National Institute for Health and Care Excellence

Multiple Technology Appraisal

Infliximab, Adalimumab and Golimumab for Treating Moderately to Severely Active Ulcerative Colitis after the Failure of Conventional Therapy

AbbVie's Response to the Appraisal Consultation Document

Executive Summary

AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD).

We are disappointed with the preliminary decision not to recommend adalimumab, infliximab or golimumab for treating moderately to severely active ulcerative colitis (UC) after the failure of conventional therapy. We are committed to working with NICE in order to address the Committee's key uncertainties as outlined in the ACD and we hope NICE can work with us to find a solution that will enable appropriate UC patients to access anti-Tumour Necrosis Factor (anti-TNF) therapy.

The negative recommendations for anti-TNF therapy are based on the ICERs not representing a cost-effective use of NHS resources. AbbVie disagrees with this conclusion and is concerned that the appraisal decision has been made without taking sufficient time to do so. We are also disappointed that the Institute has failed to take into consideration all the evidence provided by consultees in response to the Assessment Report. Consequently, the ACD lacks clarification on a number of critical issues raised in response to the Assessment Report.

We will revisit the evidence that was provided, but not considered, in **Error! Reference source not found.**. As we believe that the impact of all the evidence on the estimates of cost effectiveness was not fully explored, we will also address the relevant issues. Lastly for section 1 and in Appendix 1, we will provide additional evidence on the efficacy of adalimumab and UC-related cost applicable to the NHS.

We are also concerned that the summaries of clinical and cost-effectiveness evidence are not reasonable interpretations of some of the evidence and this will be addressed in **Error! Reference source not found.**. In this section we will also highlight our concerns relating to the presentation of the ICERs in the ACD and the definitions of health states in the Assessment Group model. As an Appendix to this document, we have highlighted factual inaccuracies identified in the ACD.

Therefore, we do not believe that the provisional recommendations are sound or a suitable base for guidance to the NHS. Anti-TNF therapy is a step change therapy for people who have failed conventional therapy and are left with no treatment options other than surgery. We consider it is important for patients to have the opportunity to receive anti-TNF therapy particularly as those who subsequently fail anti-TNF therapy will still be left with surgery as a last resort. In contrast, surgery is irreversible and patients consistently show a strong preference for exhausting all medical options first.

Anti-TNF therapies such as adalimumab are considered as effective treatment options for people with moderate to severe UC who have failed conventional therapy and used in these patients as standard of care across Europe. Anti-TNFs are also widely reimbursed in major European countries. AbbVie believes that patients in the UK should have the opportunity to receive the same standard of care as in the rest of Europe.

Section 1. Has all of the relevant evidence been taken into account?

1.1 All the evidence presented has not been considered

1.1.1 No consideration was given to the updated model submitted by AbbVie in response to the Assessment Report critique

AbbVie notes that the Committee considered the most likely ICER for adalimumab compared with conventional therapy (£34,400 in the AbbVie model and £50,600 in the Assessment Group model) to be in excess of the NICE thresholds for cost-effectiveness.

However, there appears to have been no consideration of the results from the updated AbbVie model that was developed in response to the Assessment Group's critique and submitted on the 5th of August. AbbVie is therefore concerned that the ACD recommendations have been developed without assessing the updated AbbVie model and the most likely ICER from the updated AbbVie's model for adalimumab vs. conventional care was not referred to in the ACD.

We therefore again present a short discussion of the updated model and the results.

The updated AbbVie model incorporates changes in response to the critique from the Assessment Group regarding the NICE Reference Case and final NICE scope by extending the time horizon to lifetime.

The critique that AbbVie used a questionable source of surgery rate is also addressed in the updated model. This has been achieved by using a surgery rate that was amended to reflect a sample-weighted average of the surgery rates in Actis et al. (2007), Molnar et al. (2011), Mocciaro et al. (2012), and Gustavsson et al. (2007) - publications from the list of literature summarized in Table 67 of the Assessment Report. The Gower-Rousseau et al. publication was excluded because it focused on paediatric UC patients rather than adult UC patients. Solberg was excluded as AbbVie maintains that the study underestimates the rate of surgery in the evaluation population: Solberg et al. focuses on newly diagnosed UC patients, it includes patients of all severity levels, the majority of patients appeared to have mild UC and surgery rates were not reported by disease severity. AbbVie did however include Solberg in the sample-weighted average in a sensitivity analysis. We believe, in light of the uncertainty around the true surgery rates in this population, that the sample-weighted average is the most appropriate approach.

The discontinuation rate for adalimumab after year 2 has also been modified in the updated AbbVie model in order to align this with the Assessment Group model. In the original submission model, the discontinuation rate from the ULTRA3 trial was used; in the updated submission model, adalimumab-treated patients who relapse to a moderate-to-severe UC disease state after year 2 will discontinue adalimumab - the same rule for discontinuation that was utilised in the Assessment group model.

We report the results from this model again and request due consideration is given to the revised AbbVie model results in the Institute's deliberations.

Table 1 on the next page reports the base case ICER for the anti-TNF naïve population in the updated AbbVie model. It shows that adalimumab adds 2.71 quality adjusted life years (QALYs) at an additional cost of £62,409, resulting in an ICER of £23,027/QALY when comparing adalimumab with conventional therapy at lifetime

Table 1. Cost-effectiveness output from updated AbbVie model comparing adalimumab with conventional therapy

	Adalimumab + Conventional therapy	**Conventional therapy**	**Adalimumab + Conventional therapy vs. Conventional therapy**
Costs			
Pre-surgery costs	£134,816	£53,364	£81,452
Adalimumab costs	£90,349	£0	£90,349
Standard of care costs	£6,826	£4,823	£2,003
Pre-surgery medical costs	£37,641	£48,541	-£10,900
Surgery and post-surgery costs	£34,021	£52,961	-£18,941
Terminal care costs	£1,099	£1,201	-£103
Total costs	£169,935	£107,527	**£62,409**
Effectiveness			
Life years (LYs)	20.00	19.16	0.84
QALYs	14.25	11.54	**2.71**
Incremental Cost-Effectiveness Ratio			
Incremental cost per QALY gained			**£23,027**

Several deterministic sensitivity analyses have been added to the updated AbbVie model in response to other points of criticism in the Assessment Report. A complete description was provided in the AbbVie response to the Assessment Report and is summarised briefly below Table 2.

These sensitivity analyses showed that the ICER was robust, ranging from £18,218 to £25,594 per QALY gained. The probability that adalimumab is cost-effective at the willingness to pay threshold of £30,000 per QALY gained was 73% compared with conventional therapy (Figure 1).

