CS,[1] no statistically significant difference was observed between the vedolizumab and placebo groups for the proportion of people in clinical remission at Week 6. Of the 158 people who received vedolizumab, 24 (15.2%) achieved clinical remission at Week 6 compared with 19 of 157 (12.1%) people who received placebo. The treatment difference from placebo was 3.0% (95% CI: -4.5, 10.5; P=0.433) (Table 3).

Clinical remission at Week 10 in the failure subpopulation

GEMINI II

Clinical remission at Week 10 in the TNF-α antagonist failure population was achieved by 14.3% of vedolizumab patients and 8.6% of placebo patients (95% CI for difference from placebo: (-3.7, 15.1; P value not tested by the company) (Table 3). GEMINI II patients treated with vedolizumab had higher rates of clinical remission (CDAI< 150), regardless of sub-group. As GEMINI II was not designed to assess subgroups, the analyses of the TNF-α antagonist failure sub-population are considered exploratory, p-values have not been presented and in a number of cases 95% confidence intervals indicate statistical non-significance. Furthermore, only week 6 outcomes were considered as primary outcomes in the original analysis, therefore week 10 outcomes should be considered exploratory, as stated by the company. They also present additional exploratory analyses using the safety population (rather than the ITT population) for clinical remission at week 6 – during clarification the company stated that the primary reason for using the safety population was in order to include cohort 2 patients.

GEMINI III

26.6% of vedolizumab-treated patients and 12.1% of placebo-treated patients achieved clinical remission at Week 10; the treatment difference from placebo was 14.4%. The proportion of TNF-α antagonist failure patients who achieved clinical remission at Week 10 increased from 15.2% at Week 6 to 26.6% at Week 10 in the vedolizumab group with the placebo group unchanged from Week 6 (12.1%; P=0.001) (Table 3). The analyses of clinical remission presented for GEMINI III are those presented in the original CS,[1] as this study was designed to assess the failure subgroup – as the primary endpoint was not achieved, clinical remission at week 6, all other analyses are considered exploratory. Although, in this new document p-values are presented for an analysis of the proportion of TNF-α antagonist failure patients who achieved clinical remission at Week 10 compared with week 6 in the vedolizumab group compared with the placebo group, showing a significant difference between the treatment groups favouring vedolizumab.

Sustained clinical remission in the failure sub-population

GEMIMI III

The proportion of people who achieved sustained clinical remission (defined as a ≥150-point reduction in the CDAI score at both Week 6 and Week 10) in the TNF-α antagonist failure population was 12.0% of vedolizumab-treated patients and 8.3% receiving placebo; the treatment difference from placebo was 3.7%. There were no significant differences between the treatment groups.

Table 3 Clinical remission at Week 6 and Week 10 in TNF-α antagonist failure patients - Induction studies GEMINI II and GEMINI III, and sustained clinical remission in TNF-α antagonist failure patients from GEMINI III (reproduced from Table 2, pg. 21 from the ACD response document[4])

Endpoint	**GEMINI II**		**GEMINI III**	
Clinical remission at Week 6a				
N	PLA N=70	VDZ N=105	PLA N=157	VDZ N=158
Number (%) achieving clinical remission	3 (4.3)	11 (10.5)	19 (12.1)	24 (15.2)
95% CI	(0.9, 12.0)	(5.3, 18.0)	(7.0, 17.2)	(9.6, 20.8)
Difference from placebo[b]		6.2		3.0
95% CI for difference from placebo		(-9.1, 21.3)		(-4.5, 10.5)
P value	NT	NT		0.433
Clinical remission at Week 10a				
N	PLA N=70	VDZ N=105	PLA N=157	VDZ N=158
Number (%) achieving clinical remission	6 (8.6)	15 (14.3)	19 (12.1)	42 (26.6)
95% CI	(2.0, 15.1)	(7.6, 21.0)	(7.0, 17.2)	(19.7, 33.5)
Difference from placebo[b]		5.7		14.4
95% CI for difference from placebo		(-3.7, 15.1)		(5.7, 23.1)
P value	NT	NT		0.001
Sustained clinical remission				
N			PLA N=157	VDZ N=158
Number (%) achieving clinical remission			13 (8.3)	19 (12.0)
95% CI			(4.0, 12.6)	(7.0, 17.1)
Difference from placebo[b]				3.7
95% CI for difference from placebo				(-2.9, 10.3)
P value				0.2755

Abbreviations: PLA = placebo; VDZ = vedolizumab; CI = confidence interval; NT = not tested

a Clinical remission is defined as CDAI score ≤ 150 points.

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

Sustained clinical remission is defined as clinical remission at both Week 6 and Week 10

Source: Sands et al., 2014; [14] CSR C13007;[16] CSR C13011. [16]

Clinical response (CDAI-70) and enhanced clinical response (CDAI-100) in the failure sub-population

GEMINI II

In the exploratory analysis of people who had failed TNF-α antagonist treatment in the safety population of GEMINI II, the percentages of people achieving CDAI-100 response and CDAI-70 response at Week 10 were greater with vedolizumab than with the placebo. The company report that percentages of people achieving both outcome measures were greater in the vedolizumab group compared with placebo. However, no p-values are presented and the 95% confidence interval indicates statistical non-significance.

GEMINI III

The percentage of people achieving CDAI-70 response was consistently greater in the vedolizumab group than the placebo group at Week 6 and Week 10. P-values were not presented. Greater efficacy with vedolizumab over placebo was also observed for CDAI-100 response at Week 6 in GEMINI III.

Table 4 Clinical response (CDAI-70) and Enhanced clinical response (CDAI-100) at Weeks 6 and 10 in studies GEMINI II and GEMINI III (TNF-α antagonist failure population) (Reproduced from Table 1, p.g. 3 response to clarification questions[10] question 3)

Endpoint	**GEMINI II**		**GEMINI III**	
Clinical response at Week 6a				
N	PLA N=70	VDZ N=105	PLA N=156	VDZ N=155
Number (%) achieving clinical remission	20 (28.6)	37 (35.2)	50 (32.1)	79 (51.0)
95% CI	(18.0, 39.2)	(26.1, 44.4)	(24.7, 39.4)	(43.1, 58.8)
Difference from placebob		6.7		18.9
95% CI for difference from placebo		(-7.3, 20.6)		(8.2, 29.7)
P value		NT		NT
Clinical response at Week 10a				
N	PLA N=70	VDZ N=105	PLA N=156	VDZ N=155

Endpoint	GEMINI II		GEMINI III	
Number (%) achieving clinical remission	16 (22.9)	34 (32.4)	58 (37.2)	87 (56.1)
95% CI	(13.0, 32.7)	(23.4, 41.3)	(29.6, 44.8)	(48.3, 63.9)
Difference from placebob		9.5		18.9
95% CI for difference from placebo		(-3.8, 22.8)		(8.1, 29.8)
P value		NT		NT
Enhanced clinical response at Week 6c				
N	PLA N=70	VDZ N=105	PLA N=157	VDZ N=158
Number (%) achieving clinical remission	16 (22.9)	25 (23.8)	35 (22.3)	62 (39.2)
95% CI	(13.0, 32.7)	(15.7, 32.0)	(15.8, 28.8)	(31.6, 46.9)
Difference from placebob		1.0		16.9
95% CI for difference from placebo		(-11.8, 13.7)		(6.7, 27.1)
P value		NT		0.0011
Enhanced clinical response at Week 10c				
N	PLA N=70	VDZ N=105	PLA N=157	VDZ N=158
Number (%) achieving clinical remission	12 (17.1)	29 (27.6)	39 (24.8)	74 (46.8)
95% CI	(8.3, 26.0)	(19.1, 36.2)	(18.1, 31.6)	(39.1, 54.6)
Difference from placebob		10.5		22.0
95% CI for difference from placebo		(-1.8, -22.8)		(11.4, 32.6)
P value		NT		<0.0001

Abbreviations: PLA = placebo; VDZ = vedolizumab; CI = confidence interval; NT = not tested

a Clinical response is defined as a >=70-point decrease in CDAI score from baseline

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

c Enhanced clinical response is defined as a >=100-point decrease in CDAI score from baseline

2. - Efficacy of vedolizumab in CD patients based on the number of previously failed TNF-α antagonist therapies – reanalysis of data from the CSR C13007[15] and CSR C13011[16]

The proportion of people in GEMINI II[13] (induction) and GEMINI III[14] who had previously failed TNF-α antagonist therapy (and achieved clinical remission at Week 6 for GEMINI II) are summarised by treatment group and number of previously failed TNF-α antagonist therapies in Table 5). It should be noted that these data were not used in the updated economic model.

ERG Comments:

- These analyses were not presented in the original CS,[1] but were available from the CSRs at that time.
- These analyses are exploratory only as previously confirmed by the company.
- The ERG note that p-values are not reported and that 95% confidence intervals indicate statistical non-significance.

<u>GEMINI II at week 6</u>

The company report a trend favouring vedolizumab for at least 2 failed TNF-α antagonist therapies, with a greater proportion of vedolizumab-treated patients achieving clinical remission at Week 6 (12.5%) compared with those who received placebo (2.4%). The treatment difference from placebo was 10.1% (95% CI -10.2, 29.8). They also report, little difference among people who had previously failed only 1 TNF-α antagonist therapy. Trends for people whose 'worst previous TNF-α antagonist failure type' was inadequate response or loss of response - greater proportions of vedolizumab-treated patients achieved clinical remission at Week 6 (10.7% and 12.5%, respectively) compared with people who received placebo (2.4% and 0%, respectively). The treatment differences from placebo were 8.3% (95% CI -11.9, 27.9) and 12.5% (95% CI -13.5, 37.7), respectively.

<u>GEMINI III</u>

A greater percentage of people receiving vedolizumab compared with placebo achieved clinical remission and support the clinical relevance of vedolizumab induction treatment. Across the two sub-groups by number of TNF-α antagonists failed and 3 sub-groups by reason for failure in GEMINI III, the percentage of people in clinical remission at Week 6 was generally greater in the vedolizumab treatment group than in the placebo group, and the treatment effect favouring vedolizumab increased from Week 6 to Week 10 in all sub-groups, regardless of the number of agents failed or the reason for failure (Table 5). Interaction tests were not reported. The company suggest that the increased frequency of clinical remission with vedolizumab treatment at Week 10 supports the need for additional dosing in people who have not initially responded.

