NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Contains AIC, CIC

Premeeting briefing
Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

This slide set is the premeeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company , the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

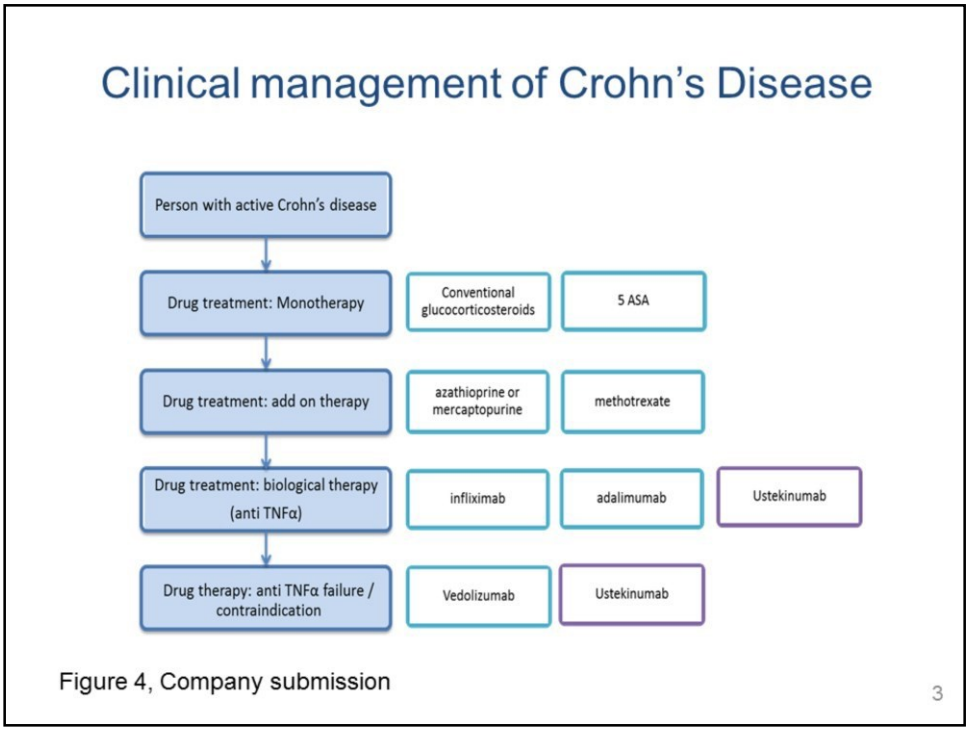
Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Disease background

- Crohn's disease is a chronic inflammatory and incurable condition of the gastrointestinal tract
- May affect any part of the gastrointestinal tract (from mouth to anus)
- People have recurrent attacks, with acute exacerbations ('flares') in between periods of remission or less active disease
- Caused by a combination of genetic, immune system and environmental factors
- Common symptoms include chronic diarrhoea, abdominal pain, extreme tiredness, unintended weight loss, and blood and mucus in stools.
- Complications associated with worsening digestive damage include strictures (a narrowing of the intestines), fistulas (an abnormal connection that forms between two organs or vessels), and abscesses
- There are currently at least 115,000 people in the UK with Crohn's disease (prevalence 145 per 100,000 population)
- More common in people aged 16-30 years but can affect people of any age

2

Further detail and discussion on the background to the disease can be found in section 3.1, pages 38 to 43, of the company submission and on pages 29 and 30 of the ERG report.



The clinical pathway of care for Crohn's disease is depicted in Figure 4 of the company's submission, adapted from NICE Clinical Guideline 152. The company considers that ustekinumab fits into the clinical pathway of care at the positions highlighted and offers an alternative treatment to TNF-alpha inhibitor treatment and vedolizumab, or the continuation of conventional therapy. During biologic treatment, patients may still receive conventional therapy for additional symptom control.

NICE guideline 152 recommends monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, budesonide may be considered. In people who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, *5-aminosalicylate* (5-ASA) treatment may be considered.

If there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered, the guideline recommends

adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or to budesonide to induce remission, or adding methotrexate to a conventional glucocorticosteroid or to budesonide in people who cannot tolerate azathioprine or mercaptopurine.

The tumour necrosis factor (TNF)–alpha inhibitors, infliximab and adalimumab, are recommended by NICE as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Vedolizumab is recommended by NICE as an option for treating moderately to severely active Crohn's disease if a TNF-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment) or a TNF-alpha inhibitor cannot be tolerated or is contraindicated.

The company estimates that over 4,000 patients in England and Wales have failed all available therapies in current practice.

Current NICE guidance

Guidance		Outcome
Technology appraisals		
TA352 (Aug 2015)	Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy	**Recommended** if a TNF-alpha inhibitor has failed, cannot be tolerated or is contraindicated
TA187 (May 2010)	Infliximab and adalimumab for the treatment of Crohn's disease (appraisal covered severe active Crohn's disease only)	**Recommended** if disease has not responded to conventional therapy (incl. immunosuppressive and/or corticosteroid treatments) or if conventional therapy is not tolerated or contraindicated
Clinical guidelines		
CG152 Crohn's disease: management' (Oct 2012)		Last updated May 2016

4

Further detail on NICE guidance can be found in the company submission section 3.5 pages 49 to 53.

Ustekinumab

Marketing authorisation

- Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha antagonist or have medical contraindications to such therapies.
- Also has a marketing authorisation for treating:
  - adult patients with moderate to severe plaque psoriasis
  - adult patients with active psoriatic arthritis

5

Further detail can be found in the company submission pages 31 and 32.

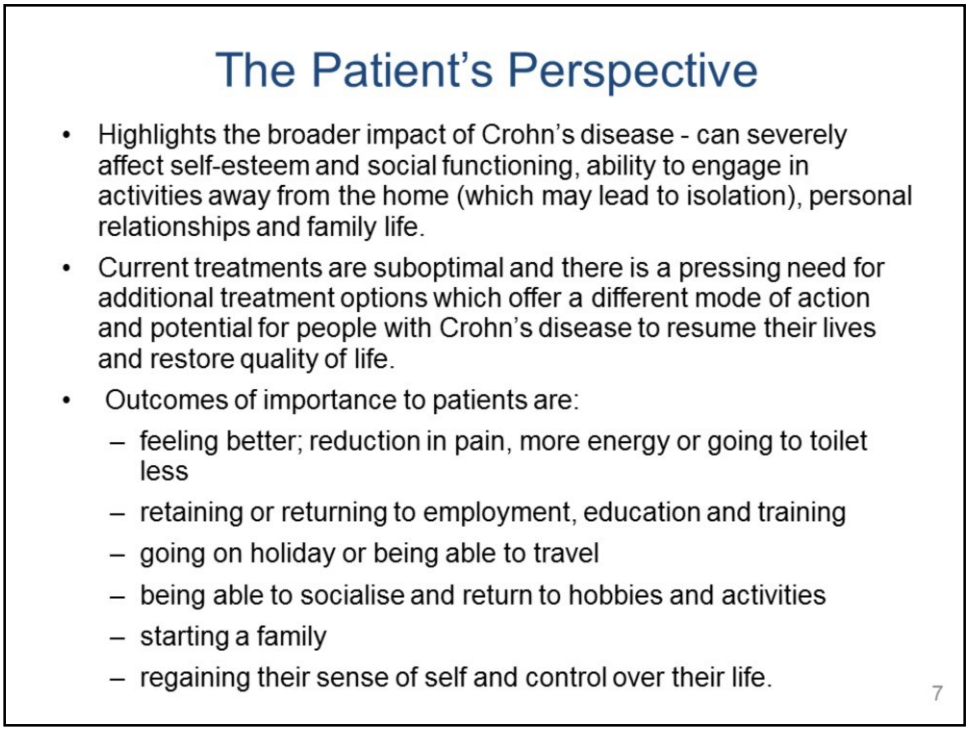
Ustekinumab (2)

Mode of administration	• Administered as intravenous infusion at induction and as subcutaneous injection at maintenance.
Dosage	• 1 intravenous induction treatment (dose depend on body weight and is approximately 6mg/kg • Maintenance subcutaneous treatment at week 8 (90mg) then every 12 weeks.
Mechanism of action	• Human monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin-12(IL-12) and interleukin-23 (IL-23) which cause bowel tissue to become inflamed.
Cost	• 130mg vial concentrate for solution for infusion: £2,147; 90mg vial solution for injection; £2,147 (list price MIMS) • Induction year; annual treatment cost at list price is £15,029 • Maintenance year (year 2 onwards); annual cost is £9,339 • xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx • xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx • xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Further detail can be found in the company submission, Table 5 on page 32.