Table 2. Deterministic sensitivity analyses comparing adalimumab with conventional therapy

Parameter	**ICER**	
	Using the lower input value	**Using the higher input value**
Treatment regimen		
Dose escalation for ADA (±5% points)	£21,627	£24,426
Medical costs and resource utilisation		
Disease state costs (±25%)[i]	£25,594	£20,459
Hospitalisation costs (±25%)	£23,212	£22,841
Hospitalisation rate (As reported by Tsai et al. 2008)	£24,301	

Utilities		
Pre-surgery disease states and surgery state use values reported by Tsai et al. 2008	£22,113	
All disease states use values reported by Tsai et al. 2008	£24,378	
All disease states as per Assessment group model	£25,470	
Chronic complication utility as per Assessment Group model	£23,652	
Transition probabilities		
Rate of surgery (combined base case and Solberg et al. 2009)[ii]	£25,030	
Moderate-to-severe patients switch directly to surgery after induction[iii]	£18,218	
Induction period transition probabilities based on trial data only[iv]	£23,115	
Model population		
All patients (anti-TNF naïve and experienced)[v]	£22,809	
Annual discount rate (1.5%, 6%)	£21,542	£25,001

i. Costs for all disease states (pre-surgery, surgery and post-surgery disease states) were varied here.
ii. The 2-week transition probability from moderate-to-severe UC patients on both the adalimumab arm and conventional therapy arm to surgery was varied here. Briefly, in this sensitivity analysis, the surgery rate was calculated based on the rates reported in Actis et al. 2007, Gustavsson et al 2007, Molnar et al. 2011, Mocciaro et al. 2012, and Solberg et al. 2009, weighted by the sample size in each study.
iii. All patients who relapse to moderate-to-severe disease state in both arms switch directly to surgery after the induction period of 8 weeks. This is in contrast to the assessment group model assumption that anti-TNF patients switch to surgery ONLY after failing anti-TNFs AND failing conventional treatment, and then only 1% per year of those that have failed conventional treatment, proceed to surgery.
iv. During the induction period of 8 weeks, patients only transition at the end of the induction period (i.e. at week 8). Using this assumption, all transition probabilities during the induction period are based on the ULTRA2 trial data, and there is no use of external data. This is comparable to using an 8-week cycle for the induction period as was done in the Assessment model.
v. Transition probabilities and dose intensities were estimated based on the entire trial population consisting of both anti-TNF-α naïve and experienced patients. The dose escalation rates for adalimumab were estimated based on the observed dose escalation in ULTRA 2 (year 1) and ULTRA 1/2 extension (year 2 and onward) trials.

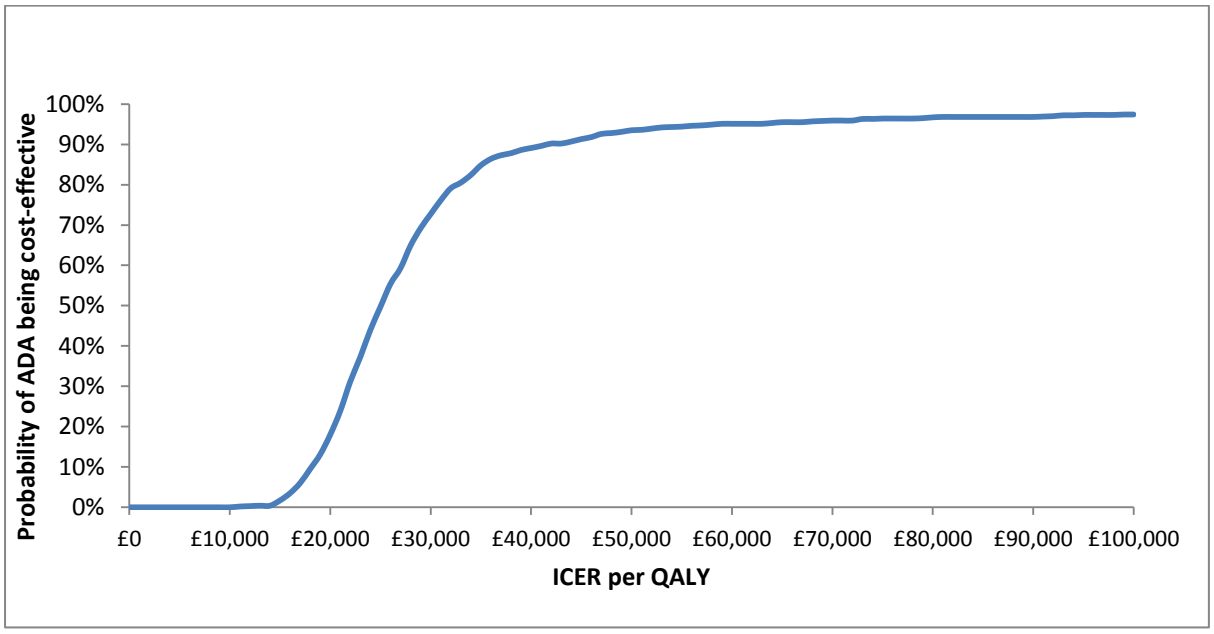

Figure 1. Cost-effectiveness curve for adalimumab compared with conventional therapy

AbbVie believes that the revised model represents the most likely ICER for adalimumab vs. conventional therapy, based on the following:

- The model reflects the patient treatment pathway whereby some patients who fail on adalimumab, proceed directly to surgery whilst the remainder proceed to conventional therapy
    - The clinical experts AbbVie have consulted, the British Society of Gastroenterology (BSG) and the clinical expert at the Appraisal committee meeting have stated that patients who fail anti-TNFs will go on to receive alternative treatments immediately thereafter, including surgery.
    - Results from small observational studies further support this view. In an observational study with 88 patients treated with adalimumab Armuzzi et al.[1] found that surgery was performed after a median of 5.5 months in 22 patients who required colectomy after treatment failure. Garcia-Bosch et al.[2] reports in their study on 48 patients treated with adalimumab that colectomy was required in 11 patients, with a significantly reduced time free of colectomy in week 12 non-responders (148 days) compared to responders (226 days). Similarly, in a study with 30 patients the median time to colectomy was 16 weeks in six patients who failed to respond to adalimumab after 12 weeks of therapy[3]. In their study with 23 patients, McDermott et al.[4] report that 9 out of 15 patients who failed treatment with adalimumab required a colectomy, with a median time to colectomy of 5 months from commencing adalimumab. Another small observational study[5] with 13 patients on adalimumab found that the probability of undergoing colectomy after treatment failure was 7.7%, 15.4% and 30.8% at 1, 3 and 6 months, respectively. Lastly, Gies et al.[6] state in their prospective study that 3 out of 10 patients choose to undergo surgery as therapy after loss of response to either adalimumab or infliximab.
    - Clinical opinion, strongly supported by observational studies, therefore highlight that patients who do not respond to anti-TNFs or loose response later on, proceed to surgery relatively shortly thereafter. They do not necessary receive conventional therapy after treatment failure nor do they remain on conventional therapy for lengthy periods before receiving a colectomy. A treatment pathway whereby some patients who failed anti-TNF therapy proceed to surgery and others to conventional therapy is therefore the most appropriate representation of clinical practice.
- The model uses health states that corresponds to clinically meaningful disease states
    - The health states in the model used the absolute Mayo scores the patient presented with at the time of evaluation, to classify the patient's pre-surgery health state as "In remission", "Mild" or "Moderate to severe". Not only does this provide a clinically meaningful indication of the symptoms and the severity thereof, it also allows the health states to be linked to utility scores for remission, mild, moderate and severe UC reported in the literature.
- The model allows for the effect of dose escalation for adalimumab to be incorporated should a patient who initially responded, lose response after week 8
    - The Summary of Product Characteristics for adalimumab states that some patients who experience a decrease in their response may benefit from an increase in dosing frequency to 40mg every other week. Using the data from the ULTRA2 study, the AbbVie model incorporates this recommendation.
- The model incorporates chronic complications of surgery such as infertility, sexual dysfunction and chronic pouchitis that have a significant effect on patients' quality of life and on health care costs.
- The model uses observed UC-related hospitalisation rates from the pooled data of ULTRA1 and ULTRA2 trials
    - Mixed effects regression models were used to estimate the frequency of hospitalisations among UC patients, given a patient's treatment arm (adalimumab or placebo) and disease severity (remission/mild, moderate, or severe) at the beginning of each cycle. Additionally, because UC severity was evaluated at varying intervals throughout the trials, the model controlled for the length of each time interval (i.e., the

number of weeks from a particular evaluation until the next evaluation or end of the follow-up period).