Table 5 Clinical remission at Week 6 in GEMINI II and GEMINI III, and at Week 10 in GEMINI III, and enhanced clinical response at Week 6 in GEMINI III by number of TNF-α antagonist therapies previously failed and reason for failure (TNF-α antagonist failure sub-population) (reproduced from Table 4, pg. 26 from the ACD response document[10])

	GEMINI II (Induction, Cohort 1)		GEMINI III			
	Week 6		Week 6		Week 10	
Sub-population	PLA N=148	VDZ N=220	PLA N=157	VDZ N=158	PLA N=157	VDZ N=158
Clinical remissiona						
1 TNF-α antagonist failure, n	28	49	43	59	43	59
Number (%) achieving clinical remission	2 (7.1)	4 (8.2)	6 (14.0)	6 (10.2)	7 (16.3)	20 (33.9)
95% CI	(0.9, 23.5)	(2.3, 19.6)	(3.6, 24.3)	(2.5, 17.9)	(5.2, 27.3)	(21.8, 46.0)
Difference from placebo		1.0		-3.8		17.6
95% CI for difference from placebo		(-22.1, 24.1)		(-16.7, 9.1)		(1.3, 34.0)
≥2 TNF-α antagonist failures, n	42	56	111	96	111	96
Number (%) achieving clinical remission	1 (2.4)	7 (12.5)	13 (11.7)	17 (17.7)	12 (10.8)	21 (21.9)
95% CI	(0.1, 12.6)	(5.2, 24.1)	(5.7, 17.7)	(10.1, 25.3)	(5.0, 16.6)	(13.6, 30.1)
Difference from placebo		10.1		6.0		11.1
95% CI for difference from placebob		(-10.2, 29.8)		(-3.7, 15.7)		(1.0, 21.2)
Enhanced clinical response at Week 6c						
1 TNF-α antagonist failure, n	NR	NR	43	59	NR	NR
Number (%) achieving clinical response	NR	NR	8 (18.6)	27 (45.8)	NR	NR
95% CI	NR	NR	(7.0, 30.2)	(33.1, 58.5)	NR	NR

Sub-population	GEMINI II (Induction, Cohort 1)		GEMINI III			
	Week 6		Week 6		Week 10	
	PLA N=148	VDZ N=220	PLA N=157	VDZ N=158	PLA N=157	VDZ N=158
Difference from placebo	NR	NR		27.2	NR	NR
95% CI for difference from placebob	NR	NR		(9.9, 44.4)	NR	NR
≥2 TNF-α antagonist failures, n	NR	NR	111	96	NR	NR
Number (%) achieving clinical response	NR	NR	26 (23.4)	33 (34.4)	NR	NR
95% CI	NR	NR	(15.5, 31.3)	(24.9, 43.9)	NR	NR
Difference from placebo	NR	NR		11.0	NR	NR
95% CI for difference from placebob	NR	NR		(-1.4, 23.3)	NR	NR
Reason for failure						
Inadequate response	41	56	67	66	67	66
Number (%) achieving clinical remission a	1 (2.4)	6 (10.7)	7 (10.4)	14 (21.2)	7 (10.4)	19 (28.8)
95% CI	(0.1, 12.9)	(4.0, 21.9)	NR	NR	NR	NR
Difference from placebo b		8.3		10.8		18.3
95% CI for difference from placebo		(-11.9, 27.9)	NR	NR	NR	NR
Loss of response	22	40	103	100	103	100
Number (%) achieving clinical remission a	0 (0.0)	5 (12.5)	13 (12.6)	15 (15.0)	14 (13.6)	
95% CI	(0.0, 15.4)	(4.2, 26.8)	NR	NR	NR	NR
Difference from placebob		12.5		2.4		11.4
95% CI for difference from placebo		(-13.5, 37.7)	NR	NR	NR	NR

Sub-population	GEMINI II (Induction, Cohort 1)		GEMINI III			
	Week 6		Week 6		Week 10	
	PLA N=148	VDZ N=220	PLA N=157	VDZ N=158	PLA N=157	VDZ N=158
Intolerance	7	9	69	63	69	63
Number (%) achieving clinical remission a	2 (28.6)	0 (0.0)	8 (11.6)	8 (12.7)	6 (8.7)	16 (25.4)
95% CI	(3.7, 71.0)	(0.0, 33.6)	NR	NR	NR	NR
Difference from placebob		-28.6		1.0		16.7
95% CI for difference from placebo		(-70.9, 19.8)	NR	NR	NR	NR

Abbreviations: PLA = placebo; VDZ = vedolizumab; CI = confidence interval; NR = not reported

a Clinical remission is defined as CDAI score ≤150 points

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

c Enhanced clinical response is defined as a≥100-point reduction in CDAI score from baseline

Source: CSR C13007;[15] CSR C13011.[16]

3 - Efficacy of Induction treatment with vedolizumab on clinical remission and CDAI-100 response at Week 6 and Week 10 - a pooled analysis of the GEMINI II and GEMINI III trials for the failure sub-population

A post hoc pooled analysis of data from the GEMINI II[13] and III[14] studies was reported by the company.

For the TNF-α antagonist failure subgroup, proportions of people in clinical remission (CDAI ≤150) and those with a CDAI-100 response (≥100 point decrease in CDAI score) were evaluated at Weeks 6 and 10. Week 6 responders in GEMINI II who were re-randomised to placebo were included in the Week 10 analyses.[8]

Table 6 Clinical remission and CDAI-100 response at Week 6 and 10 in TNF-α antagonist failure and TNF-α antagonist naïve patients – a pooled analysis of GEMINI II and GEMINI III (reproduced from Table 5, pg. 35 from the ACD response document[4])

Endpoint	Number (%) of patients [P-valuea]	
	TNF-α antagonist failure	
	PLA N=227	VDZ N=263
Week 6 clinical remission	22 (9.7) [-]	35 (13.3) [0.157]
Week 10 clinical remission	25 (11.0) [-]	57 (21.7) [0.0008]
Week 6 CDAI-100 response	51 (22.5) [-]	87 (33.1) [0.005]
Week 10 CDAI-100 response	51 (22.5) [-]	103 (39.2) [<0.0001]
Abbreviations: PLA = placebo; VDZ = vedolizumab; CDAI = Crohn's Disease Activity Index; TNF = tumour necrosis factor a P-value versus placebo and based on the CMH chi-square test		

Source: Sandborn et al,[8]

The company report, for the failure subgroup, the proportion of people in clinical remission was significantly higher with vedolizumab than with placebo at Week 10, but not at Week 6. CDAI-100 response rates were significantly higher (P=0.005) with vedolizumab than with placebo at week 10 and at week 6.

ERG comments:

- The company were asked during clarification (see clarification response[10] question 7) to provide the CDAI-70 response data for these analyses. However, the company suggested that these data were not available as they were not defined as primary or secondary endpoints in the GEMINI trials. The ERG is unclear with the response from the company as these data appear to be used in the economic model.
- These analyses are reported from a new reference.[8]

4 - Clinical response in vedolizumab-treated patients who did not achieve response at Week 6 (TNF-α antagonist failure population from GEMINI II) - a post hoc analysis

The company reported that of those people who had not responded to vedolizumab during induction (n = 86 from Cohort 1; n = 265 from Cohort 2; total = 351), 6.8% (24 people) achieved clinical remission at Week 10 (an additional 4 weeks of treatment/1 additional infusion), and 10.5% (37 people) achieved clinical remission at Week 14 (an additional 8 weeks of treatment/2 additional infusions).[9] It should be noted that these data were not used in the updated economic model.

Further, they reported a post hoc subgroup analysis of these endpoints by prior TNF-α antagonist failure status. This indicated more patients who had not previously failed this type of therapy achieved clinical remission and enhanced clinical response at Week 52 compared with those who had previously failed TNF-α antagonist therapy.

ERG comments:

- These analyses are reported from a new reference.[9]
- No p-values were presented for these data, and in a number of cases the 95% confidence intervals indicated statistical non-significance.

5 - Patient reported outcomes (Induction Phase GEMINI II and GEMINI III) in the failure sub-population

The company reports that as rated by IBDQ, SF-36 (physical and mental components), and EQ-5D VAS instruments, improvements in HRQoL at Week 6 were numerically greater for people who received vedolizumab compared to people who received placebo. The magnitude of improvement in total score as well as in the IBDQ subscales in vedolizumab-treated people was clinically meaningful according to minimally important difference cut-offs. The company conclude, the induction data from GEMINIII and GEMINI III shows that TNF-α antagonist failure patients with experience with 1 to 3 prior agents, the clinical effect takes longer to be realised (Week 6), but is significant by Week 10. In all people studied, the early benefit of vedolizumab treatment is further seen after 1 year of therapy.

ERG comments:

- It should be noted that these data were not used in the updated economic model.
- These data were already presented in the original CS.[18]

3.2.3.2 Maintenance

In the ACD response document[4] the company present the results of GEMINI II but just for the subgroup failure or intolerant to prior TNF-α antagonist, who had who responded to vedolizumab Induction treatment. These are labelled exploratory subgroup analyses and the results of these analyses were briefly summarised in the original CS[1].

In the failure subgroup the company states; a greater proportion of vedolizumab-treated people in the Q8W and Q4W treatment groups achieved the primary endpoint of clinical remission at Week 52, and the secondary endpoints of enhanced clinical response and corticosteroid-free remission at Week 52 compared with people who received placebo (see Table 7). The company states that the results observed in this subgroup were consistent with the statistically significant treatment differences observed in the overall Maintenance Study ITT Population. The other treatment differences favoured the vedolizumab groups, but the 95% confidence intervals indicate statistical non-significance. No probability values were presented for any of these comparisons.

Treatment differences from placebo for the endpoints of clinical remission and corticosteroid-free clinical remission at Week 52 were higher for the vedolizumab Q8W treatment group than for the Q4W treatment group, whereas for the endpoint of enhanced clinical response, the treatment difference from placebo was greater in the Q4W group (Table 7).

The company concludes that the results at Week 52 in GEMINI II support the efficacy with continued vedolizumab treatment beyond Week 6 seen in GEMINI III.

ERG comments:

- The company confirmed during clarification that CDAI-70 response endpoints were not assessed at week 52. The company were asked during clarification (see clarification response[10] question 10) to provide the CDAI-70 response data for these analyses. However, the company suggested that these data were not assessed as an endpoint in the maintenance phase. The ERG is unclear with the response from the company as these data appear to be used in the economic model.
- No new evidence was presented as part of this analysis.
- The results of these exploratory analyses were used in the updated cost-effectiveness model.