The company submission states that all patients should receive an intravenous induction dose followed by a maintenance subcutaneous dose at week 8. After this, dosing every 12 weeks is recommended. Patients who have not shown adequate response 8 weeks after the first subcutaneous dose (that is, at week 16) may receive a second subcutaneous dose at this time. Patients who lose response on maintenance dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks; patients may subsequently be dosed every 8 or 12 weeks according to clinical judgement.

The anticipated care setting is hospital setting for induction and home setting for maintenance. Patients may self-inject if a physician determines that this is appropriate.



Comments from consultees

This section summarises comments from:

Crohn's and Colitis UK

Full details of the consultee comments can be found in the committee papers.

Decision problem

	NICE scope	Company's decision problem
Population	People with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a TNF-alpha inhibitor, or who are intolerant to either of them	As scope
Intervention	Ustekinumab	As scope

Comparators	• Conventional therapy
	  ○ corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate
	  ○ aminosalicylates
	  ○ budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate
	• TNF-alpha inhibitors (infliximab & adalimumab)
	• Vedolizumab
		As scope

8

Further detail about the decision problem can be found in the company submission Section 1.1, pages 17 to 19.

The NICE scope states that the availability and cost of biosimilars should be taken into consideration. The company considers biosimilars as separate comparators within its economic analysis, in a scenario analysis.

Decision problem

	NICE scope	Company's decision problem
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Adverse effects of treatment • Health-related quality of life	As scope
Subgroups	If evidence allows, the following subgroups may be considered: • People who have not previously received a TNF-alpha inhibitor; • People for whom at least 1 TNF-alpha inhibitor has failed; • People for whom TNF-alpha inhibitors are not suitable because of intolerance or contraindication. • Location of Crohn's disease (Ileal, colonic and perianal)	As scope

9

Further detail about the decision problem can be found in the company submission, section 1.1 (pages 17 to 19) and in section 3 (pages 31 to 33) of the ERG report.

UNITI-1 included patients who had failed, or who were intolerant to anti-TNFα in line with the indication for ustekinumab and the scope of the submission. Location of Crohn's disease was addressed very briefly in the company submission, with a statement that in subgroup analysis across the UNITI trial programme, ustekinumab was shown to be effective irrespective of location of Crohn's disease.

Key clinical trial evidence – 3 phase III multicentre double-blind trials

Trial	Location	Population	Trial drugs	Comparator
UNITI-1 (N=741)	177 locations worldwide including UK	Adults with moderately to severely active Crohn's* whose disease has not responded to or are contraindicated to, TNFα inhibitor therapy	• Ustekinumab 130mg IV infusion (n=245) • Ustekinumab ~6mg/kg IV infusion (n=249)	Placebo (n=247)
UNITI-2 (N=628)	226 locations worldwide including UK	Adults with moderately to severely active Crohn's* whose disease has not responded to conventional therapy	• Ustekinumab 130mg IV infusion (n=209) • Ustekinumab ~6mg/kg IV infusion (n=209)	Placebo (n=210)
IM-UNITI (N=397)	220 locations worldwide including UK	Adults with moderately to severely active Crohn's induced into clinical response with ustekinumab in the UNITI-1 or UNITI-2 induction studies	Ustekinumab 90mg subcutaneous injection • every12 weeks (n=132) • every 8 weeks (n=132)	Placebo (n=133)

*Moderately to severely active Crohn's disease defined as a Crohn's Disease Activity Index (CDAI) score of 220-450

10

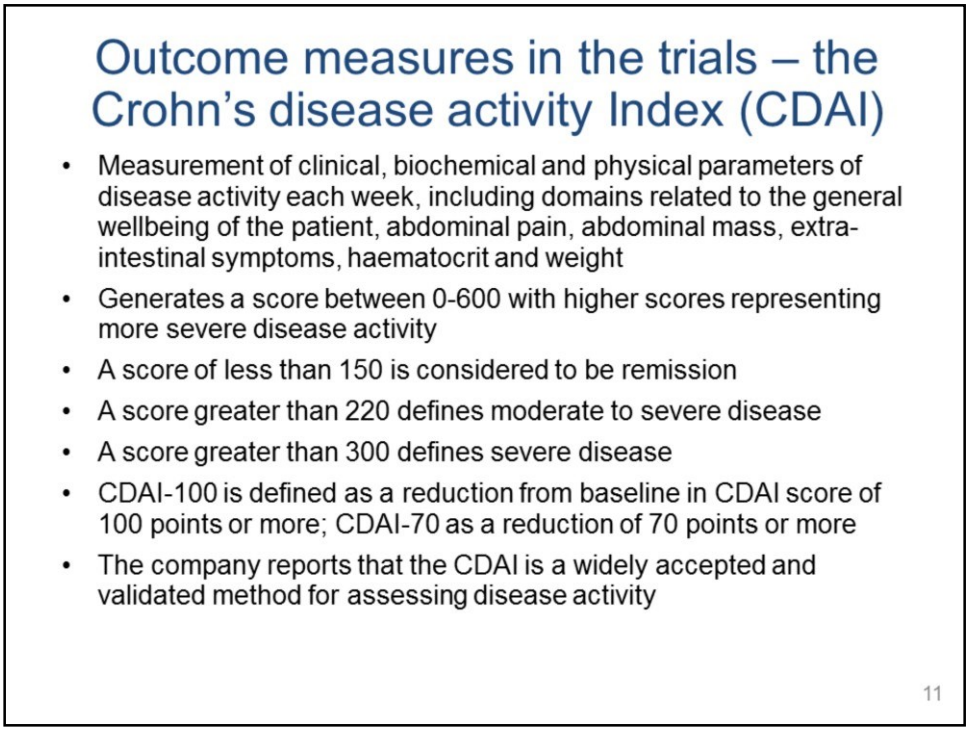
The company presents the clinical effectiveness evidence in section 4 of the company submission (from page 56).

The clinical trial programme for ustekinumab includes 3 pivotal randomised-controlled trials (RCTs) (two 8-week induction trials and one 44-week maintenance trial) in patients who have failed either conventional care and/or TNF-alpha inhibitor therapy (or are contraindicated to TNF-alpha inhibitor therapy). The design of the induction studies was essentially identical except for the trial populations. In UNITI-1, patients had received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of Crohn's disease, and either did not respond, responded initially but since lost response, or were intolerant to the medication (according to strict predefined failure criteria as specified in the protocol). In UNITI-2, patients had failed conventional therapy of corticosteroids and/or immunomodulators and/or corticosteroids, including patients who were corticosteroid dependent. Patients in UNITI-2 could have been exposed to TNF-alpha inhibitor therapy previously but must not have met the failure criteria specified for UNITI-1. Patients were randomised in a 1:1:1 ratio to receive a single (fixed) intravenous administration of ustekinumab 130mg, ustekinumab weight-based dosing equivalent to approximately 6mg/kg, or placebo. Throughout both studies, patients were permitted to receive concomitant corticosteroid and/or immunosuppressant drugs, representing clinical practice and allowing the

placebo group to act as a proxy for, and thus provide a comparison to, conventional therapy.

In the IM-UNITI study, patients with a clinical response to ustekinumab in either of the two induction trials (UNITI-1, UNITI-2) at week 8 were randomised to receive subcutaneous administrations of ustekinumab 90mg every 12 weeks (q12w), ustekinumab 90mg every 8 weeks (q8w), or placebo up to week 44 (52 weeks after induction). The company reported that, in an advancement to previous maintenance trials, all other patients enrolled in UNITI-1 and UNITI-2 could also be included in IM-UNITI. To evaluate the long-term safety and efficacy of ustekinumab, patients who completed the safety and efficacy evaluation at week 44 of IM-UNITI and who, in the opinion of the investigator, may benefit from continued treatment, were offered the opportunity to participate in a study extension starting at week 44 through week 272 (remaining on the same study agent and dosing regimen being received at the end of IM-UNITI). The first data cut of this study extension became available 2 weeks prior to submission, providing data up to week 92. No statistical comparisons between ustekinumab and placebo are presented by the company for the 92 week data. For more information, see section 4.7.9 of the company submission.

Prior to the UNITI trial programme, ustekinumab for the management of Crohn's disease was investigated in the Phase II RCT, CERTIFI. A summary of the CERTIFI study and its main efficacy results are presented in Appendix 3 of the company's submission. This study is not presented in detail within the main body of the submission, because the company states that the focus is on the Phase III data, on which the marketing authorisation was granted and on which the cost-effectiveness modelling is based. The company states that the CERTIFI study does not provide comparable evidence to these data in the respect that patients received a 1, 3 or 6 mg/kg induction dose, rather than the vial-based dose approximating to 6mg/kg as per licence terms. However, it reports that, broadly speaking, the results from this Phase II study supported those from the Phase III trial programme. The ERG considered that CERTIFI is relevant to the decision problem.