- The model uses a surgery rate that correspond to colectomy outcomes observed in the ULTRA2 study
    - In the model the predicted percentage of patients who underwent surgery (using the sample weighted average method previously explained), at one year was 4% in the adalimumab cohort and 5% in the conventional therapy cohort. This corresponds with the results reported by Feagan[7] from ULTRA2 at week 52 for the adalimumab and conventional therapy arm: 4% and 5%, respectively. Both the predicted and observed surgery rates quoted above are lower than the observed rate in the ACT1 and 2 studies (10% vs. 17% for infliximab and conventional therapy, respectively). However, in the ULTRA studies patients were allowed to cross over to adalimumab from the placebo arm, thus the rates may appear artificially low compared to ACT 1 and 2, where patients could not cross over to infliximab. Nonetheless, the surgery rates in the ACT and ULTRA studies illustrates that the rate of surgery in one year is higher than the 1% observed by Solberg et al.
- The colectomy rate over the life time horizon corresponds with trends seen in clinical practice.
    - Predicted results in the model showed that fewer patients will undergo surgery in the adalimumab arm (61.1%) compared with the conventional therapy arm (89.6%) over the life time horizon. This is similar to the trend reported in a recent publication which found that since the introduction of anti-TNF therapy, the rate of total colectomy decreased for medically refractory UC as the use of anti-TNF therapies increased[8]. This high rate of surgery in patients who failed anti-TNFs and conventional therapy is also reflective of comments made by the BSG in response to the Assessment Report that the majority of patients who fail treatment will eventually undergo surgery. Data from the Stockholm County Council[9] from 2012 also demonstrated 76% of patients who received colectomy had never received a TNF whereas 24% had received anti-TNF. Therefore, also suggesting the use of anti-TNF may have an impact on surgery rates for patients with UC.
- The cost of surgery in the model reflects clinical practice whereby some patients undergo more than one surgical procedure.

We also note that the updated AbbVie model is similar to the Assessment Group model in the following aspects:

- Both models use a life time horizon
- Both models include natural mortality and mortality due to surgery
- Both models consist of an induction and maintenance phase
- Both models have an on-treatment phase with biological and conventional therapy and a surgical / post-surgical phase incorporating complications
- In both model patients who do not respond at 8 weeks discontinue treatment as per the adalimumab SPC
- In both models adalimumab-treated patients who relapse to a moderate-to-severe UC disease state after year 2 will discontinue adalimumab
- Both models estimate service usage such as consultant visits, blood tests, elective and emergent endoscopy based on the publication by Tsai et al.

To conclude, the Institute should reconsider the conclusion that the results from the AbbVie model is in excess of the NICE cost-effectiveness threshold based on the updated model and the results presented above.

1.1.2 The correct assumption for adalimumab dose escalation in the Assessment Group model was not considered

We agree with the Assessment Group that it is reasonable that the rate of dose escalation in the Assessment Group model should be based on the ULTRA2 study, given that all efficacy figures in the model were also derived from the ULTRA studies.

However, it appears to AbbVie that the Assessment Group misunderstood our comment that the modelled assumption relating to dose escalation in the Assessment Group model (27%) does not employ an escalation rate that is reflective of the population under evaluation.

AbbVie therefore wishes to re-emphasize and clarify this point. The 27.4% dose escalation rate used in the Assessment Group model is derived from both week 8 responders and non-responders in the ULTRA2 trial, for ant-TNF naïve and experienced patients. As non-responding patients in the Assessment Group model discontinue adalimumab therapy at week 8 in line with the licence, the dose escalation rate for only the week 8 responders should be used. And as the base case ICER is for the treatment naïve population, only the dose escalation rate in the anti-TNF naïve population should be used. The dose escalation rate in this population was 14/88 (15.9%) as shown in Table 3.

Table 3. Adalimumab subjects who dose escalated to every week administration

	Anti-TNF naïve*	**Anti-TNF experienced***	**Subtotal****
Week 8 responders	14/88 (15.9%)	6/35 (17.1%)	20/123 (16.3%)
Week 8 non-responders	22/62 (35.5%)	26/63 (41.3%)	48/125 (38.4%)
Subtotal	36/150 (24.0%)	32/98 (32.7%)	68/248 (27.4%)

*Additional analyses on patient level data conducted by AbbVie.
**Published by Wolf et al.[10]

As a result of the Assessment Group model applying the higher dose escalation rate (27.4%), the cost of adalimumab in the model has been overestimated and the ICER is higher than it should be.

AbbVie requests that the dose escalation rate in the Assessment Group model be corrected to 15.9% to reflect the clinical trial evidence and dosage and administration guidance.

1.1.3 It has not been taken into account that the most appropriate hospitalisation rate for adalimumab was not used in the Assessment Group model

AbbVie is disappointed that the Assessment Group model used a hospitalisation rate that is not reflective of the most appropriate evidence. Whilst we note in their response that the Assessment Group used the results reported in the MSD submission, they also stated that *"Arguably the Feagan reference should be used however this was not included in the NMA* [network meta-analysis] *by MSD."* And although the response states that *"If the relative risk is assumed to be 50% this has a negligible impact upon the model results.",* this effect on the model has not been quantified nor does it appear that was it discussed at the Appraisal Meeting.

AbbVie wants to reiterate that it is not appropriate to use the hospitalisation rate from the MSD NMA for adalimumab. We request that the relative risk from the Feagan publication[7] be used in the model as this is the most relevant and appropriate hospitalisation data for adalimumab compared with conventional therapy.

1.1.4 The assumptions on types of surgical complications and complication rates employed in the Assessment Group model were not considered

AbbVie notes that several comments on the types and rates of post-surgical complications were sent by consultees in response to the Assessment Report. We understand that the Assessment Group did not undertake a systematic review of studies reporting post-surgical complications and they have acknowledged awareness of further studies on complication rates. However, it does not appear that a clinical viewpoint had been sought before or during the Appraisal Meeting regarding surgical complications. It would appear necessary to gain a greater understanding on the complication types, which complications have the biggest impact on patients' quality of life or most costly to the NHS should be gained. Nor does it appear that any sensitivity analyses have been conducted to explore the impact of incorporating the most relevant complications and the rates thereof.

AbbVie therefore suggests that consideration should be given to using more appropriate sources for post-surgical complications and that clinical input be sought on this point. The ICER should then be updated to incorporate all relevant chronic complications, including the cost of treating these additional complications. Consideration of chronic complication risk such as infertility, pouch failure, increased faecal frequency, faecal incontinence and chronic pouchitis appears to be critical in patient's preference for medical therapy versus surgery and the wish to delay or avoid this surgery if possible.

1.1.5 The impact of the cost of death due to surgery was not considered

AbbVie notes the Assessment Group's opinion that the cost of death is not routinely incorporated into cost-effectiveness analyses, but disagrees with this viewpoint.

It would be reasonable to assume that some deaths in UC patients occur in hospital and as such, would incur costs to the NHS. This assumption is supported by results from the 2014 IBD audit[11] which showed that of those who were admitted to hospital and subsequently died, the median length of stay was 26 days. Similar data is not available for those patients who underwent surgery and subsequently died, but it could reasonably be assumed that there is a cost associated with terminal care due to surgery related death in addition to the cost of the surgical procedure. Not incorporating a cost of death due to surgery underestimates the true costs of the treatment options.

It does not appear that this point was discussed during the Appraisal Meeting and AbbVie suggests that consideration should be given to incorporating this cost to the ICER.

1.2 The impact on the estimates of cost effectiveness using all the evidence was not fully considered

1.2.1 The Assessment Group model does not take into account feedback from consultees that when patients on anti-TNF therapy relapse, they could receive alternative therapies other than conventional therapy.