Table 7 Key Maintenance efficacy endpoints in TNF-α antagonist failure patients – Maintenance study ITT population (GEMINI II) (reproduced from Table 9, pg. 35 from the ACD response document[4])

Response at Week 52	Patients with prior TNF-α antagonist failure		
	PLA N=78	VDZ Q8W N=82	VDZ Q4W N=77
Number (%) achieving clinical remissiona	10 (12.8)	23 (28.0)	21 (27.3)
95% CI	(5.4, 20.2)	(18.3, 37.8)	(17.3, 37.2)
Difference from placebob		15.2	14.5
95% CI for difference from placebo		(3.0, 27.5)	(2.0, 26.9)
Number (%) achieving enhanced clinical responsec	16 (20.5)	24 (29.3)	29 (37.7)
95% CI	(11.6, 29.5)	(19.4, 39.1)	(26.8, 48.5)
Difference from placebob		8.8	17.1
95% CI for difference from placebo		(-4.6, 22.1)	(3.1, 31.2)
	N=38	N=41	N=43
Number (%) achieving corticosteroid-free clinical remissiond	0	10 (24.4)	7 (16.3)
95% CI	(0.0, 9.3)	(12.4, 40.3)	(6.8, 30.7)
Difference from placebob		24.4	16.3
95% CI for difference from placebo		(2.4, 45.1)	(-5.7, 37.0)

Abbreviations: PLA = placebo; VDZ = vedolizumab; Q8W = dosing every 8 weeks; Q4W = dosing every 4 weeks; CI = confidence interval

a Clinical remission is defined as CDAI score ≤ 150 points.

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

c Enhanced clinical response is defined as a ≥ 100-point reduction in CDAI score from baseline.

d Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52.

Source: CSR C13007.[15]

The company also presents an additional analysis of the proportions of failure patients in the Maintenance Study population who achieved clinical remission, enhanced clinical response, and corticosteroid-free clinical remission at Week 52 by treatment group and worst failure type; and by number of previously failed therapies. In the main, these analyses were reported to favour vedolizumab but is was noted that p values were not reported and in a number of cases 95% confidence intervals indicate statistical non-significance.

The company concluded the results were consistent with the overall maintenance study ITT population.

ERG comments:

- Again these analyses can only be considered exploratory as indicated by the company.
- These analyses were not used in the updated cost-effectiveness model.

3.2.3.2 Long-term efficacy in the failure sub-population

As part of the ACD response document[4] the company presented updated analyses on the long term efficacy of vedolizumab in all eligible people from GEMINI II (i.e. those that completed Induction (0-6 weeks) and Maintenance phases (weeks 6-52). These analyses extended the data from 1 year, cited from the GEMINI LTS,[19] which was included in the original CS,[1] to up to 2 years, and used a new citation.[7]

Of 814 people treated with vedolizumab in GEMINI II,[13] 295 completed Week 52 assessments and entered into the open-label GEMINI LTS.[19] Clinical remission outcomes at Weeks 52, 80, and 104 are shown in Table 8.

Table 8 Clinical remission up to 2 years in GEMINI II completers - TNF-α failure population (reproduced from Table 12, pg. 40 from the ACD response document[4])

Endpoint	TNF-α antagonist failure (n=136) (%)
Clinical remission (HBI score ≤4 points)	
Week 52	70 (52)
Week 80	76 (56)
Week 104	69 (51)
Clinical response (decrease in HBI score of ≥3 points from baseline)	
Week 52	NR
Week 104	95 (70)

Among completers with previous TNF-α antagonist failure, clinical remission was seen in 51% of people and clinical response in 70% of people at Week 104.[7]

ERG comments:

- This analysis was not used in the updated cost-effectiveness model.
- It should be noted that the Harvey-Bradshaw Index (HBI) was used to assess the proportion of people in clinical remission (i.e. HBI score ≤4 points) and clinical response (i.e. decrease in HBI score of ≥3 points from baseline) at Weeks 52, 80, and 104, rather than the CDAI which was used in all other analyses presented by the company for these endpoints. This makes comparisons difficult. During clarification the company confirmed that CDAI values were not available up to 2 years.

3.3 Critique of trials identified and included in the network meta-analysis, and of the networks constructed

In its original submission to NICE,[1] in the absence of any direct head-to-head RCTs comparing vedolizumab and infliximab or adalimumab for the treatment of moderate to severe CD, the company presented results from a NMA for vedolizumab against adalimumab (induction phase only) in people for whom a TNF-α antagonist had failed. In summary, the ERG noted that the population in the adalimumab clinical trial included in the NMA was not comparable to the population included in the vedolizumab trial as the adalimumab trial[20] only included secondary failure patients (primary failure patients were excluded, defined as lack of response to the induction phase). This was recognised by the AC.[3] No NMA was reported for vedolizumab against infliximab in the absence of data for infliximab in this population. The ERG refers the reader to the original ERG report[2] for a critique of the NMA conducted by the company for the failure population.

In response to the ACD,[4] the company presented additional results for the comparison between adalimumab and vedolizumab in the maintenance phase (not presented in the original submission to NICE). Despite potential limitations (only providing data on clinical remission as an outcome and not on durable response, and a lack of information on patient characteristics by treatment arm for adalimumab 40mg or placebo/CT) recognised in the ACD response document[4], as for the induction phase, the NMA in the maintenance phase uses data from one adalimumab trial in a secondary failure population (CHARM)[21] in order to provide an indication of the relative efficacy of vedolizumab and adalimumab in maintenance treatment.

Overall, this analysis shows no significant difference in clinical remission in the maintenance phase between vedolizumab and adalimumab (Table 9), although there was a trend for a greater efficacy for adalimumab.

Table 9 Pairwise comparisons for clinical remission in Maintenance Phase (TNF-α antagonist failure sub-population)*

Treatment regimen (Maintenance)	Clinical Remission: Each biologic vs. placebo/conventional therapy Odds Ratio (95% CrI)	Clinical Remission: Vedolizumab vs. each TNF-α antagonist Odds Ratio (95% CrI)
Vedolizumab 300mg Q8W	2.7 (1.1, 6.5)	-
Vedolizumab 300mg Q4W	2.6 (1.2, 6.3)	1.1 (0.5, 2.1)
Adalimumab 40mg eow	4.1 (1.8, 10.4)	0.7 (0.2, 2.1)
Adalimumab 40mg ew	4.8 (2.0, 12.1)	0.56 (0.2, 2.0)

*Fixed effects model. There was a lack of contrasts in the network in order to perform random effects modelling. Q8W = every 8 weeks, Q4W=every 4 weeks, eow = every other week, ew = every week

ERG comments:

The ERG refers the reader to the original ERG report[2] for a critique of the method used for the NMA. Although the company conducted a NMA between vedolizumab and adalimumab, as for results for the induction phase previously reported,[4] results are uncertain given the differences in populations. The company has access to trial data from the vedolizumab trial. Thus, the ERG believes that a more useful comparison would have been to conduct the NMA in a similar population as the one included in the adalimumab trial. Clarification was requested from the company (see clarification response[10] question 12). The company responded that *"Whilst this would be useful analysis, the data was not readily available for vedolizumab from the CSRs of the GEMINI trials in order to extract evidence for efficacy outcomes in a secondary failure population (i.e. patients that lost response) that matches secondary failure patients in the adalimumab trials"*. Despite limitations, the exploratory NMA conducted by the company showed no statistical difference between adalimumab and vedolizumab (although this is conducted in different population), with adalimumab having greater efficacy. Unfortunately, there are no data for infliximab in the failure subgroup. Data in the anti-TNF naïve subgroup suggest that infliximab may have a greater efficacy compared with vedolizumab and adalimumab. It is unclear whether infliximab would have a greater, similar or lower efficacy to vedolizumab when used after adalimumab.

3.4 ERG critique of the additional clinical effectiveness analyses

- All analyses, with the exception of the long-term efficacy analysis up to two years, are based on data which was available at the time of the original CS and do not provide any new evidence over and above that.
- The analyses presented here for GEMINI II should be considered exploratory as the study was not designed to assess the failure subgroup, and should also be considered exploratory for GEMINI III as the primary endpoint of that study was not achieved.
- The ERG concludes that these new analyses add very little to the clinical effectiveness evidence presented in the original CS.
- The main conclusion presented by the company as a result of this response document relates to treatment differences at 10 weeks in the induction phase, which appear to favour vedolizumab, and that exploratory failure sub-group analyses up to 52 week were consistent with the overall maintenance study ITT population reported in the original CS.
- Long term efficacy at two years is presented, and does constitute new evidence since the original CS, however it should be noted that these data are based on HBI rather than the CDAI.
- Results of the NMA are uncertain given the differences in populations

4 COST-EFFECTIVENESS

This section presents a critique of the additional cost-effectiveness evidence presented in the ACD response document submitted by the company to NICE.[4] The company submitted a revised economic model.[5] The following modifications were made to the economic analysis originally submitted to NICE[22]:

- focusing on people for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist),
- lifetime horizon,
- assessment time of response in line with the SmPC,[23]
- inclusion of a revised patient access scheme (PAS) that offers vedolizumab at a new reduced price of [redacted] per 300mg vial ([redacted] discount on the list price of £2,050 per vial),
- amendment to inputs to reflect some of key concerns raised by the Appraisal Committee (AC)[3] and evidence review group (ERG),[2]
- amendments to the Markov trace and calculations,
- the incorporation of an exploratory analysis comparing vedolizumab against a second TNF-α antagonist in people for whom a prior TNF-α antagonist has failed.

These had the effect of reducing the company's base case deterministic (probabilistic) ICER from £98,452 (not reported) to £21,620 (£27,428).

These elements are discussed in turn

4.1 Population

In the original submission to NICE,[1] the company reported results for adults with moderate to severe disease (defined as CDAI score >220) for three patient groups;

- a mixed population representing the intention to treat (ITT) population of the GEMINI trials (referred to as the mixed-ITT population), which includes both people who have never received a TNF-α antagonist therapy (referred as TNF-α antagonist naïve) and people who have previously been exposed to a TNF-α antagonist agent (referred as TNF-α antagonist failure),
- an TNF-α antagonist naïve subgroup,
- and a TNF-α antagonist failure subgroup, which includes intolerance to TNF-α antagonist agents, primary failure (no initial response to TNF-α antagonist agents) and secondary failure (loss of response after initially responding to TNF-α antagonist agents).