More information on the CDAI is given on pages 38 and 69 of the company's submission.

The primary endpoint in UNITI-1 and UNITI-2 was clinical response at week 6, defined as a reduction from baseline in the Crohn's disease activity index (CDAI) score ≥100 points. A major secondary outcome was clinical remission, defined as a CDAI score of <150 points.

Key efficacy endpoints – UNITI-1 and UNITI-2

Outcomes	UNITI-1 (failed anti-TNF therapy)			UNITI-2 (failed conventional therapy)		
Primary	Placebo n=247	UST ~6mg/kg n=249	UST 130mg n=245	Placebo n=209	UST ~6mg/kg n=209	UST 130mg n=209
CDAI-100 response at 6 weeks n (%)	53 (21.5)	84 (33.7)*	84 (34.3)*	60 (28.7)	116 (55.5)**	108 (51.7)**
Secondary						
Clinical remission at 8 weeks n (%)	18 (7.3)	52 (20.9)**	39 (15.9)*	41 (19.6)	84 (40.2)**	64 (30.6)*
CDAI-100 response at 8 weeks n (%)	50 (20.2)	94 (37.8)**	82 (33.5)*	67 (32.1)	121 (57.9)**	99 (47.4)**
CDAI -70 response at 6 weeks n (%)	75 (30.4)	113 (46.1)**	109 (43.8)*	81 (38.8)	123 (58.9)**	135 (64.6)**

CDAI= Crohn's disease activity index ,UST=ustekinumab
*p<0.01 UST vs placebo, ** p<0.001 UST vs placebo

12

Further detail can be found in section 4.7 of the company submission. This slide has been adapted from Table 15 on page 88 of the company submission. Results are based on the intention to treat (ITT) population.

UNITI-1:

The proportion of patients in clinical response (CDAI-100) at week 6 was significantly greater in both the ~6 mg/kg (33.7%) and 130 mg (34.3%) ustekinumab groups compared with the placebo group (21.5%; p=0.003 and p=0.002, respectively). The proportion of patients in clinical remission (CDAI score of <150 points) at week 8 was significantly greater in both the ~6 mg/kg (20.9%) and 130 mg (15.9%) ustekinumab groups than in the placebo group (7.3%; p<0.001 and p=0.003, respectively). There were also statistically significant differences between ustekinumab (both doses) and placebo for clinical response at 8 weeks and CDAI ≥70-point response at 6 weeks.

UNITI-2

The proportions of patients in clinical response (CDAI-100) at week 6 was significantly greater in both the ~6 mg/kg (55.5%) and 130 mg (51.7%) ustekinumab groups than in the placebo group (28.7%, p<0.001 for both comparisons). The proportions of patients in clinical remission (CDAI score of

<150 points) at week 8 was significantly greater in both the ~6 mg/kg (40.2%) and 130 mg (30.6%) ustekinumab groups than in the placebo group (19.6%, p<0.001 and p=0.009, respectively). There were also statistically significant differences between ustekinumab (both doses) and placebo for clinical response at 8 weeks and CDAI ≥70-point response at 6 weeks.

.

Key efficacy endpoints – IM-UNITI

Outcomes	IM-UNITI (Intention to treat population)		
Primary	**Placebo n=131**	**Ustekinumab 90mg every 12 weeks n=129**	**Ustekinumab 90mg every 8 weeks n=128**
Clinical remission at 44 weeks n (%)	47 (35.9)	63 (48.8)*	68 (53.1)**
Secondary			
CDAI-100 response at 44 weeks n (%)	58 (44.3)	75 (58.1)*	76 (59.4)*
Corticosteroid free clinical remission at 44 weeks n (%)	39 (29.8)	55 (42.6)*	60 (46.9)**
Clinical remission at 44 weeks in patients refractory or intolerant to TNF*a* inhibitors	16 (26.2)	22 (38.6)	23 (41.1)

CDAI= Crohn's disease activity index,
*p<0.05 ustekinumab vs placebo, ** p<0.01 ustekinumab vs placebo

13

Further detail on the clinical effectiveness results from IM-UNITI can be found in section 4.7.3 of the company submission. This slide has been adapted from Table 16 on page 91 of the company submission. Results are based on the intention to treat (ITT) population.

The primary endpoint in IM-UNITI was clinical remission at week 44, defined as a CDAI score <150 points. The proportion of patients in clinical remission at week 44 (1-year post treatment initiation) was significantly greater in both the 90mg every 12 weeks (48.8%) and 90mg every 8 weeks (53.1%) ustekinumab groups than in the placebo group (35.9%; p=0.040, p=0.005, respectively).

Regarding the secondary outcomes, the proportion of patients in clinical response (CDAI-100) at week 44 was significantly greater in both the 90mg every 12 weeks (58.1%) and 90mg every 8 weeks (59.4%) ustekinumab groups than in the placebo group (44.3%; p=0.033 and p=0.018, respectively). Among the approximately 60% of patients (n=156) who were in clinical remission at baseline (week 8 post ustekinumab intravenous induction), a significantly greater proportion of patients in the ustekinumab 90mg every 12 weeks group maintained clinical remission at week 44 (66.7%) compared with the placebo group (45.6%; p=0.007). Maintenance of clinical remission was

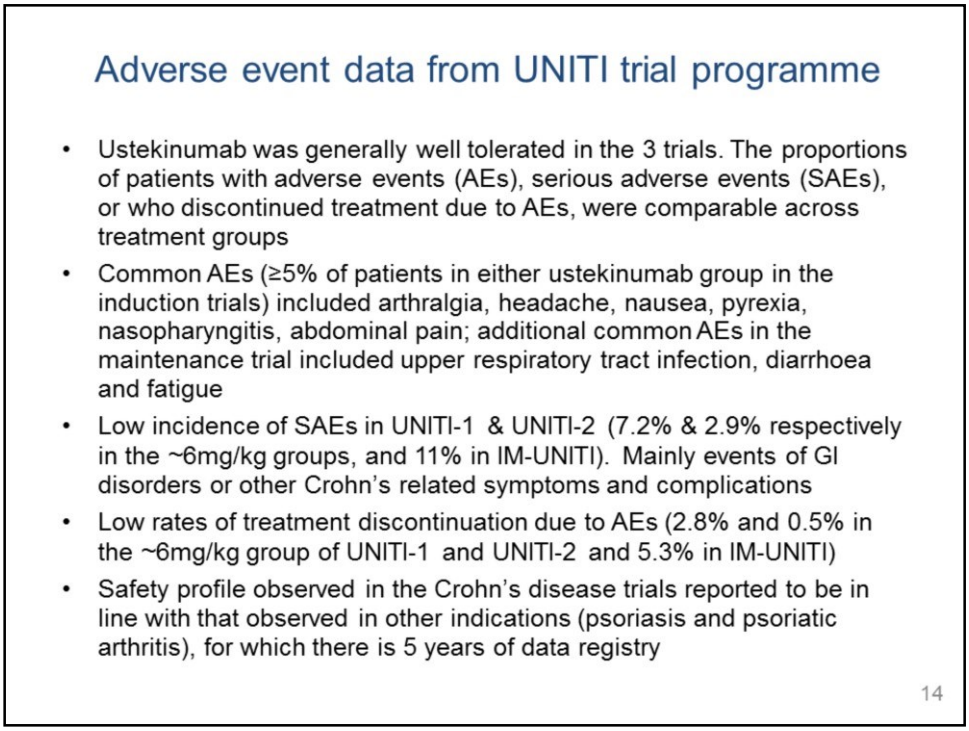
also numerically higher in the ustekinumab 90mg every 12 weeks group (56.4%) compared with the placebo group; however, this result did not achieve statistical significance (p=0.189).

Corticosteroid-free remission at week 44 was achieved by a greater proportion of patients in the ustekinumab 90mg every 12 weeks and 90mg every 8 weeks groups (42.6% and 46.9%, respectively) compared with the placebo group (29.8%).

Among patients who were refractory or intolerant to TNF-alpha inhibitor therapy (n=113), clinical remission rates at week 44 were numerically greater in the 90mg every 12 weeks (38.6%) and 90mg every 8 weeks (41.1%) ustekinumab groups compared with the placebo group (26.2%). The company reported that, although the relative treatment effects were similar to those in the overall population, there was not sufficient power to detect a significant difference from placebo as only 44.8% of the patients in the primary study population were included in this analysis.