AbbVie understands that the treatment pathway in the Assessment Group model is an assumption. However, AbbVie also notes that the ACD provides information on the patient pathway based on clinical expert input on clinical practice at the Appraisal Meeting (relevant text underline):

"4.53. The Committee discussed with the clinical expert the treatment pathway for moderately to severely active ulcerative colitis. It heard that in UK clinical practice, standard practice for patients with moderately to severely active ulcerative colitis (but not acute disease) would be to start on conventional therapy. This may include corticosteroids and/or 5-aminosalicylates (for example, mesalazine), with the possibility of then adding on azathioprine. The clinical expert indicated that approximately 8 to10% of patients cannot tolerate azathioprine. At this point in the pathway, treatment becomes individualised and may include long-term corticosteroids or ciclosporin. Alternatively, a patient with ulcerative proctitis (where the inflammation is limited to the rectum) may use topical enemas. The Committee understood that if response to conventional therapy was inadequate, patients may have TNF-alpha-inhibitor treatment. <u>After subsequent relapses, patients could have an alternative TNF-alpha inhibitor, conventional therapy or colectomy."</u>

The ACD corroborates feedback that AbbVie received from clinical experts that patients who failed conventional treatment then subsequently failed anti-TNFs could proceed directly to surgery. The current patient pathway in the Assessment Group model moves <u>all</u> anti-TNF failures to conventional therapy. AbbVie wants to reiterate that in a population who has already failed or are intolerant to conventional therapy it seems counterintuitive to require that <u>all</u> patients who failed anti-TNFs return to a failed treatment or one they are intolerant to. Therefore, in line with clinical expert comments, it

would be appropriate that other treatment options, such as surgery directly after anti-TNF failure, should be considered in the Assessment Group model.

Data from patients who had failed adalimumab and went on to colectomy during ULTRA 1&2, demonstrated the duration of time from last dose of adalimumab to colectomy ranged from 5-41days. During this time, the most frequently prescribed therapy was corticosteroids, with a duration ranging from 2-19 days. This theme has also been reinforced by clinical expert comments. Therefore it seems appropriate that other treatment options, such as surgery, directly after anti-TNF failure, should be considered in the Assessment Group model. It should be borne in mind that the population under evaluation in this appraisal have failed all other treatment and should they also fail anti-TNFs, they are more likely to proceed directly to surgery as conventional therapy has not previously worked
As noted in point 1.1.1 of this document, evidence from the literature also supports surgery as a treatment option shortly after anti-TNF failure. Armuzzi et al. found that over a five year period, surgery was performed after a median of 5.5 months in 22 out 88 patients who required colectomy following adalimumab treatment failure, a similar rate to the study by McDermott et al. which report a median time to colectomy of 5 months from commencing adalimumab in 9 out of 15 patients who failed treatment over the two year follow up period. Taxonera, in a study with 30 patients and a median of 48 weeks' follow up, found that the median time to colectomy was 16 weeks in six patients who failed to respond to adalimumab. Another small observational study with 13 patients on adalimumab found that 6 out of 13 patients underwent colectomy during the 100 week study period, with the probability of undergoing colectomy being 7.7%, 15.4% and 30.8% at 1, 3 and 6 months, respectively. Lastly, Gies et al.[12] state that in their prospective study, 3 out of 10 patients choose to undergo surgery as therapy after loss of response to either adalimumab or infliximab.

AbbVie is therefore concerned that the Institute has not taken into account that the Assessment group model does not reflect the patient treatment pathways and as such, reached a conclusion on the cost effectiveness of anti-TNF therapy that does not reflect all the evidence.

AbbVie requests that the treatment pathway in the Assessment Group model be amended to reflect the comments received on this matter.

1.2.2 The ACD acknowledges that certain input parameters in the model may be different than those which the Assessment Group modelled, but the effect of these on the ICER were only considered in isolation

AbbVie notes the conclusion in the ACD that the actual surgery rate and cost of conventional therapies may be higher than that used in the Assessment Group model, but we are unable to determine the impact on the ICER as it does not appear that the Assessment Group reported the resulting ICER.

Additionally, after receiving feedback that the cost of surgery was underestimated and that the cost of caring for stoma and maintaining the ileostomy was not included in the Assessment Group model, the ACD concluded that the cost of surgery was not a key driver in the cost-effectiveness model.

Whilst AbbVie agrees that in isolation these parameters may not have a substantial effect on the cost-effectiveness of anti-TNFs, we believe that the impact of varying a number of these parameters combined in scenario analyses should be explored. This will provide an ICER that reflects the most relevant evidence.

1.2.3 An ICER from a model which has a number of programming errors was evaluated in the appraisal

AbbVie notes that MSD has identified a number of small errors with calculations within the Assessment Group model. The Assessment Group agrees that there were minor programming errors; however, based on the version of the model AbbVie received, these errors have not been corrected. To our knowledge based on our attendance at the open session of the Appraisal Meeting, this has not been discussed.

AbbVie therefore believes that ICERs were provided based on a model with minor programming errors and requests that these be corrected so that the revised estimates can be used in the Institute's decision.

1.3 AbbVie has obtained additional evidence on cost and efficacy for adalimumab

1.3.1 The Assessment Group requested amended data from AbbVie where dose-escalators are categorised based on their Mayo scores

As noted in the AbbVie response to the Assessment Report, the definition of treatment efficacy of adalimumab in the ULTRA1 and 2 studies were based on non-responder imputation (NRI). NRI categorises all patients who dose-escalate on adalimumab as non-responders irrespective of Mayo scores. In the Assessment Group model patient data based on NRI results was used. As highlighted by AbbVie, the cost of dose escalation was captured but not the effect of improved efficacy in those that dose escalated. AbbVie suggested that the appropriate approach would be not to incorporate the cost of dose escalation, or that the model incorporates the additional benefit that dose escalation with adalimumab offers.

The Assessment Group has indicated that they understood the difficulties the NRI dataset poses in determining the efficacy of adalimumab. In order to model the outcome of dose escalation on response rates, the Assessment Group has requested that AbbVie provide the dataset where patients who have dose escalated, are categorised based on their Mayo scores.

AbbVie therefore provides additional data using dose escalators' Mayo scores for week 8 to 52, for the ITT population (anti-TNF treatment naïve and experienced patients) and the anti-TNF treatment naïve subgroup. We are still looking into obtaining the breakdown of the data according to week 8-32 and weeks 32-52 for both populations.

The data provided illustrate the difference between using the NRI approach and the approach whereby dose-escalators' Mayo scores are used (i.e. when they are not classed as non-responders). Table 4, for example, show that there was a decrease from the NRI patient numbers for those who were considered non-responders at week 52 when dose escalators were classified according to their Mayo score (107 decreased to 98, 51 decreased to 42, 15 decreased to 14). As expected, the same number or more patients were classed as achieving remission or response when dose escalators' Mayo scores were used.

Table 4. ULTRA 2 trial (week 8 to 52 weeks) - Anti-TNF treatment naïve and experienced patients

	Adalimumab (160mg/80mg/40mg)	
	NRI analysis – dose escalators counted as non-responders	**Additional analysis – Dose escalators' Mayo score are used**
Number of patients who had neither response nor remission at 8 weeks who had not responded at 52 weeks	107	98
Number of patients who had neither response nor remission at 8 weeks who achieved response (without remission) at 52 weeks	9	17
Number of patients who had neither response nor remission at 8 weeks who achieved remission at 52 weeks	7	8
Number of patients who had response (without remission) at 8 weeks who lost response at 52 weeks	51	42
Number of patients who had response (without remission) at 8 weeks who maintained response	18	24

(without remission) at 52 weeks		
Number of patients who had response (without remission) at 8 weeks who achieved remission at 52 weeks	15	18
Number of patients who had remission at 8 weeks who lost response at 52 weeks	15	14
Number of patients who had remission at 8 weeks who maintained response (without remission) at 52 weeks	5	5
Number of patients who had remission at 8 weeks who achieved remission at 52 weeks	21	22

The same pattern was observed in the subgroup of patients who were anti-TNF naïve (Table 5): Fewer patients were considered non-responders by week 52 and the same or a higher number of patients achieved remission or response.