In response to the ACD,[3] the revised economic analysis[4,5] focuses on a TNF-α antagonist failure subgroup. No analysis is presented for either the mixed population or the TNF-α antagonist naïve subgroup.

ERG comments:

The ERG is satisfied with the population included in the revised economic model.[4,5]

4.2 Comparators

The revised base-case economic analysis compares the cost-effectiveness of vedolizumab versus conventional non-biologic therapy (a combination of 5-ASAs, immunomodulators and corticosteroids) in a subgroup of patients for whom TNF-α antagonists have failed.

An exploratory analysis is conducted comparing vedolizumab against the use of a second TNF-α antagonist after failure or intolerance to an initial TNF-α antagonist (either infliximab or adalimumab used as second TNF-α antagonist). This exploratory analysis takes the form of a cost-minimisation.

ERG comments:

The ERG is satisfied with the base-case analysis (comparison of vedolizumab versus conventional non-biological therapy). As acknowledged by the company (see Section 4.3 of the ACD response document[4]) there are limited data to conduct a robust comparison of vedolizumab against the use of a second TNF-α antagonist after failure or intolerance to an initial TNF-α antagonist. A critique of the exploratory analysis undertaken by the company is presented in Section 5.6.

4.3 Time horizon

It the original submission to NICE,[1] the company's economic analysis used a 10 year time horizon. The revised economic analysis[4,5] uses a lifetime horizon.

ERG comments:

Although the ERG believes that a lifetime horizon is probably more appropriate than a 10- year time horizon, the ERG notes that given the short duration of the clinical trials[13,14] used to inform the model (maximum 54 weeks), the extrapolation of the available data over a lifetime horizon is subject to considerable uncertainty.

Reducing the time horizon to 10 years increases the ICER from £21,620 to £49,405 per QALY gained.

4.4 Assessment time for response

In the original submission to NICE,[1] the company's economic analysis assumed people to be assessed for response at Week 6 (following 2 doses) to reflect the dosage and assessment time in the GEMINI II trial.[13] In response to comments raised by the AC[3] and ERG,[2] the revised economic model[4,5] assumes assessment to happen at Week 10. Patients are assumed to receive 3 induction doses of 300mg of vedolizumab (at 0, 2 and 6 weeks) with the assessment of response at Week 10. Responders start an 8-weekly 300mg maintenance regimen beginning at Week 14. The company acknowledges that in practice (see Table 14 in the ACD response document[4]), non-responders may be offered a further dose at Week 10 as per the marketing authorization.[23] This was not included due to the limited data available.

ERG comments:

The ERG is satisfied with this amendment. As previously noted by the ERG (see Section 5.2.4 of the original ERG report[2]), assessment at Week 10 is more in line with the SmPC[23] and expected clinical practice. The ERG recognises that the labelling[23] recommends that in some patients who do not respond at week 10, an additional dose may be given but recognises that this cannot be captured without assumptions being required. The impact on the ICER is uncertain.

4.5 Revised Patient Access Scheme (PAS)

Vedolizumab is available as a powder for concentrate for solution for infusion. Each pack contains one vial containing 300mg of vedolizumab. The basic NHS list price of vedolizumab is £2,050 per 300mg vial.[24] In the original submission to NICE,[1] the company's model[17] included an initial agreed Patient Access Scheme (PAS) which reduced the price of vedolizumab to [redacted] per 300mg vial (a reduction of [redacted] of the NHS list price) for the NHS.

The revised economic model[4,5] includes a revised PAS that offers vedolizumab at a new price of [redacted] per 300mg vial ([redacted] discount on the list price of £2,050 per vial).

Of note, the revised PAS has only a moderate impact on the ICER reducing the ICER from £27,266 using the PAS agreed at the time of the original submission to £21,620 per QALY gained.

4.6 Summary of amendments made to input parameters

A series of amendments (discussed in turn) were made to inputs, some to reflect key concerns raised by the AC[3] and ERG[2] and some that were believed by the company to improve the model, including:

- the probabilities of response and remission to the induction phase,
- the percentage of non-remitting responders with moderate to severe CD,
- re-calibration of the transition matrices,
- the probabilities of surgery,
- the cost of surgery and post-surgery complications,
- the cost of each disease health states (remission, mild, moderate to severe CD),
- revision of AEs list, probabilities, impact on quality of life and costs,
- CD excess mortality,
- the cost of CT and proportion of patients treated with vedolizumab receiving CT.

4.6.1 The probabilities of response and remission to the induction phase

Efficacy data used in the induction phase have been updated to reflect the revised assessment time (10 Weeks vs. 6 Weeks used in the original submission[1]). The pooled probabilities of response and remission to the induction phase at Week 10 from the GEMINI trials[13,14] were used in the economic model (Table 10). Scenario analyses were conducted using the probabilities from GEMINI II[13] and III[14] separately as there were differences between the two trials in the probabilities of response and remission (Table 10).

Table 10 Probabilities of response and remission to the induction phase (adaptation of Table 17 and 18 in the ACD response document submitted by the company to NICE[4])

Treatment	Vedolizumab	CT
Induction Phase – Pooled GEMINI trials		
	N=260	N=226
Clinical response at week 10	121 (46.54%)	74 (32.74%)
	N=263	N=227
Remission at week 10	57 (21.67%)	25 (11.01%)
Induction Phase – GEMINI III		
	N=155	N=156
Clinical response at Week 10	87 (56.1%)	58 (37.2%)
	N=158	N=157
Remission at Week 10	42 (26.6%)	19 (12.1%)
Induction Phase – GEMINI II		
	N=105	N=70
Clinical response at week 10	34 (32.4%)	16 (22.9%)
Remission at week 10	15 (14.3%)	6 (8.6%)

P values not reported

ERG comment:

The ERG is satisfied with this amendment. The ERG is unclear why the denominator used is different between outcomes for clinical response and remission. It should also be noted that pooling data may not be as accurate as meta-analysis.

4.6.2 The percentage of non-remitting responders with moderate to severe CD

Following a concern raised by the ERG[2] (see p.150-154 of the original ERG report[2]), the company amended the calculation to estimate the proportion of responders with moderate to severe CD in the economic model. In the revised analysis,[4,5] the company calculates the percentage of non-remitting responders with moderate to severe CD from a pooled analysis of the GEMINI trials.[13,14]

The company reported that 33 patients were responders with moderate to severe CD amongst 86 non-remitting responders (see Section 4.444 of the ACD response document[4]) across all trials arms. As in its original submission to NICE,[1,17] the company assumed this proportion to be applied regardless of the treatment arm.

ERG comments:

Although the ERG is satisfied with the new approach used by the company to calculate this proportion in the economic model, the ERG has some concerns regarding the transparency of the data used.

According to the company (see Section 4.444 of the ACD response document[4]), the percentage of non-remitting responders with moderate-severe CD is calculated amongst all trial arms from both the GEMINI II[13] and III trials.[14] In the ACD response document submitted by the company to NICE,[4] the company suggests that across all arms and trials, there are 86 responders not in remission at Week 6 for the TNF-α antagonist failure subgroup. However, in the original submission to NICE[1] (Table 11), the company reported that there were 187 responders and 57 patients in remission in total in the TNF-α antagonist failure population across the two treatment arms of the GEMINI trials at Week 6, equating to a total of 130 responders not in remission. The ERG is not able to verify the accuracy of the value used by the company. The ERG already commented on this issue in the original ERG report (see p.150-154 of the original ERG report[2]).

Clarification (see economic clarification response[10] question 7) were also requested to the company on the reason why the proportion of responders not in remission with moderate to severe disease is calculated across patients randomised to both arms (vedolizumab and conventional therapy) rather than in each individual arms. In response, the company stated that *"for sample size reasons, we consider a larger number of responders would be more robust especially since the maintenance trials used a merged patient population before re-randomisation".*

Table 11 Numbers of responders and patients in remission (taken from page 445-447 of the original CS[1])

Source	Treatment arm	Number of responders (drop in CDAI score of 70 points or more)	Number of patients in remission
CSR13011	Placebo	50	20
CSR13011	Vedolizumab	79	23
CSR13007	Placebo	20	3
CSR13007	Vedolizumab	37	11
TOTAL		187	57

The ERG disagrees with this statement and believes that the data should be used for both arms separately as this would impact the derivation of the transition probabilities. It should be noted that the ERG commented on this issue in the original ERG report (see p.150-154 of the original ERG report[2]).

4.7.3 Transition probabilities

Transition probabilities were re-calibrated because the induction vector and probabilities of surgery were amended. Re-calibrated transition probabilities are summarised in Table 12.

Table 12 Re-calibrated transition probabilities for the vedolizumab and CT arms in each 8-week cycle (reproduction of Table 19 in the ACD response document submitted by the company to NICE[4])

From/To health state	Remission	Mild	MS	Surgery	Sum
Vedolizumab					
Remission	0.989	0.011	0.000	0.000	1.000
Mild	0.000	0.500	0.500	0.000	1.000
Moderately to severely active (MS)	0.000	0.000	0.989	0.011	1.000
Surgery	0.787	0.115	0.087	0.011	1.000
CT					
Remission	0.831	0.169	0.000	0.000	1.000
Mild	0.000	0.601	0.399	0.000	1.000
Moderately to severely active	0.000	0.030	0.959	0.011	1.000
Surgery	0.787	0.115	0.087	0.011	1.000

ERG comments:

The ERG expresses the same concerns as in the original ERG report.[2] Although the ERG recognises that calibration method may be necessary when input parameters are not directly observable. The calibration approach adopted by the company "estimates" seven unknown parameters by fitting to two data-points conditional on a number of assumptions regarding what these probabilities might be, as represented by constraints in the Microsoft Excel Solver routine, an assumed initial matrix for the linear program and the model structure. The reader is referred to the ERG report[2] (see p.157-160 of the original ERG report[2]) for further critique regarding the calibration approach.