Patients who failed to achieve clinical response (CDAI-100) with ustekinumab intravenous induction infusion were treated with ustekinumab 90mg subcutaneous injection at week 0 of the maintenance trial (8 weeks after intravenous ustekinumab). The company reports that, although these patients were not considered in the primary study population for IM-UNITI, this group provides data in line with the licensed dosing for ustekinumab. Further information is given in section 4.7.6 of the company submission.

Note that the IM-UNITI trial results are not presented separately for the two induction dose groups (fixed 130 mg or the licensed ~6mg/kg dose).



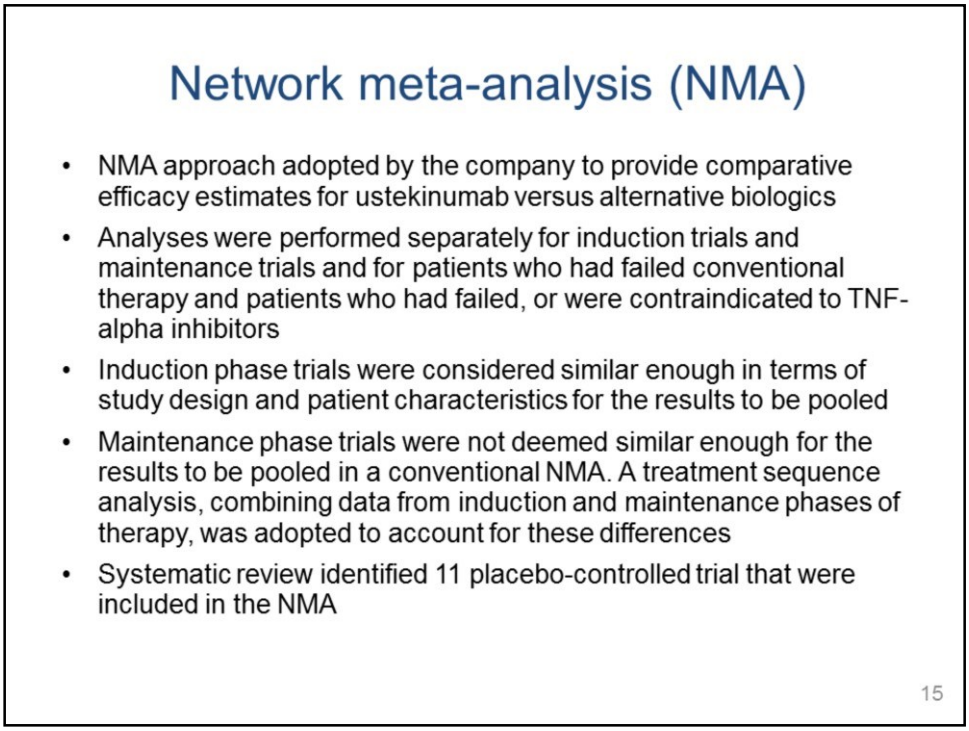
Further detail on adverse events is presented in section 4.12, pages 148 to 157, of the company submission and on pages 71 to 73 of the ERG report.

The company reported that intravenous ustekinumab was generally well tolerated in the induction trials. The proportions of patients with adverse events (AEs) and serious adverse events (SAEs) were comparable across treatment groups, with no evidence of an ustekinumab dose effect. Similarly, the proportions of patients who discontinued due to AEs were comparable (ustekinumab no higher than placebo) across treatment groups with no evidence of an ustekinumab dose effect. Common AEs emerging with ustekinumab treatment across trials (≥5% of patients in either ustekinumab group) were arthralgia, headache, nausea, pyrexia, nasopharyngitis, abdominal pain and CD, as summarised in Table 25 of the company submission. SAEs that occurred in patients treated with ustekinumab were predominately events of GI disorders, or other CD related symptoms and complications, as summarised in Table 26 of the company submission.

In the maintenance trial, subcutaneous ustekinumab at doses of 90mg every 12 weeks or every 8 weeks was generally well tolerated. As was observed in the induction trials, the proportions of patients with AEs and SAEs were

comparable across treatment groups, with no evidence of an ustekinumab dose effect. Similarly, the proportions of patients who discontinued due to AEs were comparable (ustekinumab no higher than placebo) across treatment groups, with no evidence of an ustekinumab dose effect. Common AEs emerging with ustekinumab treatment through week 44 of IM-UNITI (≥5% of patients in ustekinumab combined group) were arthralgia, CD, headache, nasopharyngitis, abdominal pain, upper respiratory tract infection, pyrexia, diarrhoea, fatigue, and nausea, as summarised in Table 28 of the company submission. As was the case during induction, maintenance ustekinumab was associated with very few SAEs, and those that did occur were predominately events of GI disorders or other CD related symptoms and complications, as summarised in Table 29 of the company submission.

The company reported that the safety profile observed in the Crohn's disease trials is generally in line with that observed in other indications (psoriasis and psoriatic arthritis), for which 5 years of data registry provide conclusive evidence of the favourable long-term safety profile of ustekinumab. In a recent pooled analysis involving 6,280 patients treated with at least one dose of ustekinumab for Crohn's disease or psoriatic disease; rates of AEs, SAEs, and infection/serious infection were comparable across ustekinumab and placebo groups. Further details on the pooled safety analysis are presented in Appendix 6 of the company submission.



Further detail on the network meta-analysis (NMA) can be found in the company submission section 4.10, pages to 110 to 148.

The company reported that potential treatment effect modifiers in the induction phase were determined based on the literature. The following characteristics were assessed and deemed comparable across trials: duration of disease, CDAI score at baseline, C-reactive protein (CRP) concentration and fistula at baseline, and administration of concomitant/allowed therapies.

Due to multiple sources of heterogeneity between the maintenance trials, the company considered that a treatment sequence analysis was more appropriate than a conventional NMA.

The company reported that NMA analyses were conducted within a Bayesian framework, preserving the ranDom-disation of each trial, and using a standard NMA approach, as recommended by NICE. The relative goodness of fit of the models was assessed using the Deviance Information Criterion (DIC). All analyses was performed in WinBUGS V1.4[169] using the MCMC (Markov Chain Monte Carlo) simulation method. Additional details of the methods of analysis are provided in Appendix 5 of the company submission.

The company did not consider that a NMA of safety endpoints was feasible due to the lack of comparability between trials' definitions of adverse events.

Studies included in the induction phase NMA

Trial	Subpopulation	Intervention	Trial length
Targan 1997	Conventional care failure	Infliximab	Week 4
CLASSIC I	Conventional care failure	Adalimumab	Week 4
Watanabe 2012	Conventional care failure & TNF failure	Adalimumab	Week 4
GAIN	TNF failure	Adalimumab	Week 4
GEMINI II	Conventional care failure & TNF failure	Vedolizumab	Week 6
GEMINI III	Conventional care failure & TNF failure	Vedolizumab	Week 10
UNITI-1	TNF failure	Ustekinumab	Week 8
UNITI-2	Conventional care failure	Ustekinumab	Week 8
CERTIFI*	TNF failure	Ustekinumab	Week 8
Key: TNF, tumour necrosis factor. *CERTIFI was excluded from the company's base case economic modelling			

Table 20, Company submission

16

Endpoints for the NMA of the induction phase were selected based on published data availability across trials.

- Clinical response, defined as a reduction in CDAI score of 70 points
- Clinical response, defined as a reduction in CDAI score of 100 points
- Clinical remission, defined as a CDAI score of or inferior to 150 points

Time point selection was based on comparability to the time of assessment of the primary endpoint in ustekinumab trials: 6 weeks. For infliximab and adalimumab, data at 4 weeks were used. For vedolizumab, data at 6 weeks were used. This selection of times of assessment was in line with the primary endpoints of each trial included in the analysis.

The company reported that, in the failed conventional care population, placebo rates were generally comparable across trials, except for two small studies. The lowest placebo response rates were observed in a small Japanese study (Watanabe 2012, 15% CDAI-100 placebo response rates), and a small Phase II study (Targan 1997, 17% CDAI-70 placebo response rates). The latter study was also impacted by a proportion of missing data in the placebo arm (3/25 patients in the placebo arm [12%] had missing data), which were classed as

non-responders; in addition, a smaller magnitude of effect in the higher doses of infliximab were reported, than in the lower doses. The company reports that the results of Targan *et al*. 1997 (study of infliximab) should therefore be interpreted with caution.