Table 5. ULTRA 2 (week 8 to 52 weeks) – Subgroup of patients who were anti-TNF naïve

	Adalimumab (160mg/80mg/40mg)	
	NRI analysis – dose escalators counted as non-responders	**Additional analysis – dose escalators' Mayo score are used**
Number of patients who had neither response nor remission at 8 weeks who had not responded at 52 weeks	50	45
Number of patients who had neither response nor remission at 8 weeks who achieved response (without remission) at 52 weeks	6	10
Number of patients who had neither response nor remission at 8 weeks who achieved remission at 52 weeks	5	6
Number of patients who had response (without remission) at 8 weeks who lost response at 52 weeks	32	26
Number of patients who had response (without remission) at 8 weeks who maintained response (without remission) at 52 weeks	13	16
Number of patients who had response (without remission) at 8 weeks who achieved remission at 52 weeks	12	15
Number of patients who had remission at 8 weeks who lost response at 52 weeks	13	12
Number of patients who had remission at 8 weeks who maintained response (without remission) at 52 weeks	3	3
Number of patients who had remission at 8 weeks who achieved remission at 52 weeks	16	17

1.3.2 Results from an interim analysis of INSPIRADA have been presented by AbbVie to provide further information on real world evidence on efficacy, quality of life and resource use in UK patients who received adalimumab

INSPIRADA (M13-045) (NCT01550965) is an open-label multicentre observational study to evaluate the impact of adalimumab on quality of life, health care utilisation and costs of UC subjects in the usual clinical practice setting[13]. Although it is estimated to complete 2015, AbbVie has conducted an interim analysis on available data for UK patients in order to inform areas of uncertainty within the Assessment Group model.

Patients eligible for the study were those with moderate to severe disease activity as per physician's global assessment (PGA) and an Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score of ≤ 45, aged 18-75 years with a confirmed diagnosis of UC greater than 90 days prior to baseline and who have failed conventional treatment. Patients with a history of surgery for UC or planned bowel surgery were excluded, as were those who have previously received treatment with adalimumab. Patients were also excluded if they have previously used any other anti-TNF within 56 days of baseline or who have used anti-TNFs and have not clinically responded at any time unless they experienced a treatment limiting reaction. Subjects who have received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days of Week 0 were also excluded. The complete inclusion and exclusion criteria are included in presented in Table 7, Appendix 1.

The primary outcome measures were change in the SIBDQ at Week 26 from baseline and change in costs of UC-related medical care excluding adalimumab costs[13]. The SIBDQ is the shortened form of the Inflammatory Bowel Disease Questionnaire (IBDQ) and provides a gauge of the subjective health status of quality of life in patients with inflammatory bowel disease (IBD). It measures the impact of IBD on social and emotional domains as well as physical symptoms using 10 questions from the IBDQ, which explain 90% of the variance in the IBDQ of UC patients. The total score ranges from 10 (worst health) to 70 (best health). The SIBDQ can be administered and scored quickly and easily and therefore is of potential value to the physician in the clinical setting.[14]

Secondary outcome measures related to change in UC and non-UC related resource use prior to and after the start of adalimumab and change in disease measures, quality of life and work productivity from the start of adalimumab therapy.

Baseline and demographic results are reported in Table 8, Appendix 1. It shows that the mean age for patients in the study was 38.5 years, with a mean disease duration of 7.7 years. The majority (78.8%) of the patients were considered to have moderate disease, with the remainder (21.3%) having severe disease. About half of the patients had extensive UC and the quality of life was reported to be low as demonstrated by a mean SIBDQ of 29. Almost all the patients took concomitant conventional therapy at baseline with about two thirds of patients being on corticosteroids and more than half of the patients receiving thiopurines. Nineteen (23.8%) patients had previous exposure to an anti-TNF.

Results for the SIBDQ primary endpoint show that use of adalimumab was associated with a statistically significant improvement at week 26 from baseline: 18.36 (95% CI: 14.89-21.84; p<0.001). Adalimumab use six months after start of treatment was also associated with a statistically significant reduction in UC-related cost compared with the six months prior to the start of treatment: -£1,296 (95% CI: -£1,729 to -£863; p<0.001). Statistically significant improvements in SIBDQ, Simple Clinical Colitis Activity Index (SCCAI)[i], EQ5D-5L and PGA[ii] were seen as early as week 2 and these statistically significant improvements were maintained at week 26. At Week 26, 55.0% of patients were in SCCAI remission (defined as a SCCAI ≤ 2). Lastly, using the SCCAI and PGA as measures of response, 62 of 80 (77.5%) and 54 of 80 (67.5%) participants were considered responders at week 8 and 26, respectively.

Full results are reported in Appendix 1.

In conclusion, the INSPIRADA study provides data from a more real-world experience of adalimumab in patients with UC in the UK, complimenting data from the ULTRA studies. Adalimumab led to

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[i] The SCCAI (0-19) is based on five clinical criteria: bowel frequency at day (0-3 points), , bowel frequency at night (0-2 points), blood in stool (0-3 points), urgency of defecation (0-3 points), general well-being (0-4 points) and extra-colonic features (1 per manifestation). (Walmsley RS et al. A simple clinical colitis activity index. Gut. 1998;43:29–32; D'Haens et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132(2):763-86.)

[ii] The PGA considers subject reported information such as number of stools, rectal bleeding, abdominal discomfort and functional assessment during the previous day prior to the visit, and other observations such as physical findings, and the subject's performance status at the time of the visit. The score indicates: 0= Normal, 1= Mild disease, 2= Moderate disease, 3 = Severe disease

significant reduction in UC-related costs and clinically meaningful improvements in quality of life as well as disease activity measures.

2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

2.1 The ACD does do not reasonably interpret some elements of clinical and cost-effectiveness associated with adalimumab

2.1.1 Misunderstanding of how the Mayo scores were used in the anti-TNF clinical trials

It appears, in the way the ACD is written, that there is a misunderstanding about the difference between the Mayo scoring methods used across the adalimumab, infliximab, and golimumab trials.

Section 4.4 in the ACD states *"To assess clinical response or remission, all trials except the study by Probert et al. used the Mayo score, which the Assessment Group considered to be applied consistently in the individual trials".*

As per our response to the Assessment Report, AbbVie maintains that the differences in Mayo scoring methods across the adalimumab, infliximab, and golimumab trials can cause the efficacy for adalimumab to be underestimated relative to the other anti-TNFs and placebo. This point was not addressed by the Assessment Group or discussed during the Appraisal Meeting but we consider this merits detailed analysis when comparative effectiveness across trials is being assessed.

2.1.2 Misinterpretation of surgery rates modelled by AbbVie

AbbVie would like to clarify a statement from the Assessment Report, which may influence the current and future interpretation of the AbbVie model results.

Please refer to the underlined text from Section 4.34 below:

"In addition, it stated that the company used a shorter cycle length than the time point for assessing induction in ULTRA2 (6 weeks); did not transform the data collected in ULTRA2 using SF-36 to SF-6D utility values; assumed that surgery improves the utility score by only 0.06 compared with active disease; and inaccurately modelled the rate at which patients had surgery."

AbbVie did not inaccurately model the surgery rates. "Inaccurately modelled" implies that the modelling method used was wrong, incorrect or imprecise but it should be noted that the Assessment Report questioned the study used by AbbVie in the AbbVie model. Subsequently it was acknowledged by the Assessment Group in their response to comments that the surgery rate is very uncertain. This uncertainty was also acknowledged in Section 4.70.