Patient-level data from the GEMINI II trial are available and could have been used to estimate the transitions between remission/mild/moderate-to-severe within the maintenance phase in patients treated with conventional non-biologic therapy and vedolizumab. Clarification was requested from the company (see economic clarification response[10] question 13) on why the model uses a calibration approach when observed data are available for the first year. The company responded that : *"It would technically be possible to use the 1-year observed data, but it would be inappropriate largely because of the re-randomization issue in the main part of the trial for which separate placebo cohorts act as the control arm for the Induction (weeks 0-6) and for the Maintenance (week 6 to 52) Phases. So using the GEMINI patient-level data would less accurately reflect a placebo patients experience than the approach we have adopted. There is a cohort who originally received placebo who continued to receive placebo (see flow diagram above) but these did not represent a control arm and outcomes for these were not fully evaluated."*

The ERG disagrees with the company response and believes that the transition probabilities could have been derived from the trial. The company states that patients included in the placebo arm were not a control arm (see economic clarification response[10] question 13): the ERG disagrees with this statement. The model could have been adapted to estimate the transition probabilities whilst on CT (instead of the approach used by the company which uses data for patients on placebo in the maintenance phase who responded to vedolizumab) as patients originally randomised to placebo at the induction phase remained on placebo for the remaining of the trial (although as suggested by the company these patients were not evaluated for outcomes in the maintenance phase).

It should also be noted that although clarifications were obtained from the company on the calibration process (see clarification response[10] question 5), the ERG was not able to replicate the same transition matrix as estimated by the company.

4.6.4 Probabilities of surgery

In response to the AC,[4] the company reduced the probabilities of surgery from 16.3% to about 7% annually (equating to a probability of 1.11% during each 8-week cycle). The company reports that the revised probability of surgery was derived from HES data.

Furthermore, in the original submission to NICE,[1] the company assumed that approximately a third of patients undergoing surgery undergo subsequent surgery in the next cycle (8-weekly). The ERG[2] and ACD[3] commented that this value was possibly high. In the revised economic analysis, the company assumed that 1.1% of patients would undergo further surgery in the next cycle.

ERG comments:

Although the ERG believes the values used in the revised economic analysis[4,5] to be more accurate than the values used in the original submission to NICE,[1] the ERG notes the uncertainty in the values used. It should be noted that in a previous response to a request for clarification (see p.164 of the original ERG report[2]) the company reported that within the maintenance phase of the GEMINI II trial[13] (which lasted 46 weeks), 3.3% (5/153) of patients randomised to placebo and 1.3% (4/308) of patients randomised to vedolizumab underwent bowel surgery. Data from the GEMINI II trial[13] suggests that the probability of surgery may be lower than estimated by the company from the HES data. The ERG also notes that it is unclear whether the probabilities are constant over time.

4.6.5 Cost of surgery and post-surgery complications

In response to the ACD,[3] the cost of surgery was reduced from £10,580 to £6,704[4] which was stated to be derived from an analysis of the HES dataset.

The cost of treating post-surgery complication was also updated using cost from the NHS Reference Costs 2013-14 (from £365.44 to £322.26).

ERG comments:

The ERG is satisfied with the transparency of the data used in the revised analysis[4,5] compared with the original submission to NICE[1,17] and believes the revised cost of surgery to be more accurate.

The ERG notes that the impact on the ICER is minimal (a reduction in the ICER from £21,620 to £20,344 per QALY gained).

4.6.6 Health state costs

In the original submission to NICE,[1] health state costs were taken from Bodger et al (2009).[25]

Although not requested by the AC,[3] the company updated the cost of the different health states[4] using resource use estimates for medical (non-surgical) CD symptom management from a clinical expert survey conducted in February 2015 amongst 8 clinical experts (see section 4.4.9 of the ACD response document[4]). The resources and frequency estimated by the clinical experts included: outpatient visits; laboratory tests; radiology investigations; endoscopies; hospital admissions and other resources. Further details on the estimated resource use by health state and unit costs are available in Table 29 of the ACD response document submitted by the company to NICE.[4]

The company justify this amendment by stating that the cost in Bodger et al (2009) are old and may be out of date. The estimated per-cycle costs by health state using the clinician survey and Bodger et al[25] are presented in Table 13.

Table 13 Summary of healthcare costs by health state per 8-week cycle (adaptation of Table 31 in the ACD response document submitted by the company to NICE[4])

Health state	8 week cycle cost applied in the modified model[4,5]	Cost from Bodger et al (2009) used in the original CS[1,17]
Remission	£100	£110
Mild	£205	£313
Moderately to severely active CD	£1,239	£490

ERG comments:

Although the ERG is not able to provide a full critique of the clinician survey conducted by the company, the ERG has no immediate concerns with the methodology used. Resource use from the clinician survey estimated by the company was sent to our clinical advisors for validation. Although only one clinical advisor was able to comment on this, he felt that the estimated resource use were reasonable.

The ERG recognises this is an uncertainty and that there are limitations with either estimates from Bodger et al (2009) or costs estimated from the clinician survey conducted by the company.

This amendment to health state costs had a considerable impact on the ICER. The revised base-case ICER estimated by the company was £21,620 per QALY gained using the updated cost for the CD health states based on the clinician survey.[4] Using the original management cost for the CD health states from Bodger et al (2009)[25] increased the ICER to £46,025 per QALY gained.

4.6.7 Cost of conventional non-biological therapy

Although not requested by the AC,[3] the company updated the cost of CT from £70.16 to £49.10 to reflect changes to the drug costs in the British National Formulary 68 (November 2014)[24] and the dose regimen for azathioprine and mercaptopurine. Further details are available in the ACD response document submitted by the company to NICE in Section 4.4.7.3 of the ACD response document.[4]

The company also updated the proportion of CT used alongside vedolizumab (and any other biologics) from 50%[1] to 75%[4] of the regimen prescribed to patients in the CT arm (£36.82 per cycle) to reflect views expressed in the clinical expert survey conducted by the company.

ERG comments:

The ERG is satisfied with these amendments and notes that the impact on the ICER is minimal (a reduction in the ICER from £21,620 to £21,066).

4.6.8 Vedolizumab administration costs

Similarly, although not requested by the AC,[3] the company updated the cost of administration for Vedolizumab IV infusion from £308 to £328 per administration of vedolizumab. Clarification was requested to the company on why the cost was updated (see clarification response[10] question 3). The company responded that *"£308 was taken from the Payment-by-Results Mandatory Tariff 2012/2013 database, and therefore, £308 is a financial value and as such does not reflect the concept of opportunity cost adequately….In contrast, £328 is a cost estimate derived from the NHS reference cost schedule 2013-2014, which provides a better representation of the value of resources in terms of opportunity costs ".*

A scenario analysis is conducted assuming half the cost (i.e. £164 per administration) to reflect the shorter administration in the maintenance phase.

ERG comments:

The ERG is satisfied with this amendment and notes that the impact on the ICER is minimal (increase in the ICER from £21,620 to £20,986 per QALY gained).

4.6.9 CD excess mortality

In the original model submitted to NICE,[1,17] the company assumed a differential mortality between health states, leading to a survival gain for patients on vedolizumab. Following a comment from the ERG (see p.164-166 of the original ERG report[2]), no excess mortality risk is assumed in the base-case in the revised analysis.[4,5]

ERG comments:

The ERG is satisfied with this amendment. As previously noted in the ERG report (see p.164-166 of the original ERG report[2]) the Lichtenstein study suggests no statistical differences in mortality between infliximab and non–infliximab-treated patients.[26] Furthermore, no increased mortality rate was observed in patients randomised to the placebo arm in the GEMINI II trial.[13]

The ERG notes that the impact on the ICER is minimal (an increase in the ICER from £21,620 to £23,066 per QALY gained).

4.6.10 Revision of AEs list, probabilities, impact on quality of life and costs

Although not requested by the AC,[3] the company made several amendments to the list of AEs, AEs probabilities, impact of AEs on quality of life and costs of AEs. Further details are available in Section 4.4.4.4 and 4.4.4.6 in the ACD response document submitted by the company to NICE.[4]

ERG comments:

The ERG notes that AEs have a limited impact on the ICER. Assuming no AEs lead to a small increase in the ICER from £21,620 to £22,003 per QALY gained. Given the number of amendments made by the company, time and resource constraints and the limited impact on the ICER, the ERG did not critique the revised input parameters used for AEs.

4.6.11 Utility values

Although no changes were made by the company to utility values, the ERG requested (see clarification response[10] question 10) the company to provide utility data for the failure population as the economic analysis focuses on this population. The company did not supply these data stating that *"Utility values broken down by naïve and failure subgroups are not available, as for CD we assumed that quality of life is health state dependent and not dependent upon whether or not you have failed a prior anti-TNF. This assumption was corroborated by previous evidence of the analysis of EQ 5D utility data in GEMINI I for UC, where minimal difference in mean utility between the naïve and failure populations was found. We can provide this UC utility data if the ERG would find it useful to see".*

The ERG believes it is possible for the utility to be different between the naïve and failure subgroups. The company mention the case of UC to justify the absence of difference. However these values may not be generalizable to CD. The ERG notes that given the small QALY gained, different utility values could markedly change the ICER, although the change is unclear.

4.7 Summary of amendments made to the economic model reported by the company

In addition to changes to input parameters, the following amendments were reported by the company;

- the approach regarding the impact of AEs on costs and QoL,
- timing and separation of drug and administration costs
- calculation of the proportion of responders with moderate to severe disease.

ERG comments:

The ERG is satisfied with these amendments and refers the reader to the ACD response document submitted by the company to NICE[4] for further details (see Table 14 of the ACD response document[4]).

4.8 Summary of other amendments made to the economic models

In addition to the changes reported by the company, the ERG identified the following changes to the calculations in the model;

- updated calculation for the discontinuation in the maintenance phase,
- allowing patients to continue on an intervention after surgery,

Clarification was requested (see clarification response[10] question 8) to the company on why the calculation for the discontinuation rate in the maintenance phase was updated increasing the discontinuation rate from 1.36% to 1.54%. The company reported that the rate of 1.36% was not correct because it was derived assuming a 52 week duration but should be calculated assuming a 46 week duration. The ERG is satisfied with the explanation provided by the company.

The ERG sought clarification to the company (see clarification response[10] question 9) on the reason why the model was amended to allow patients to continue on biologic after surgery (in the second cycle) compared with the original model. The company initially stated that no change was made compared with the original model. The ERG requested further clarifications to the company demonstrating the changes compared with the original model (see response to further queries[27] question 2). The company responded that the changes highlighted by the ERG were made to be consistent with other cycles. The ERG is satisfied with this explanation.