In patients who had failed anti-TNF therapy, similar placebo rates were observed across trials, even though adalimumab trials were conducted in a more restricted patient population (secondary failure patients only).

Summary of results of induction phase NMA

OR (95% CI) ustekinumab vs	Response (CDAI-70)	Response (CDAI-100)	Remission
Conventional care failure population			
Adalimumab 80/40mg	0.98 (0.46; 2.05)	1.39 (0.64, 2.97)	1.14 (0.44, 2.82)
Adalimumab 160/80mg	0.92 (0.43; 1.91)	1.03 (0.47, 2.20)	0.64 (0.25, 1.53)
Placebo	2.89 (1.95; 4.32)	3.12 (2.08, 4.68)	2.5 (1.60, 3.98)
Infliximab 5mg/kg*	0.11 (0.02; 0.48)	N/A	0.08 (0.01, 0.59)
TNF failure population			
Vedolizumab 300mg	0.96 (0.57, 1.62)	1.05 (0.59, 1.85)	1.53 (0.69, 3.39)
Placebo	1.79 (1.24, 2.60)	1.87 (1.26, 2.80)	2.34 (1.37, 4.08)

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; OR, odds ratio.

Table 23, Company submission

17

The results of the NMA are presented in section 4.10.6 of the company submission.

The company reported that, in induction phase analysis of the conventional care failure subpopulation, for whom TNF-alpha inhibitor treatment is the relevant comparator based on current UK practice, ustekinumab was associated with a high probability of reaching CDAI-100 response (80%, odds ratio [OR] 1.39, credible interval [CrI] 0.64 to 2.97) and a similar probability of reaching clinical remission (60%, OR 1.14, CrI 0.44 to 2.82) compared to adalimumab standard induction dose. CDAI-100 data were not available for infliximab; however, this treatment was associated with the highest chance of being in clinical response, based on CDAI-70 data post induction. The company believes that these results should be interpreted with caution due to concerns of bias, including low patient numbers (n=52), missing data in the placebo control group (that were classed as treatment failures), and inverse dose relationships observed in the infliximab group of the induction treatment trial providing data for this treatment.

In induction phase analysis of the TNF failure subpopulation, for whom vedolizumab is the relevant comparator based on current UK practice,

ustekinumab was associated with a similar probability of reaching CDAI-100 response (56%, OR 1.05, CrI 0.59 to 1.85) and a high probability of reaching clinical remission (85%, OR 1.53, CrI 0.69, 3.39).

None of the differences described above between ustekinumab and other biologics are statistically significant.

Treatment sequence analysis to predict long term outcomes*

Study	Treatment	Patient selection	Study design
IM-UNITI	Ustekinumab	Ustekinumab responders (CDAI-100) at Week 8	Double blind for induction and maintenance
CHARM	Adalimumab	Adalimumab responders (CDAI-70) at Week 4	Induction phase not blinded and not comparative Induction dose received: 80/40mg
ACCENT I	Infliximab	Infliximab responders (CDAI-70) at Week 2	Induction phase not blinded
GEMINI II	Vedolizumab	Vedolizumab responders (CDAI-70) at Week 6	Most patients from unblinded induction phase (96/461)

Key: CDAI, Crohn's Disease Activity Index.

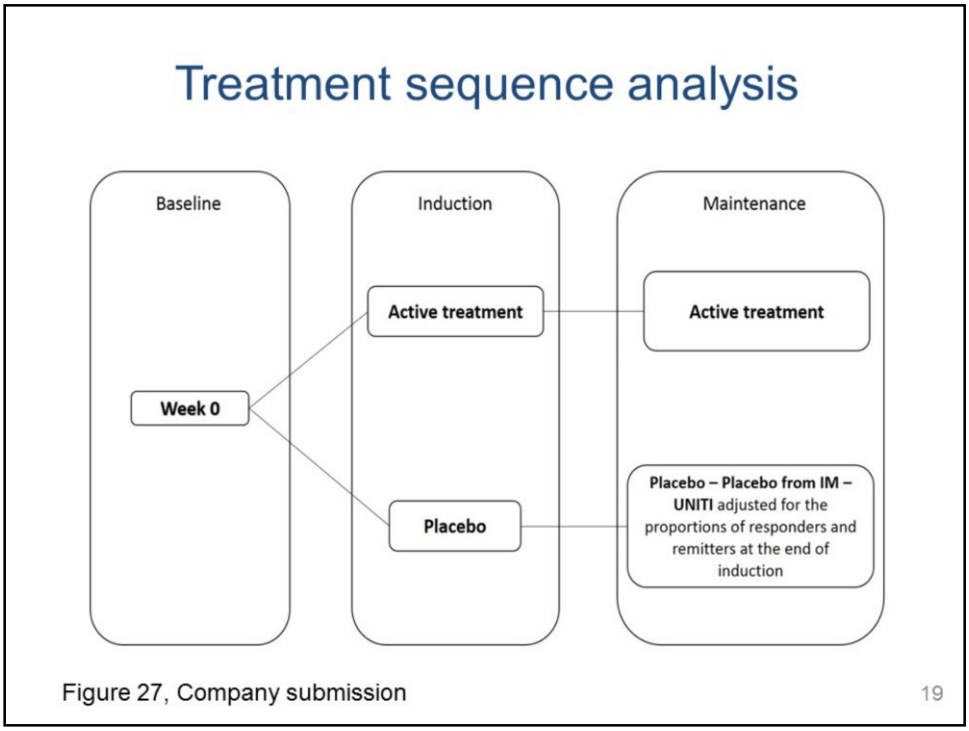
*Maintenance phase NMA not considered possible by the company
Table 21, Company submission

18

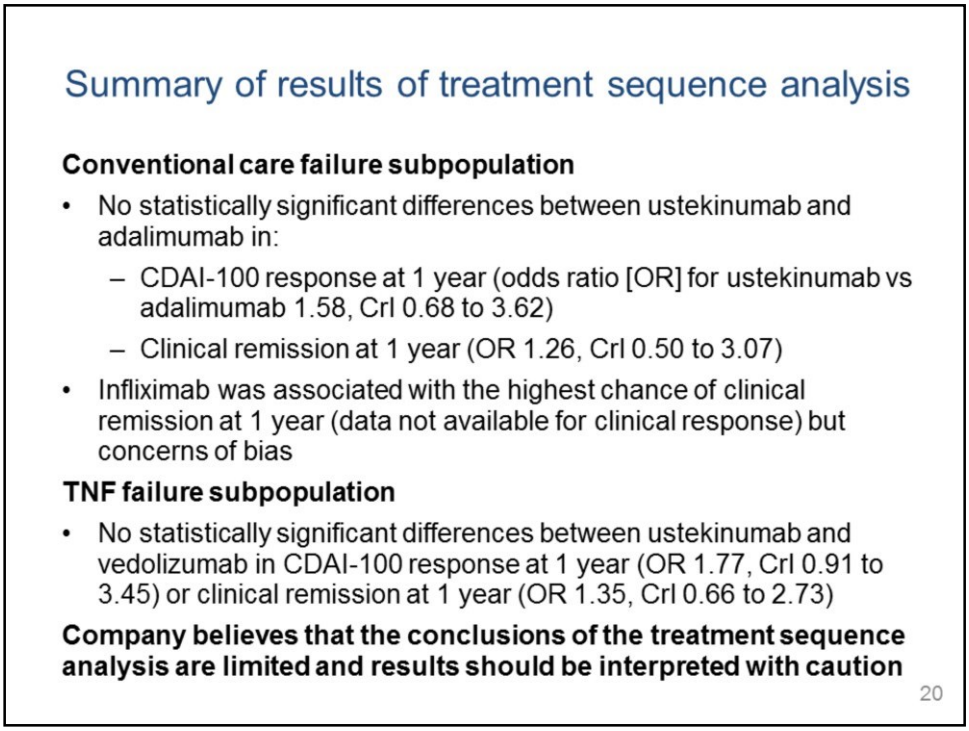
The company highlighted several challenges that arise in the comparison of maintenance trials in Crohn's disease. Multiple sources of heterogeneity in study design complicate the assessment of relative treatment efficacy in the maintenance phase due to a lack of comparability between 'placebo' arms across trials. Placebo arms in maintenance studies are not comparable and cannot readily be used as a common comparator in the network of evidence because patients who enter the maintenance phase were initially selected for their ability to respond to the intervention being evaluated. The company also reported that the number of prior failures to TNF-alpha inhibitor therapy is likely to impact the comparison of ustekinumab to other biologics. For example, patients in adalimumab trials had failed only infliximab, while patients in IM-UNITI may have failed up to three different TNF-alpha inhibitors. The company reported that a third element of heterogeneity lies in the difference between primary and secondary failure of TNF-alpha inhibitors. For example, adalimumab trials only included secondary failure patients with contraindications to infliximab whereas trials evaluating ustekinumab and vedolizumab included both primary and secondary failures to TNF-alpha inhibitor therapy. Therefore, trials evaluating ustekinumab and vedolizumab are more inclusive and are comprised of patients with more severe disease that may not respond to treatment with ustekinumab/vedolizumab. This key difference may underestimate the relative treatment effect of ustekinumab (and vedolizumab) when indirectly compared to adalimumab. The company

also tested the statistical heterogeneity and found a significant level of heterogeneity, suggesting that placebo arms are not appropriate common comparators.