AbbVie wishes the Institute to understand that AbbVie considers the statement in Section 4.34 of the ACD to be misleading and requests that our comments on this matter be borne in mind when considering the results from the AbbVie models.

2.2 Presentation of the ICERs in the ACD

AbbVie is concerned about the presentation of the results from the pairwise analyses comparing adalimumab, golimumab, and infliximab head-to-head with conventional therapy using direct evidence from the respective randomised controlled trials.

The ACD states that the ICER vs. conventional therapy in the head to head trials was £70,075, £90,720 and £96,682 for adalimumab, golimumab and infliximab, respectively. This appears to be the results from the deterministic ICER, whereas other ICERs presented in the ACD were probabilistic.

We have noted that for the base case ICER for adalimumab, there is a large and unexplained difference between the deterministic ICER (£68,890/QALY) and probabilistic ICER (£50,624/QALY)

vs. conventional therapy. We are concerned that there appears to have been no consideration of the differences between the probabilistic and deterministic ICERs from the Assessment Group model and that the deterministic ICERs are cited interchangeably with the probabilistic estimates. As such AbbVie is unable to understand which ICERs are being considered by the Institute as the best estimates of the cost effectiveness of adalimumab vs. conventional therapy.

AbbVie does not believe that presenting the probabilistic ICER for the base case analysis and then presenting the deterministic ICER for this sensitivity analysis allows a reasonable interpretation of the cost-effectiveness evidence. AbbVie therefore requests that the probabilistic ICER results are consistently calculated for each sensitivity analyses and presented as such so that the cost-effectiveness results can be clarified.

2.3 The health states used in the Assessment Group model may not be reflective of the disease impact on quality of life and therefore may not offer a reasonable interpretation of the clinical effectiveness of the treatments under evaluation

In the Assessment Group model, health states are defined as remission, response, and non-response based on relative improvement from baseline Mayo score. AbbVie believes this is problematic as it may not offer a reasonable interpretation of the clinical effectiveness of the treatments under evaluation.

To illustrate the limitation of this approach, an example using two hypothetical UC patients, A and B are provided in the table below.

Table 6. Illustrative example of the limitations of the approach taken to defining health states in the Assessment Group model

Patient	Baseline Mayo Score	1 year and onward Mayo Score	Δ	Assessment Group model states: Remission, Response, Non-responder*	Utility**	AbbVie model states: Remission, mild, moderate-severe***	Utility**
A	8	5	3	Responder	0.76	Mild	0.76
B	7	5	2	Non-responder	0.41	Mild	0.76

* Based on decrease from baseline Mayo i.e. Δ in this example
** Based on the abstract by Woehl, used in the Assessment Group model
*** Based on absolute Mayo score at the time of measurement i.e. 1 year and onward Mayo score

In this example, both patients A and B have a Mayo score of 5 points at the end of 1 year and for all the remaining time in the model as long as they continue on treatment, i.e. before switching to surgery or death. In the Assessment Group model patient A had a baseline score of 8 and is classified as a responder at the end of year 1 and for all the remaining time on treatment and patient B has a baseline Mayo score of 7 and is classified as a non-responder at the end of year 1 and for all the remaining time on treatment. Using this approach, patient B will have a worse quality of life score at the end of year 1 than patient A (0.41 vs. 0.76), even though they both have the same disease severity (Mayo score 5)

In contrast, the AbbVie model uses absolute Mayo scores to define health states, and both patients will be classified as being in the mild disease state in the model based on their Mayo scores of 5. This, in our view, is a more reasonable assumption.

It should also be noted that the Woehl utility is estimated based on remission, mild and moderate-to-severe disease states and not based on remission, response and non-response states.

AbbVie understands that a similar approach to the one used in the Assessment Group model in this appraisal was considered problematic by the Assessment Group in the Crohn's Disease appraisal of infliximab and adalimumab. In the Crohn's appraisal responders were defined as patients whose Crohn's Disease Activity Index (CDAI) improved by a pre-specified amount following administration of

anti-TNF, based on clinical trial results. This approach was found to be problematic because it says nothing about the relative improvement in health in an individual for any given reduction in CDAI score. Defining responders using a pre-specified improvement in disease score also does not differentiate between patients for whom treatment controls the disease and patients for whom treatment merely reduces the severity of the symptoms. Thus it is not possible to ascribe a robust utility value for the health of responders defined in this way. As a result, the health states in that appraisal were defined based on the absolute CDAI score, not the relative change.[15]

AbbVie therefore believes the approach in the Assessment Group model may not offer a reasonable interpretation of the clinical effectiveness of the treatments under evaluation and requests that this point be considered when evaluating their clinical and cost-effectiveness.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Due to the points discussed above, AbbVie does not believe that the provisional recommendations are sound or a suitable basis for guidance to the NHS.

As noted in the ACD, UC shares common genetic factors with Crohn's disease and is characterised by the same chronic symptoms which, in some patients, cannot be treated effectively by conventional therapy. In Crohn's disease the use of infliximab and adalimumab is currently recommended by NICE and AbbVie believes that UC patients should have the same treatment opportunities as Crohn's patients.

AbbVie also believes that the current analysis does not capture the benefits of anti-TNFs on improving work productivity and activity, a benefit to society which is not incorporated through the Institutes' reference case which only considers the costs incurred by the NHS.

There is currently a high unmet need for patients in the UK with moderately to severely active UC who have failed on standard of care with no recommended non-surgical options in this patient population. Anti-TNF therapy offers a step change therapy for people who have failed conventional therapy and are left with no treatment options other than surgery. We consider it is important for patients to have the opportunity to receive anti-TNF therapy as those who fail anti-TNF therapy will still be left with the surgical option as a last resort. Surgery compromises multiple procedures, is irreversible and when done as an emergency procedure, is associated with poor outcomes. Data from the IBD Audit used in the Assessment Group model indicates that 3 in 100 patients die due to surgery. It is therefore not surprising that patients show a strong preference for exhausting all medical options first. The availability of anti-TNF therapy for the treatment of moderate to severe UC gives patients and clinicians the opportunity to delay this irreversible and life changing surgery.

Anti-TNF therapies such as adalimumab are considered as effective treatment options for patients with moderate to severe UC for whom conventional treatment is not an option and use in these patients are recommended by the European Crohn's and Colitis Organisation[16]. Use of these agents is standard of care across Europe and is also widely reimbursed in major European countries. AbbVie believes that patients in the UK should receive the same standard of care as in the rest of Europe.

4. Are there any aspects of the recommendations that need particular consideration to ensure NICE avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

AbbVie has no comments on this point.