In order to help the ERG assessment of the revised economic model, the ERG requested clarification from the company (see response to further queries[27] question 3) on whether any other modifications were made to the economic model. The company provided the following response:

"This is a difficult question to provide a specific response to in the time available. We believe we have identified all key changes in the modelling in the resubmission document. However, to clarify the process we took, for our evidence resubmission we did not specifically start with the original NICE submitted model of October 2014 and make stepwise changes to produce the revised model submitted to NICE in February 2015. Instead, the model had already been adapted for use in a Scottish Medicines Consortium submission and so already contained improved functionality and computations. Although we kept records of all the sets of changes we implemented at the different time-points, to try and ensure 100% that we have captured all these changes (as maybe is the premise of the ERG question) would require more time. We do appreciate the ERG efforts to check the comprehensiveness of the list of changes we implemented. However, we also feel it would be more efficient in terms of all party's time and efforts if the ERG were to focus on a direct critical appraisal of the updated model and assess it and the results generated on its merits, rather than spending time trying to anchor to the original model. Whilst we did not have time to completely build a new model to meet the resubmission of evidence deadline of end of February, the model has been significantly modified within the time constraints and so would suggest it were appraised as if it were a new model that had been submitted (but with the advantage of ERG having some familiarity with it already)".

The response provided by the company highlights inconsistencies between documents. Throughout the ACD response document,[4] the company suggests (see p.43 of the ACD response document[4]) that the model submitted is a revised model compared with the model submitted to NICE[1]). The company now seems to suggest that the economic model is a new economic model.

The ERG was not able within the time assigned to check the economic model as if it was a new model. Instead, in order to identify whether any additional substantial changes were made to the model, the ERG used the original model submitted to NICE on the 6th of October 2014[17] to replicate the company's analysis incrementally including known changes. The impact on the ICER associated with each incremental step is reported.

As previously mentioned, several amendments were made by the company in the revised economic model[5] to the approach used to include the impact of adverse events on costs and quality of life. Given the limited impact of AEs on the ICER, the ERG removed the impact AEs by setting the probability of AE to zero in both the original and revised model.

Table 14 Impact of changes made to the original model submitted to NICE

Summary of Changes	**ICER**
Original ICER generated using the original model submitted to NICE on the 6th of October 2014	£98,452
Removal of AEs (setting AEs probabilities to Zero)	£98,763
Setting the time horizon to lifetime (instead of 10 years) – as previously mentioned this is uncertain as only one year data are available	£57,481
Updating the cost of surgery	£56,223
Updating the cost of surgery complications	£56,208
Updating health state costs	£35,154
Updating the cost of CT	£35,378
Updating the proportion of CT use whilst on biologics	£35,664
Updating the cost of administration of vedolizumab (from £308 to £328)	£36,287
Updating the cost of vedolizumab (revised PAS)	£30,739
Updating the mortality assumption(assuming no differential mortality by health state)	£29,696
Updating the discontinuation rate in the maintenance phase	£29,576
Updating the calculation for the Induction vector (and probability)	£28,832
Updating the Markov trace for vedolizumab	£30,012
Updating the Markov trace for CT	£17,032
Setting Induction Phase to 10 weeks	£17,157
Updating efficacy data induction week 10	£16,918
Change in the number of doses for vedolizumab (to reflect timing of doses)	£16,595
Updating the transition probabilities in the maintenance phase*	£18,722
Updating the trace cost	£20,874
Updating the probabilities of surgery	£22,003
ICER after all changes	**£22,003**

* Transition probabilities estimated by the company were used. the ERG was not able to replicate the derivation of transition probabilities

The ERG was able to replicate the ICER estimated in the revised economic model assuming no AEs (£22,003 per QALY gained) and is thus satisfied that if any unstated amendments were made to the model, these are likely to have a limited impact on the ICER.

4.9 Model validation

In our original ERG report (see Section 5.2.12 of the original ERG report[2]), comments were made about the predictive validity of the model. The ERG refers the reader to Table 49 in the ACD response document for the company responses to comments from the ERG.

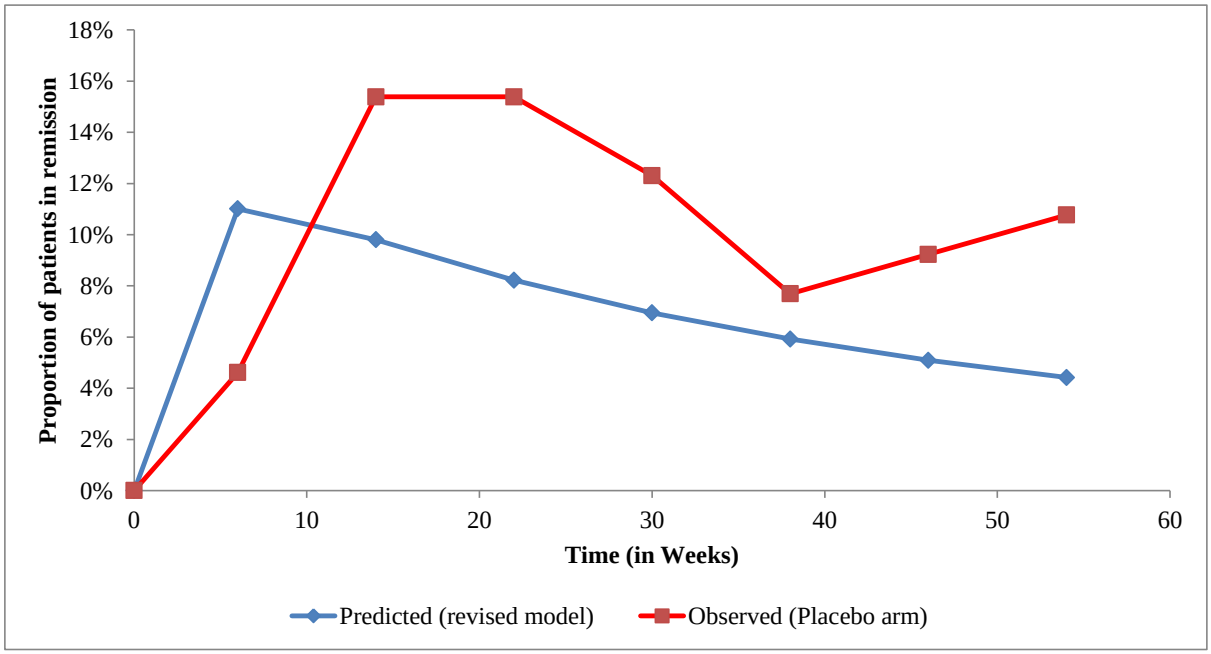
Although the ERG agrees with the second point made by company in that keeping patients who have lost response on treatment is likely to be conservative, the ERG expresses the same concerns as in the original ERG report[2] regarding the predictive validity of patients treated with conventional non-biological therapies.

In the ACD response document submitted by the company to NICE,[4] the company suggested (see Table 49 of the ACD response document[4]) that the GEMINI II trial did not follow patients randomised to placebo after induction. However, according to the trial publication by Sandborn et al.,[13] patients initially randomised to placebo remained on placebo (irrespective of response) within the trial. Following clarification (see economic clarification response[10] question 11), the company recognised that the response provided was inaccurate and that that patient initially randomised to placebo in the Induction phase (Cohort 1) continued to receive placebo in the Maintenance phase of the trial through week 52.

In the original ERG report[2], we compared (see Figure 15, p.195 of the original ERG report[2]) the proportion of patients in remission treated with conventional non-biological therapies observed and predicted by the model and demonstrated that the company's model[17] tended to under-predict the proportion of patients in remission treated with conventional non-biological therapies.

The ERG compared the proportion of patients in remission treated with conventional non-biological therapies observed in the GEMINI II trial and predicted in the revised economic model (Figure 1).[5] As in the original model, the model tended to under-predict the proportion of patients in remission treated with conventional non-biological therapies.

Figure 1 Comparison of the proportion of patients in remission treated with CT observed and predicted by the model



The ERG believes that the mismatch is attributable to the fact that the model uses data from the maintenance phase in patients experiencing an initial response to vedolizumab rather than patients on placebo. The ERG believes that observed data from the GEMINI II trial for the placebo arm should be used to derive the transition probabilities for patients treated with conventional non-biological therapies rather than using data for induction from the placebo arm and maintenance for patients who responded to vedolizumab at the induction phase. The impact on the ICER should the ERG recommended approach be used is unclear.

4.10 Base case results

In the revised analysis,[4] the base case ICER for vedolizumab vs. conventional non-biological therapy was £21,620 per QALY gained. Vedolizumab provided an incremental lifetime cost of [redacted] and incremental QALYs of 0.176 (Table 15).

Table 15 Base case - vedolizumab vs. CT in the TNF-α antagonist failure population (with updated PAS) – Reproduction of Table 34 in the ACD response document submitted by the company to NICE[4]