The company therefore considered that a treatment sequence analysis was more appropriate to reduce bias inherently associated with the analysis of long-term relative treatment effect estimates for ustekinumab.



As the maintenance of treatment effect is conditional on treatment effect observed in the preceding induction phase, the company believes that a proper assessment of the maintenance phase needs to take into account the full treatment pathway. The company reported that the objective of conducting the treatment sequence analysis was twofold: first, to increase comparability of placebo arms across maintenance phase trials, and second, to evaluate treatment effects over the entire treatment sequence. As part of the treatment sequence analysis, maintenance data for placebo arms of comparator trials were imputed using IM-UNITI individual patient level data, adjusted for the proportion of responders and remitters at the end of induction phase. This was considered necessary in order to reduce bias associated with the violation of the transitivity assumption given that the 'placebo' arms in maintenance studies are not comparable. Details on how the inputs for the treatment sequence analysis were estimated are reported in Figure 30 and Figure 31 of the company submission.



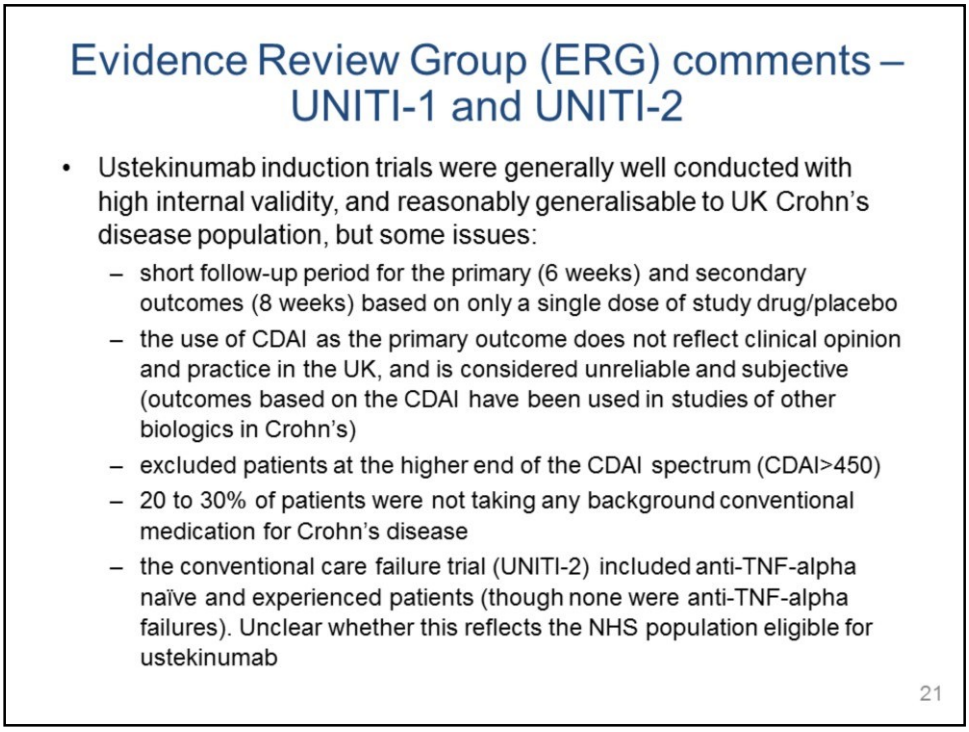
The results of the NMA are presented in section 4.10.6 of the company submission.

The company reported that, in the treatment sequence analysis that combined data from induction and maintenance phases of therapy, ustekinumab was associated with a high probability of reaching CDAI-100 response at 1 year compared to adalimumab (86%, OR 1.58, CrI 0.68 to 3.62) in the conventional care failure subpopulation. Ustekinumab was also associated with a high probability of reaching clinical remission at 1 year compared to adalimumab (69%, OR 1.26, CrI 0.50 to 3.07) in the conventional care failure subpopulation. Infliximab was associated with the highest chance of being in clinical remission at 1 year in the conventional care subpopulation (data not available for clinical response), but the company believes that the results should be interpreted with caution due to the concerns of bias.

In the TNF failure subpopulation, ustekinumab was associated with a high probability of reaching CDAI-100 response at 1 year compared to vedolizumab (95%, OR 1.77, CrI 0.91 to 3.45); similar results were observed in clinical remission analysis at 1 year (vedolizumab: 80%, OR 1.35, CrI 0.66 to 2.73).

None of the differences described above between ustekinumab and other biologics are statistically significant.

The company considered that the conclusions of the treatment sequence analysis are limited and results should be interpreted with caution. However, given the lack of head-to-head evidence and the need for the evaluation of the relative efficacy of ustekinumab, the company believes that the treatment sequence analysis may be the best possible approach given the lack of comparable maintenance data across comparators.



Further details can be found in the ERG report pages 43 to 56.

The ERG highlighted that the trials included a mixture of GI area involved (ileum only, colon only, ileum and colon, proximal GI tract and perianal GI tract) but the actual percentages varied across the trials. With regard to UNITI-1 and -2, the largest difference between the trials was for the proportion of patients with both ileum and colon disease – less than 20% compared with around 60%. The trial analysis was not stratified by site of Crohn's disease. It is unclear to the ERG if this affects the generalisability or comparability of the trials' results.

It should be noted that the ustekinumab trials included patients with a CDAI score between 220 and 450; and therefore excluded patients at the higher end of the CDAI spectrum (CDAI > 450). Advice from the clinical advisor to the ERG suggests that the number of patients with a CDAI score in excess of 450 is likely to be small and therefore the exclusion of patients is likely to have only a limited impact on the representativeness of the UNITI trials. It is however, uncertain whether patients with a CDAI score of 450 or greater would benefit to the same degree as patients with less severe disease.

Biologics for Crohn's disease are given against a background of conventional care, i.e. almost all patients in clinical practice will be receiving some form of conventional therapy as well as the biologic. In the ustekinumab trials, only 70 to 80% of patients were taking any medication for Crohn's disease at baseline. As a population they may therefore not be as optimally treated with conventional care as the clinical practice patients should be; the benefits of ustekinumab seen in the trials may be greater than those achieved in practice.

The ERG believed that the follow-up period for the primary (6 weeks) and secondary (8 weeks) outcomes were very short. Patients had received only one IV dose of active treatment or placebo. The ERG highlighted that the committee of human medicinal products (CHMP) guidance recommends that primary outcome (endpoint) should be considered after at least 2 cycles of therapy. Therefore, the ERG believes that the follow-up period was not sufficient.

The ERG was concerned that the CDAI is a composite of 8 items (components) which is prone to errors due to high inter-observer variability and subjectivity. Based on the ERG's clinical expert's opinion, this measurement is thought of as 'soft' and unreliable; the "endoscopic response" is a more objective outcome measure than CDAI. Therefore, outcome results based on this tool may be biased or may not reflect disease status accurately. In addition, the ERG highlighted that those biomarkers used in these studies are indicators of any inflammation in the body, and are not specific to Crohn's disease. This becomes a problem when concomitant inflammatory diseases are present as this may exaggerate biomarker levels.