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Inclusion and exclusion criteria

Table 7. Inclusion and Exclusion Criteria for the INSPIRADA study

Inclusion criteria	Exclusion criteria
1. Subjects must be male or female between the ages of 18 and 75 years old at the time of the Screening Visit. 2. Subjects must have a diagnosis of UC greater than 90 days prior to Week 0 (Baseline) and failed conventional treatment. 3. Subjects' diagnosis of active UC must be confirmed by a colonoscopy with biopsy or flexible sigmoidoscopy with biopsy. 4. Subjects must have active UC with a PGA score of 2 or 3 and SIBDQ ≤ 45 at Week 0 (Baseline). 5. Subjects have a negative tuberculosis (TB) Screening Assessment including a PPD test and/or QuantiFERON-TB Gold test (or equivalent) and negative chest x-ray (posteroanterior [PA] and lateral view) at Screening. If the subject has a positive PPD test (or equivalent), has had a past ulcerative reaction to PPD placement and/or a chest x-ray (CXR) consistent with prior TB exposure, the subject must initiate and complete a minimum of 2 weeks of anti-TB therapy (or prophylaxis per local guidelines) prior to starting study therapy or have documented completion of a course of anti-TB therapy because of evidence of a latent TB infection prior to Baseline. 6. Subjects must have had at least one episode of rectal bleeding within 7 days of Screening (i.e., at least blood streaks in stool is reported) and within 7 days of Week 0 (Baseline). 7. Subjects must be on a concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below): • Stable oral corticosteroid dose (prednisone ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline. or • Stable oral corticosteroid dose (prednisone < 20 mg/day) for at least 21 days prior to Baseline. and/or • At least a consecutive 12 weeks (84 days) course of azathioprine or 6-mercaptopurine (6-MP) prior to Baseline. Concurrent therapy will not be required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-	1. Subjects with a history of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy for UC or planned bowel surgery. 2. Subjects received previous treatment with adalimumab or previous participation in an adalimumab clinical study. 3. Subjects who have previously used infliximab or any anti-TNF agent within 56 days of Baseline (Week 0). 4. Subjects who have previously used infliximab or any anti-TNF agent and have not clinically responded at any time ("primary non-reponder") unless they experienced a treatment limiting reaction. 5. Subjects received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days of Week 0 (Baseline). 6. Subjects received intravenous (IV) corticosteroids within 14 days of Screening or during the Screening period. 7. Subjects with a current diagnosis of fulminant colitis and/or toxic megacolon. 8. Subjects with disease limited to the rectum (e.g., ulcerative proctitis). 9. Subjects with a current diagnosis of indeterminate colitis. 10. Subjects with a current diagnosis and/or have a history of Crohn's disease. 11. Subjects currently receiving total parenteral nutrition (TPN). 12. Subjects with positive Clostridium difficile (C. difficile) stool assay at Screening. 13. Subjects have infections requiring treatment with the following: • IV antibiotics, IV antivirals, or IV antifungals within 30 days prior to Week 0 (Baseline), or • oral antibiotics, oral antivirals, or oral antifungals within 14 days prior to Week 0 (Baseline). 14. Subjects have evidence of dysplasia or a history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix. Note: If the Screening colonoscopy/flexible sigmoidoscopy shows evidence of dysplasia or a malignancy, subjects may not be enrolled in the study. 15. History of demyelinating disease (including

MP) and, in the judgment of the investigator, have failed to respond to or could not tolerate their treatment. 8. Subjects must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections. 9. Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol. 10. Female subjects must be either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing an approved method of birth control throughout the study and for 150 days after the last dose of study drug. Examples of approved methods of birth control include the following: • Condoms, sponge, foams, jellies with diaphragm or intrauterine device (IUD); • Oral or parenteral or intravaginal contraceptives for 90 days prior to study drug administration; • A vasectomized partner. 11. Female subjects' serum pregnancy test performed at the Screening Visit and urine pregnancy test performed at the Week 0 (Baseline) Visit must be negative. 12. Subjects who are judged to be in generally good health by the investigator based upon the results of the medical history, laboratory profile, physical examination, CXR, 12-lead electrocardiogram (ECG) performed during Screening. 13. Subjects or their physicians must be able to provide complete medical care resources utilisation information of the previous 6 months from the Screening Visit.	myelitis) or neurologic symptoms suggestive of demyelinating disease. 16. History of invasive infection (e.g., listeriosis and histoplasmosis) or positive for human immunodeficiency virus (HIV). 17. Subjects with an active systemic viral infection or any active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study. 18. Hepatitis B: HBs Ag positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBs Ab positive subjects. 19. Chronic recurring infections or active TB. 20. Positive pregnancy test at Screening or Baseline. 21. Female subjects who are breast-feeding or plan to breast-feed within the 150-day period after the last dose of study drug. 22. Subjects who have poorly controlled medical condition(s), such as uncontrolled diabetes, unstable ischemic heart disease, moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident, and any other condition, which in the opinion of the investigator, would put the subjects at risk by participation in the protocol. 23. Subjects who received any investigational agent or procedure within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer. 24. Subjects who have a history of clinically significant drug or alcohol abuse during the past year. 25. Subjects with known hypersensitivity to the excipients of adalimumab as stated in Section 26. Subjects with any prior exposure to Tysabri® (natalizumab).

Baseline demographics and clinical characteristics results

Table 8. Baseline demographics and clinical characteristics

		ITT analysis (N=80, unless indicated otherwise)
Male: n (%)		46 (57.5)
Age, years: mean (SD)		38.5 (14.5)
Weight, kg: mean (SD)		75.6 (15.7)
Disease location: n (%)	Extensive	38 (47.5)
	Left-sided	42 (52.5)
Disease duration, years: mean (SD)		7.7 (8.7)
SCCAI (0-19)[i]: mean (SD)		8.3 (2.4)
PGA[ii]: n(%)	Normal	0
	Mild	0
	Moderate	63 (78.7)
	Severe	17 (21.3)
SIBDQ total (10-70): mean (SD)		29.0 (7.6)
EQ-5D-5L predicted value: mean (SD)		0.6 (0.2) [N=79]
Current smoker: n (%)		6 (7.5)
Prior ant-TNF exposure: n (%)		19 (23.8)
Concomitant medication, any*: n (%)		75 (93.8)
Aminosalicylates: n (%)		61 (76.3)
Corticosteroids**: n (%)		54 (67.5)
Thiopurines (Azathioprine or 6-mercaptopurine): n (%)		44 (55)
Methotrexate: n (%)		12 (15)

*It is possible that some a patient may have taken several medications, thus the sum of the number of patients from different categories may be higher than the number of patients.
**Route of administration not specified

[i] The SCCAI (0-19 points) is based on five clinical criteria: bowel frequency at day (0-3 points), bowel frequency at night (0-2 points), blood in stool (0-3 points), urgency of defecation (0-3 points), general well-being (0-4 points) and extra-colonic features (1 per manifestation). (Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut. 1998;43:29–43:29D'Haens et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132(2):763-86)

[ii] The PGA considers subject reported information such as number of stools, rectal bleeding, abdominal discomfort and functional assessment during the previous day prior to the visit, and other observations such as physical findings, and the subject's performance status at the time of the visit. The scores indicate: 0= Normal, 1= Mild disease, 2= Moderate disease, 3 = Severe disease

Primary endpoint results

Table 9. Change in SIBDQ at Week 26 from Baseline

	ITT analysis (N = 80)					
Visit	**Mean**	**SD**	**Range**	**Change from baseline**	**95% CI**	**p-value**
Baseline	29.0	7.64	14-43	-	-	-
Week 26	47.4	15.72	20-67	18.36	14.89, 21.84	<0.001

p-value from paired t-test

Table 10. Change in costs[i] of UC-related medical care excluding adalimumab and other concomitant medication costs

	ITT analysis (N = 80)					
Period	**Mean**	**SD**	**Range**	**Difference**	**95% CI**	**p-value**
6 months prior to adalimumab treatment	£2,204	£1,551	£151 - £7,300	-	-	-
6 months after adalimumab treatment	£908	£1,486	£2 - £8,828	-£1,296	-£1,729, -£863	<0.001

p-value from paired t-test

Other endpoint results

Table 11. Responder[ii] status by visit

Visit		**ITT analysis**	
Week 2	**N=80**	Responder; n (%)	62 (77.5)
		Non-responder n (%)	18 (22.5)
Week 8	**N=79**	Responder n (%)	62 (78.5)
		Non-responder n (%)	17 (21.5)
Week 26	**N=60**	Responder n (%)	54 (90)
		Non-responder n (%)	6 (10)

Percentages calculated based on non-missing values

Table 12. Change in SIBDQ from baseline over time

	ITT analysis (N = 80)					
Visit	**Mean**	**SD**	**Range**	**Change from baseline**	**95% CI**	**p-value**
Baseline	29.0	7.64	14-45	-	-	-
Week 2	39.2	11.59	14-64	10.23	7.99, 12.46	<0.001
Week 8	45.5	13.74	10-70	16.46	13.25, 19.67	<0.001
Week 26	47.4	15.72	18-70	18.36	14.89, 21.84	<0.001

p-value from paired t-test

[i] All costs were obtained from the 2012-13 National Schedule of Reference Costs for NHS trusts and NHS foundation trusts with the exception of outpatient primary care costs. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260405/2012-13_national_schedule_of_reference_costs.xls [Accessed October 2, 2014]. Outpatient primary care cost data was obtained from: http://www.pssru.ac.uk/project-pages/unit-costs/2013/ [Accessed October 2, 2014].