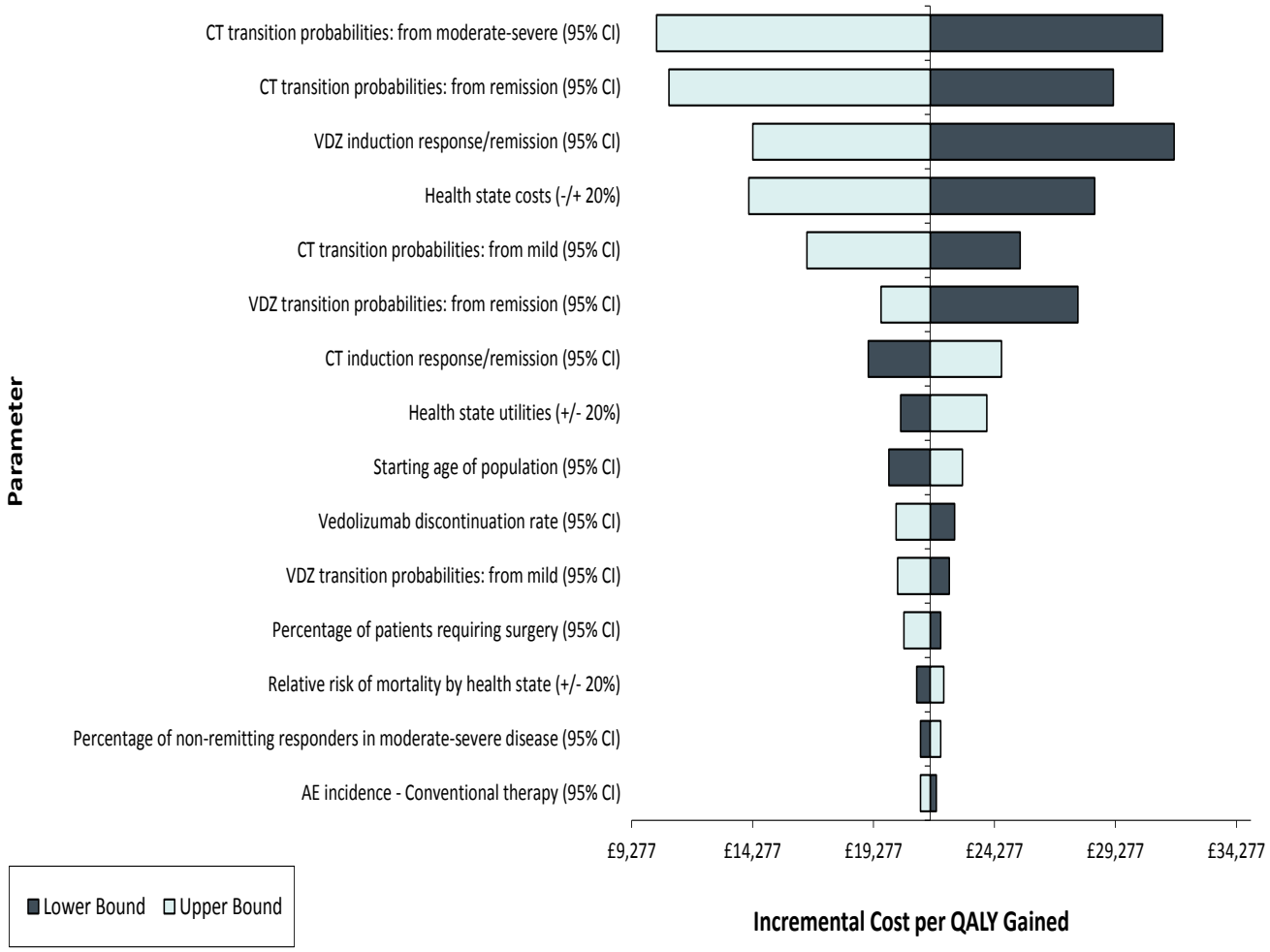
	Vedolizumab	CT	Increment
Costs			
Biologic therapy (acquisition)	[redacted]	£0.00	[redacted]
Biologic therapy (administration)	£1,830	£0.00	£1,830
Conventional therapy	£7,175	£7,225	-£50
Health-state costs	£178,363	£184,657	-£6,293
Adverse event costs	£5,277	£5,329	-£52.46
Total discounted costs	[redacted]	£197,211	[redacted]
Outcomes			
Discounted Life years gained (LYG)	22.664	22.664	0.000
Discounted QALYs gained	13.240	13.064	0.176
Incremental cost per QALY	£21,620		

The ERG notes that deterministic ICER may be an underestimate. In the PSA (see Section 5.4) the ICER increased from £21,620 per QALY gained (deterministic analysis) to £27,428 per QALY gained (probabilistic analysis). However, the ERG notes that arbitrary distributions are sometimes used which may not reflect the 'true' uncertainty which may limit the interpretation of the PSA.

4.11 Deterministic sensitivity analysis results

A range of univariate sensitivity analysis was performed on data inputs (Figure 2). The company reports that one-way sensitivity analysis showed that the ICER was most sensitive to the CT arm transition probability from the moderately to severely active state (ICER: £10,307 to £31,226), to variation in the transition probability from the remission state (ICER: £10,820 to £29,191), both response and remission outcomes at 10-week assessment (£14,284 to £31,704).

Figure 2 Tornado diagram for 15 most sensitive variables in deterministic sensitivity analysis (Reproduction of Figure 4 in the ACD response document submitted by the company to NICE[4])



As highlighted in the original ERG report[2] it should be noted that the range used is sometimes arbitrary. The company states in Table 50 of the ACD response document[4] that no revision was made given the time constraints. It is unclear whether the range used always represents the 'true' uncertainty.

4.12 Results of the Scenario analyses

Similarly, a number of scenario analyses were performed for the comparison vs. CT in patients who had failed on a TNF-α antagonist (Table 16)

Table 16 Scenario analysis results: vedolizumab vs. CT in the TNF-α antagonist failure population (Reproduction of Table 35 in the ACD response document submitted by the company to NICE [4])

	Vedolizumab vs. CT		
	Incremental Cost £	**Incremental QALY**	**Incremental cost/QALY**
Base case	[redacted]	0.176	£21,620
Scenario Analysis			
A. Time horizon = 10 years	[redacted]	0.121	£49,405
B. Induction/assessment duration = 6 weeks	[redacted]	0.121	£37,598
C. Type of response: enhanced (100-CDAI point reduction from baseline)	[redacted]	0.116	£44,349
D1. Source of efficacy data: GEMINI II C13007	[redacted]	0.129	£31,502
D2. Source of efficacy data: GEMINI III C13011 (induction) and GEMINI II C13007 (maintenance)	[redacted]	0.206	£17,981
E. Mortality RR=1.39 for the moderately to severely active state	[redacted]	0.183	£22,107
F. Buxton et al., utilities remission =0.827	[redacted]	0.287	£13,251
G. IV infusion cost = £ 164	[redacted]	0.176	£16,418
H1. Biologics treatment duration = 2 year	[redacted]	0.209	£24,695
H2. Biologics treatment duration = 3 years	[redacted]	0.236	£26,207
L1. Discounting = 0%	[redacted]	0.276	£205
L2. Discounting = 6%	[redacted]	0.146	£33,517
M1. Use of CT by patients taking biologics: 50% of the CT arm regimen	[redacted]	0.176	£21,318
M2. Use of CT by patients taking biologics: 100% of the CT arm regimen	[redacted]	0.176	£21,922
N. Vedolizumab price = £2,050 (without the PAS)	[redacted]	0.176	£39,066

4.13 Probabilistic sensitivity analysis results

The company reported the probabilistic ICER to be £27,428/QALY (95%CI: dominating to £82,947) and reported that at a willingness to pay threshold of £30,000 per QALY gained, the probability that vedolizumab is cost-effective compared to CT was 61%.

Figure 3 Scatterplot for incremental costs and QALYs for vedolizumab vs. CT in the TNF-α antagonist failure population (Reproduction of Figure 5 in the ACD response document submitted by the company to NICE[4])

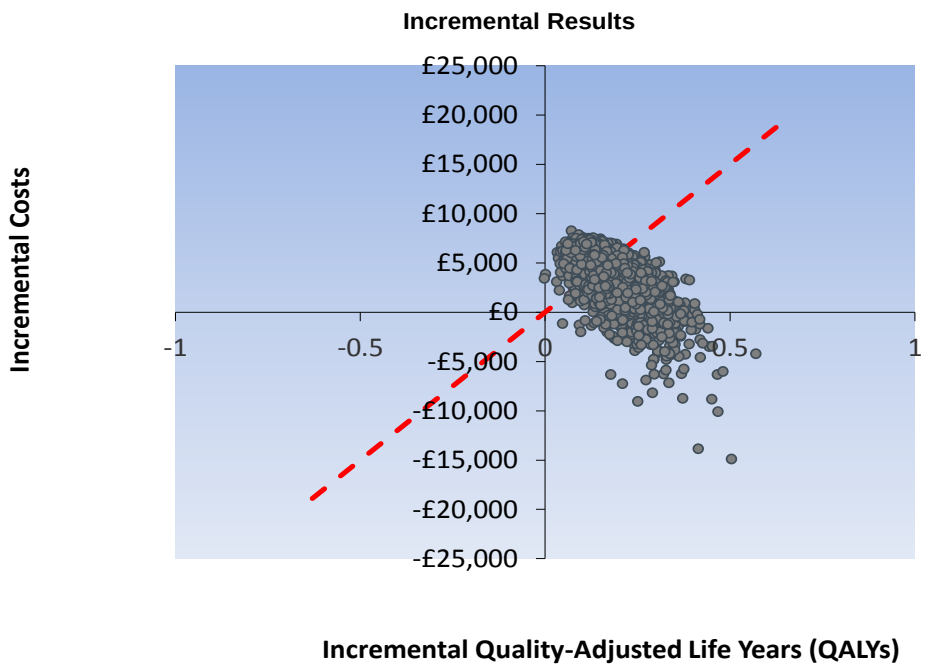
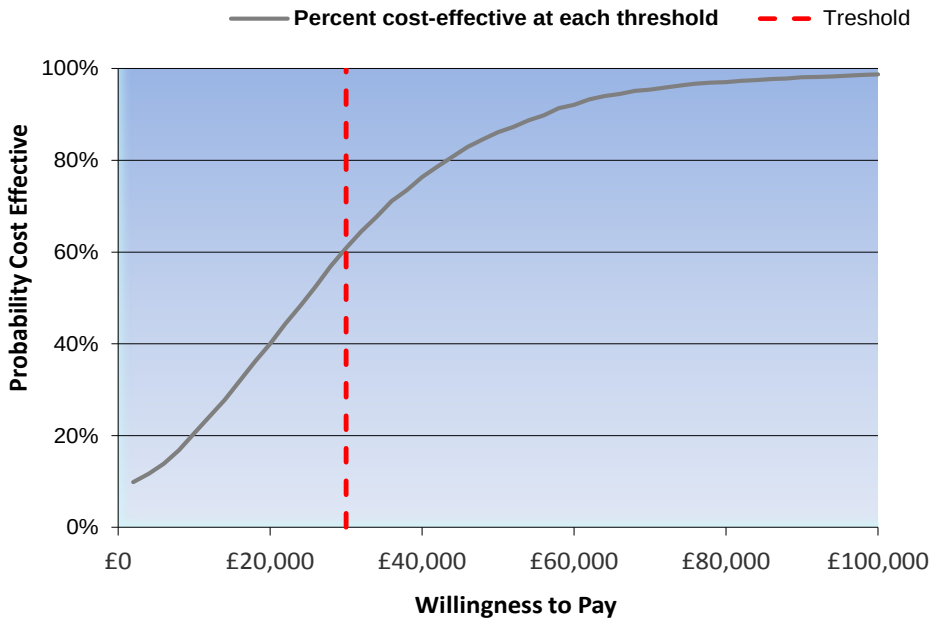


Figure 4 Cost-effectiveness acceptability curve for vedolizumab vs. CT in the TNF-α antagonist failure population (Reproduction of Figure 5 in the ACD response document submitted by the company to NICE[4])



As highlighted in the original ERG report[2] it should be noted that arbitrary distributions are sometimes used in the PSA. The company states in Table 50 of the ACD response document[4] that no revision was made given the time constraints. It is unclear whether the range and distribution used always represents the 'true' uncertainty. The ERG refers the reader to the original ERG report[2] for a critique of the range used in the PSA (see p.189-191 in the original ERG report[2]).