ERG comments – induction phase NMA

- Methods were clearly presented and generally appropriate and the results appear reliable and consistent with the trial results for ustekinumab and comparator biologics
- The 8 included trials were generally conducted to a high-standard and were generally comparable, but limitations include:
  - variability in the time at which primary outcomes were assessed (4 weeks for infliximab and adalimumab and 6 weeks for vedolizumab and ustekinumab).
  - treatment history and prior anti-TNF exposure / nature of anti-TNF failure of the various patient populations included also varied between the trials
  - poor reporting/questionable handling of missing data in 4 studies
- ERG disagrees with the exclusion of the CERTIFI phase II trial of ustekinumab - although listed in the table of included trials it was not included in the base-case NMA because the company considered that the fixed 6 mg/kg dose was not comparable to the licensed dose of approx 6mg/kg used in UNITI-1 and UNITI-2. The ERG re-ran the NMA including CERTIFI, which produced slightly different results

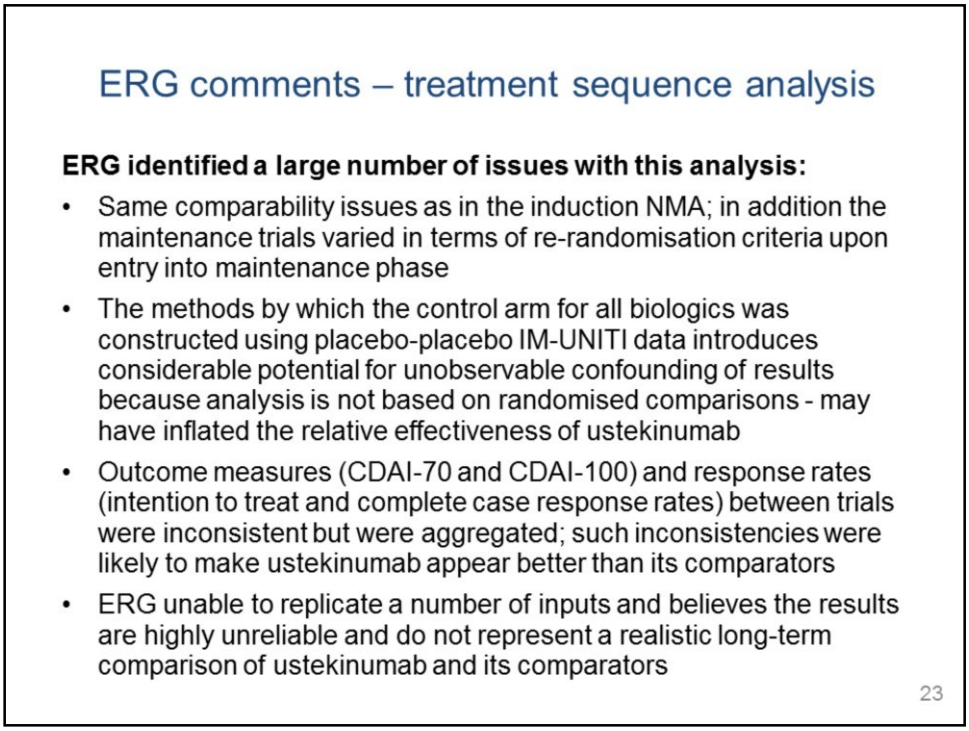
22

For further details see ERG report pages 78 to 86.

The ERG highlighted that assessing response at a later time point in the vedolizumab and ustekinumab trials may make these treatments appear more effective than if they had been assessed at the earlier time point. It also commented that the response to infliximab and adalimumab may have continued to increase over those 2 weeks.

With respect to the conventional care failure population, the ERG expressed concern about differences in previous anti-TNF-alpha treatment history across the trials: a significant proportion of participants in the UNITI-2 trial had a history of anti-TNF-alpha treatment whilst in the other conventional care failure trials all patents were anti-TNF-alpha naïve. With respect to the anti-TNF-alpha failure population there are also differences in the treatment history of the patients recruited. For example, in the GAIN trial, only secondary anti-TNF-alpha failure patients were recruited i.e. patients who had failed an anti-TNF-alpha following initial response. In at least four of the other trials included in the NMA both primary and secondary anti-TNF-alpha failure patients were included.

The ERG reran the NMA in which CERTIFI is included (section 4.6 of the ERG report). The ERG also included the results of this re-analysis into the economic model to consider it impact on the cost-effectiveness of ustekinumab (section 6 of the ERG report).



Further detail is presented on pages 83 to 86 of the ERG report.

The ERG has several concerns regarding the comparability of the trials include in the treatment sequence NMA. Most of these are those of the induction phase trials detailed in the last slide: the length of induction phase follow-up period and the types of anti-TNF-alpha patients they enrolled. In addition, the maintenance trials varied in terms of re-randomisation criteria: the adalimumab (CHARM), infliximab (ACCENT I) and vedolizumab (GEMINI II) trials used a CDAI-70 response whilst ustekinumab IM-UNITI trial used CDAI-100 as an inclusion criterion.

A key part of the treatment sequence analysis presented by the company is the reliance on the placebo-placebo UNITI-1, UNITI-2 and IM-UNITI data to provide a control arm for all biologics. The use of the UNITI trials' data in this way has substantial implications. Primarily, it removes the randomised placebo from the maintenance trials of the biologics and replaces them with an historical control. Therefore the analysis is not based on randomised comparisons and there is a risk of confounding due to differences in setting, treatments received and severity of disease. The extent that these differences are prognostic will influence the corresponding performance of the placebo arm and undermine the reliability of the presented treatment sequence analysis. It is very difficult to quantify these differences, but no attempt was

made to adjust for them. The ERG considers that caution should be taken in interpreting the present analyses due to the potential for unobserved confounding. Note this issue does not affect the comparison of ustekinumab and placebo which relies on the randomisation in the relevant induction. In addition, the ERG notes that the placebo response rate was higher in ustekinumab trials than in the trials of TNF-alpha inhibitors, particularly infliximab and adalimumab. Therefore, after adjustment, the placebo rates of the other biologics will be higher than the ustekinumab trials' comparators. This means that in the treatment sequence analysis the effectiveness of the other biologics relative to placebo will be diminished and the relative effectiveness of ustekinumab will be increased.

The ERG note that in the treatment sequence analysis, the type of active treatment response rates utilised in the model were inconsistent (a mixture of CDAI-70) and CDAI-100 (Figure 30 page 131 of the company submission): the CS stated that the induction data were based on the CDAI-70 and the maintenance data were based on CDAI-100 and CDAI≤150. These two data were then aggregated (i.e. response rates multiplied) during the treatment sequence analysis. In addition, when the maintenance placebo response rates for each of the trials were imputed, the induction CDAI scores used were not consistent across the trials (e.g. CDAI-70 for infliximab and CDAI-100 for ustekinumab).

The ERG noted that the type of active treatment response rates utilised in the analysis were not consistent across the trials (see figure 30 page 131 of the company submission). For the adalimumab, infliximab and vedolizumab trials, the ITT response rates were used, whilst for ustekinumab trial the complete case response rates were used; complete cases response rates are generally higher than ITT. This means that the active treatment maintenance phase and the overall active treatment response rates (induction + maintenance) for ustekinumab will be inflated, whilst the rates for the other biologics remain the same.

In the generation of inputs for the treatment sequence NMA, multiple trials of a single biologic were aggregated by simply adding the numbers or proportions of responses of the trials (e.g. simple pooling of UNITI-1 and CERTIFI induction data) prior to doing the NMA. The ERG notes that this approach ignores any heterogeneity between the trials of the same biologic and is methodologically incorrect; data from each of the trials should have been input separately and the overall response rate (or treatment effect) for each of the

biologics should have been estimated by the model.

The resources and time available to the ERG did not permit the ERG to carry a thorough and complete assessment of all of the inputs included in the treatment sequence analysis, but the ERG were able to carry out a limited check on some of the inputs used. This limited quality assurance exercise identified a number of inputs for treatment sequence analysis for TNF failure population which the ERG could not replicate. The ERG found quite significant differences in the rates of response and remission for vedolizumab, ustekinumab and placebo-placebo. Details of all differences between the ERG and company inputs are provided in appendix 10.2 of the ERG report. Given these differences, the ERG considers that the analysis presented by the company may be unreliable.

Key issues: clinical effectiveness

What is the expected positioning of ustekinumab in the treatment pathway?

What is duration of treatment with current biologic therapy in clinical practice, and the expected duration of treatment with ustekinumab?

What does the committee consider to be the relevant comparator for ustekinumab in the conventional care failure population and the TNF failure population?

What is the committee's view of the strength of the clinical evidence for ustekinumab compared with placebo?

- for the conventional care failure population
- for the TNF failure population
- for the induction and maintenance treatment phases

- Are the results of the studies generalisable to the UK clinical setting?

What is the committee's view on the relative efficacy of ustekinumab compared with the other biological treatments?

- how plausible are the results of the company 's NMA for the induction phase and for the treatment sequence analysis?