[ii] A Non-Responder was defined as a subject who has a PGA score ≥ 2 and does not achieve a SCCAI response [not achieving a decrease of ≥ 2 points compared to Baseline (Week 0)]. A Responder was defined as a subject who does not meet the Non-Responder definition.

Table 13. Change in costs of UC-related medical care excluding adalimumab and other concomitant medication costs – Participants who completed the study

	ITT analysis (n = 61)*					
Visit	**Mean**	**SD**	**Range**	**Difference**	**95% CI**	**p-value**
6 months prior to treatment	2121	£1,581	£151 - £7,300	-	-	-
6 months after treatment	692	£813	£2 - £4,999	-£1,429	-£1,826, -£1,033	<0.001

p-value from paired t-test
* Of the 61, 54 participants were considered responders at week 8

Table 14. Change in costs of UC-related medical care excluding adalimumab and other concomitant medication costs – Participants who prematurely discontinued study

	ITT analysis (n = 19)*					
Visit	**Mean**	**SD**	**Range**	**Difference**	**95% CI**	**p-value**
6 months prior to treatment	£2,472	£1,457	£479 - £5,603	-	-	-
6 months after treatment	£1,603	£2,612	£55 - £8,828	-£869	-£2,262, - £524	0.207

p-value from paired t-test
* The majority of these participants were considered non-responders at week 8.

Table 15. Change from baseline in SCCAI

	ITT analysis (N = 80)					
Visit	**Mean**	**SD**	**Range**	**Change from baseline**	**95% CI**	**p-value**
Baseline	8.3	2.38	2-13	-	-	-
Week 2	4.9	2.77	0-11	-3.34	-3.90, -2.77	<0.001
Week 8	4.2	3.54	0-13	-4.08	-4.93, -3.22	<0.001
Week 26	4.1	3.72	0-13	-4.18	-5.11, -3.24	<0.001

p-value from paired t-test

Table 16. Change from baseline in EQ5D-5L-predicted values

	ITT analysis (N = 79)					
Visit	**Mean**	**SD**	**Range**	**Change from baseline**	**95% CI**	**p-value**
Baseline	0.6	0.18	0.0-1.0	-	-	-
Week 2	0.7	0.17	0.0-1.0	0.09	0.05, 0.12	<0.001
Week 8	0.8	0.20	-0.2-1.0	0.11	0.06, 0.16	<0.001
Week 26	0.7	0.23	-0.1-1.0	0.10	0.05, 0.16	<0.001

p-value from paired t-test

Table 17. Change from baseline in PGA

	ITT analysis (N = 80)					
Visit	**Mean**	**SD**	**Range**	**Change from baseline**	**95% CI**	**p-value**
Baseline	2.2	0.41	2-3	-	-	-
Week 2	1.6	0.55	0-3	-0.65	-0.79, -0.51	<0.001
Week 8	1.1	0.93	0-3	-1.09	-1.31, -0.87	<0.001
Week 26	1.2	0.97	0-3	-1.05	-1.27, -0.83	<0.001

p-value from paired t-test

Appendix 2

Factual inaccuracies identified in the ACD

Original Text	Correction / Query
Section 3.10: "The price of infliximab is £419.62 for a 100 mg vial containing powder for reconstitution (excluding VAT; BNF edition 67). Assuming the patient weighs 77 kg and the recommended dosage for infliximab is followed (see section 3.8), the cost of infliximab induction therapy is £5035; the monthly cost of infliximab maintenance therapy is **£210**. Costs may vary in different settings because of negotiated procurement discounts."	AbbVie's calculations for infliximab's monthly cost during maintenance shows it to be **£839.** 1 unit = 100mg infliximab = £419.62 77kg patient x 5mg/kg dose = 385mg = 4 units 4 units x £419.62 = £1678.48 Dose frequency = every 8 weeks Monthly cost = £1678.48 / 2 = £839.24
Section 4.3: "The Assessment Group noted that none of the trials included patients who had been treated before with corticosteroids and mercaptopurine or azathioprine, even though adalimumab, golimumab and infliximab are licensed for patients whose disease has had an inadequate response to, or who are intolerant to or have medical contraindications for, such therapies"	This statement is incorrect, as patients in the ULTRA studies would have moderate-severe disease despite either still receiving corticosteroids or immunomodulators or had previously failed them. Eligibility for ULTRA studies states "Adult ambulatory patients with moderately to severely active ulcerative colitis, defined by a full Mayo score16 (including endoscopic assessment) of 6-12 with an endoscopy subscore of 2-3, despite concurrent and stable treatment with oral corticosteroids and/or immunomodulators, were included… Concurrent therapy was not required for patients who failed to respond to or could not tolerate previous corticosteroid or immunomodulator treatment, as judged by the investigator."
Section 4.6: "The most frequently reported adverse event in both RCTs was worsening or flare up of ulcerative colitis (ULTRA1: adalimumab 5.8%, placebo 9.4%; ULTRA2: adalimumab 22.6%, placebo 29.2%)"	"The most frequently reported adverse event in both RCTs was worsening or flare up of ulcerative colitis (ULTRA1: adalimumab **3.6**%, placebo **4.0**%; ULTRA2: adalimumab 22.6%, placebo 29.2%) Additionally, we are unable to determine where the 29.2% in the placebo are is quoted from and question whether this is accurate.
Section 4.7: "In ULTRA2, however, changes in IBDQ scores at week 52 were higher in the adalimumab group (27 compared with 19; p<0.05)."	In ULTRA2, however, changes in IBDQ scores at week 52 were higher in the adalimumab group **vs. placebo** (27 compared with 19; p<0.05).
Section 4.19: "Maintenance of clinical response or remission at week 32 for patients starting in remission at week 8: golimumab 50 mg had the greatest effect compared with placebo, but the effect was not statistically significant (**−0.36, 95% CrI −1.33 to 0.62**)."	From p100 in the Assessment Report: "All treatments except adalimumab were associated with beneficial treatment effects relative to placebo with the greatest effects being associated with golimumab 50mg **(-0.63; 95% CrI: -1.36, 0.11**) and golimumab 100mg (-0.61; 95% CrI: -1.32, 0.11)."
Section 4.19:	From p104 in the Assessment Report:

"Maintenance of clinical response or remission at week 52 for patients starting with a clinical response at week 32: infliximab had the greatest effect compared with placebo, but the effect was not statistically significant **(−0.42, 95% CrI −1.06 to 0.21)."**	Infliximab was associated with the greatest effect **-0.36 (95% CrI: -1.33, 0.62)** and was most likely to be the most effective treatment (probability of being the best = 0.56).
Section 4.53: "Compared with conventional therapy, the ICER for adalimumab was £70,075 per QALY gained for golimumab it was **£90,720 per QALY** gained, and for infliximab it was £96,682 per QALY gained."	AbbVie was unable to replicate this result for golimumab using the updated Assessment Group model provided and we therefore question whether this is accurate.

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