4.14 Comparison against other anti-TNF in the TNF-α antagonist failure subgroup

In addition to the base-case analysis, the company presented results from an exploratory analysis comparing vedolizumab against the use of a second TNF-α antagonist after failure or intolerance to the first (either infliximab or adalimumab used as second TNF-α antagonist). This exploratory analysis takes the form of a cost-minimisation. This was justified by the company due to limitations in the data available.

The company appears to use the economic model and assumes equal efficacy between treatments. For this analysis, the company reports that the dosing regimen and response assessment time point are in line with the licensing of the drugs.[23,28,29] The company included dose escalation for TNF-α antagonist but not vedolizumab. Drug administration costs are included for all therapies, including adalimumab. The same administration cost was assumed for vedolizumab and infliximab. The company states this is conservative.

The ERG refers the reader to Section 4.5 in the ACD response document submitted by the company to NICE.[4]

Results for vedolizumab against adalimumab and infliximab are presented in Table 17 and Table 18 respectively assuming different proportion of dose escalation for patients treated with TNF-α antagonist.

Table 17 Vedolizumab versus adalimumab with alternative assumptions regarding dose escalation of the maintenance dose of 40mg to every week (lifetime horizon) - Reproduction of Table 45 in the ACD response document submitted by the company to NICE[4]

	Vedolizumab (PAS price applied)	**Adalimumab**	**Incremental cost**
Scenario with 30% dose escalation for adalimumab (to 40mg every week)			
Biologics acquisition cost	[redacted]	£8,097	[redacted]
Biologics administration cost	£1,860	£55	£1,805
Total discounted costs*	£201,847	£199,635	£2,214
Scenario with 100% dose escalation for adalimumab (to 40mg every week)			
Biologics acquisition cost	[redacted]	£11,227	[redacted]
Biologics administration cost	£1,860	£55	£1,805
Total discounted costs*	£201,847	£202,766	-£916

NB: There is rounding of costs in the table.

*The total costs includes costs of conventional therapy, health state costs and AE costs which are (virtually) the same across the biologics in the model for the exploratory analysis. There are minor computational differences in these other costs between the biologics; hence the increment is the sum of the drug acquisition and administration increments in the rows above the total increment.

Based on a base case maximum one year duration of treatment assumed for treatment responders

Table 18 Vedolizumab versus infliximab with alternative assumptions regarding dose escalation of the maintenance dose of 5mg/kg to 10mg/kg every 8 weeks (lifetime horizon) - Reproduction of Table 46 in the ACD response document submitted by the company to NICE[4]

	Vedolizumab (PAS price applied)	Infliximab	Incremental cost
Scenario with 15% dose escalation for infliximab (to 10mg/kg)			
Biologics acquisition cost	[redacted]	£9,286	[redacted]
Biologics administration cost	£1,860	£1,697	£163
Total discounted costs*	£201,847	£202,467	-£621
Scenario with 50% dose escalation for infliximab (to 10mg/kg)			
Biologics acquisition cost	[redacted]	£10,685	[redacted]
Biologics administration cost	£1,860	£1,697.40	£163
Total discounted costs*	£201,847	£203,866	-£2,016

NB: There is rounding of costs in the table.

*The total costs includes costs of conventional therapy, health state costs and AE costs which are (virtually) the same across the biologics in the model for the exploratory analysis. There are minor computational differences in these other costs between the biologics; hence the increment is the sum of the drug acquisition and administration increments in the rows above the total increment.

Based on a base case maximum one year duration of treatment assumed for treatment responders

ERG comments:

The ERG considers this analysis to be uncertain and therefore no dept criticisms is provided. The ERG is satisfied for this analysis to be considered exploratory. However, the ERG expresses the following concerns.

The company appears to use the cost-effectiveness model setting the efficacy to be the same between all therapies (based on efficacy data for vedolizumab). It is unclear whether the original version submitted to NICE[17] or the revised economic model[5] was used to conduct this analysis. Notably, it appears that different transition probabilities are used for this analysis (see Table 41 of the ACD response document[10]) compared with the transition probabilities used in the revised model (see Table 19 of the ACD response document[10]). Given that therapies are given for one year only and the same efficacy is assumed between treatments, a simpler approach would be to estimate the one year cost associated with each therapy.

The company included dose escalation for patients on adalimumab and infliximab based on feedback from clinical experts. No dose escalation was assumed for patients treated with vedolizumab. Clarifications were requested from the company (see economic clarification response[10] question 1) on why dose escalation was not included in patients treated with vedolizumab. The company stated that *"Vedolizumab represents a biologic agent with a different mechanism of action from the TNF-α antagonists, hence it is not expected that dose escalation to every 4 weeks administration will be necessary in clinical practice when used after failure on a TNF-α antagonist, as it is the first time this type of agent will have been used. Hence, the response according to its first use will be expected to be maintained without the need for dose escalation, whereas as patients have tried and failed on a TNF-α antagonist, switching to another TNF-α antagonist typically requires dose escalation in a proportion of patients in order to maintain long term benefit (in particular remission)"*. The ERG cannot confirm whether this assumption is appropriate.

Furthermore, it is unclear how dose escalation is included; whether this is included from start of maintenance therapy which is likely to be unfavourable to adalimumab and infliximab.

Importantly, the company assumed equivalent efficacy between vedolizumab and TNF-α antagonist and stated in the ACD response document submitted by the company to NICE[4] *"For the purposes of the exploratory analyses ERG advice was followed and due to comparator data limitations comparable efficacy between the biologics was assumed"*. The ERG disagrees with this statement as there are no mention in the ERG report that similar efficacy should to be assumed between the different therapies for the induction phase for the failure subgroup. Although the ERG recognises the lack of robust data to conduct such analysis, there are no evidence to support this assumption of equal efficacy. Although the company conducted a NMA between vedolizumab and adalimumab, results are uncertain given the differences in populations. The company has access to trial data from the vedolizumab trial. Thus, the ERG believes that a more useful comparison would have been to conduct the NMA in a similar population as the one included in the adalimumab trial. Clarification was requested from the company (see clinical clarification response[10] question 12). The company responded that *"Whilst this would be useful analysis, the data was not readily available for vedolizumab from the CSRs of the GEMINI trials in order to extract evidence for efficacy outcomes in a secondary failure population (i.e. patients that lost response) that matches secondary failure patients in the adalimumab trials".* Despite limitations, the exploratory NMA conducted by the company showed no statistical difference between adalimumab and vedolizumab (although this is conducted in different population), with adalimumab having greater efficacy. Unfortunately, there are no data for infliximab in the failure subgroup. Data in the anti-TNF naïve subgroup suggest that

infliximab may have a greater efficacy compared with vedolizumab and adalimumab. It is unclear whether infliximab would have a greater, similar or lower efficacy to vedolizumab when used after adalimumab.

Compared with the original submission to NICE[1] administration costs are included for adalimumab. Clarification were requested from the company (see economic clarification response[10] question 3) which responded that *"The model applied the administration costs for the first 3 adalimumab administrations only, because we have since the original submission gathered from clinical expert's opinions that patients typically receive the first 3 administration of adalimumab in a hospital outpatient setting, as the patient needs to be trained to self-inject and needs also to be monitored initially for possible adverse reactions. In addition, according to the clinical opinion we received, some patients cannot self-inject or refuse to self-inject for the whole duration of the treatment. However, we have not included these administration costs in the model."* The ERG is satisfied with the explanation provided by the company.

Because of the limitations highlighted above and limited evidence, the ERG believes that results from this exploratory analysis need to be interpreted with caution.

4.15 Critique of the cost-effectiveness evidence

Although the ERG is satisfied with most changes made by the company, concerns expressed within the original ERG report regarding the model structure and parameterisation of the company's model remains. The health economic model submitted by the company is subject to a number of issues which limit the accuracy of the company's results. These include (a) potential omission of key aspects of the condition such as the relapsing-remitting nature of CD, (b) simplifying and debatable assumptions regarding surgery, (c) the difficultly associated with parameterising the company's chosen structure, most notably the derivation of the transition matrices, and (d) debatable assumptions such as: the end of scheduled maintenance at one year irrespective of achievement of remission; omission of discontinuation due to lack of efficacy; derivation of the efficacy whilst on placebo and the assumptions that non-responders at the induction phase on conventional non-biologic treatment remain with moderate to severe CD (and are not able to improve). The ERG notes discrepancies between the model prediction and observed data from the GEMINI II trial. Unfortunately, these issues cannot be addressed by the ERG without major restructuring of the economic model. Consequently, despite changes, the ERG believes that results from the company's model need to be interpreted with caution. The ERG is unclear whether the ICER would become more or less favourable following amendments of the identified issues. Due to these limitations, the ERG is not able to provide an estimate of the most likely ICER.

Changes made by the company in the revised economic model had the effect of reducing the company's base case deterministic (probabilistic) ICER from £98,452 (not reported) to £21,620 (£27,428) per QALY gained. It should be noted that most of the changes were attributable to amendments to the time horizon (from 10 years to a lifetime) and updating the health state costs using resource use estimated through a survey conducted amongst 8 clinical experts instead of costs from Bodger et al (2009).[25] Although the ERG believes that a lifetime horizon is probably more appropriate than a 10- year time horizon, the ERG notes that given the short duration of the clinical trials[13,14] used to inform the model (maximum 54 weeks), the extrapolation of the available data over a lifetime horizon is subject to considerable uncertainty. The ERG highlights the uncertainty in health state costs and recognises that there are limitations with either estimates from Bodger et al (2009) or costs estimated from the clinician survey conducted by the company.

5 CONCLUSION

As part of their ACD response document the company have provided further analyses of the GEMINI II and GEMINI III trials. All analyses relate to the TNF-α failure sub-population. The analyses presented for GEMINI II should be considered exploratory as the study was not designed to assess the failure subgroup. Similarly analyses should be considered exploratory for GEMINI III as the primary endpoint of that study was not achieved.

The company also submitted a revised economic model. Although the ERG is satisfied with most changes made by the company, concerns expressed within the original ERG report regarding the model structure and parameterisation of the company's model remain. The health economic model submitted by the company is subject to a number of issues which limit the accuracy of the company's results. Due to these limitations, the ERG is not able to provide an estimate of the most likely ICER.

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