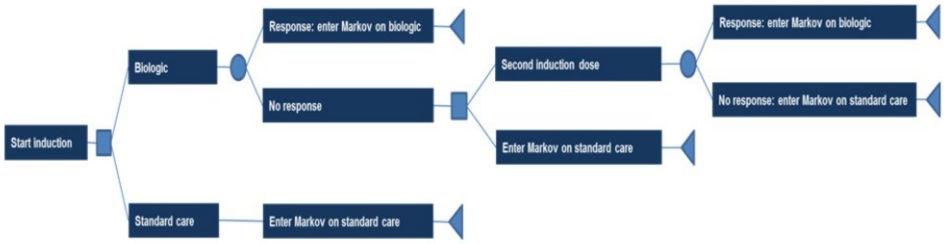
24

Cost effectiveness evidence

Model structure

- Model consists of a short-term induction phase and long-term maintenance phase
- All patients have moderate to severe Crohn's at baseline (CDAI score of 220-600)
- Time horizon: lifetime (60 years); 2-week cycle length; includes a half-cycle correction
- Discounted at 3.5% and uses a NHS and Personal Social Services perspective
- Analyses provided for 2 populations: TNF failure (vs vedolizumab) and conventional care failure (vs TNF-alpha inhibitors)

Induction phase (decision tree)



Source: Figure 40, company's submission

26

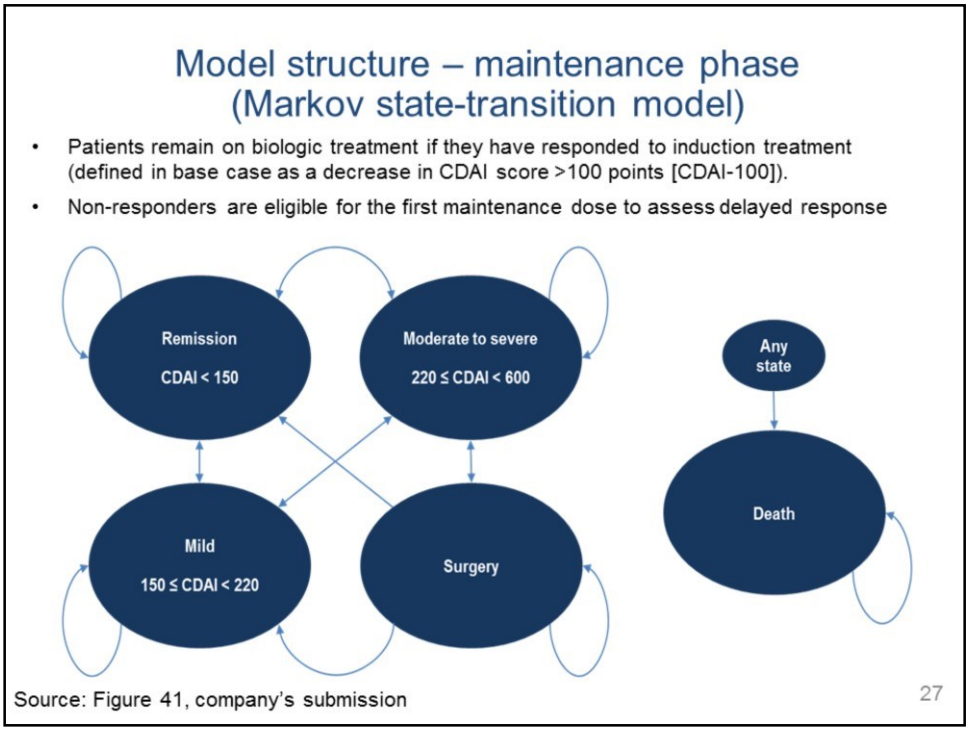
Further background information on the model is presented in section 5.2 of the company submission.

The company reports that the model structure is consistent with the work by Bodger *et al* used in TA 187 (infliximab and adalimumab) and TA 352 (vedolizumab). The population included in the cost-effectiveness analysis is patients with moderate to severe Crohn's disease (defined as a CDAI score of 220–600) at baseline. It should be noted that the inclusion criteria for baseline CDAI score in UNITI-1 and UNITI-2 was 220-450, representing a subset of the modelled population. Analyses are provided for two populations, TNF failure and conventional care failure, defined according to inclusion criteria for the UNITI-1 and UNITI-2 trials, respectively.

Beyond the first year of the model, costs and QALYs are discounted at a rate of 3.5% per annum. A NHS and personal social services (PSS) perspective was taken, in line with the NICE reference case. The company reported that a 2-week cycle length was chosen as a consequence of varying induction lengths; the shorter cycle length allows for more accurate capturing of differences between treatments than a longer cycle length, such as the 8-week cycle length used in TA352. The induction phase lengths, which vary by

treatment, were chosen to best reflect each treatment's label.

TNF-alpha inhibitors are considered as comparators in the conventional care failure population, and it is assumed that if a patient fails a TNF-alpha inhibitor, they would not receive another one as they have the same mechanism of action. The company reports that this is a simplifying assumption as cycling of biologic treatments does exist in clinical practice; however, the company highlights that this assumption was also used within the vedolizumab submission to NICE given the paucity of data. Vedolizumab has been approved by NICE only in patients for whom TNF-alpha inhibitors are not suitable or who have previously failed TNF treatment; hence, vedolizumab is a comparator only in the TNF failure population. Additionally, as of July 2015, NICE approved two infliximab biosimilars, Remsima® and Inflectra®, for the treatment of Crohn's Disease. In the absence of evidence for biosimilars in Crohn's disease, infliximab biosimilars are assumed to have equal efficacy to Remicade®. Infliximab biosimilars are only considered in sensitivity analyses due to lack of data for CDAI-100, the primary efficacy endpoint of the UNITI trial programme and the measure of response to treatment used in the base case economic analysis.

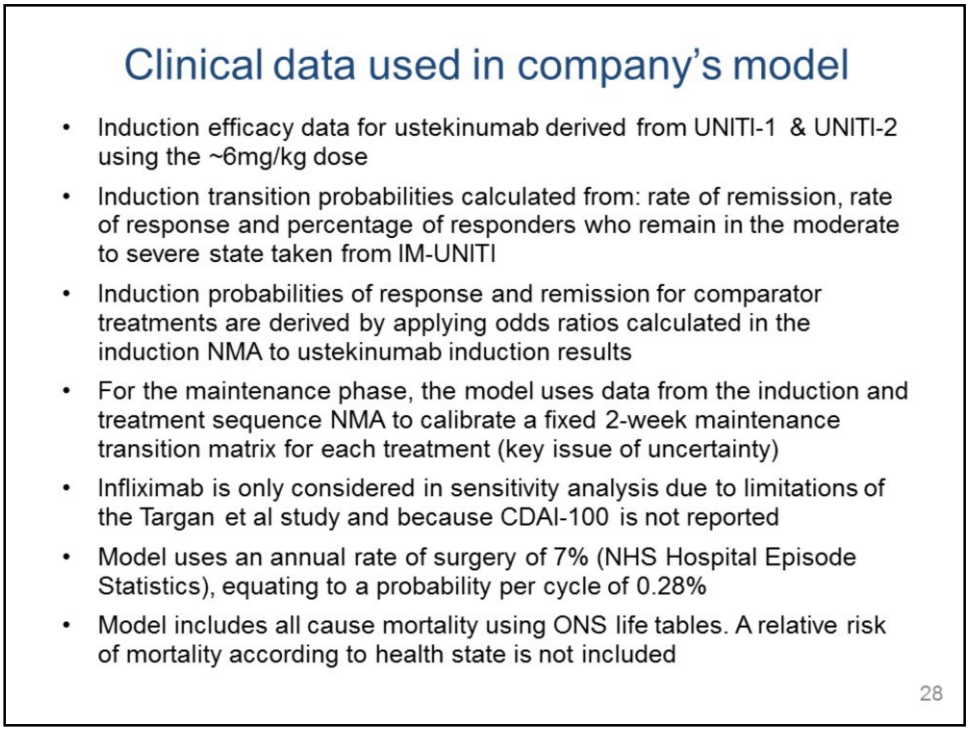


Non-responders in the induction phase switch to conventional care at the start of the maintenance phase or after the first maintenance dose where applicable. Non-responders who switch to conventional care are assumed to follow the same prognosis as those who enter the model on conventional care; the company reports that this is consistent with the work by Bodger *et al.* and in TA352 of vedolizumab. Patients who enter the model on conventional care continue to receive conventional care in the maintenance phase.

Patients enter the maintenance phase in health states dependent on their level of response to treatment in the induction phase and then move between the health states according to the transition probabilities of the treatment they are currently on.

In the base case, all patients on biologic therapies are assumed to have a maximum treatment period of 1 year, after which all patients are assumed to switch to conventional care; the company reports that this is consistent with the work by Bodger *et al.* and the final appraisal determination in TA352. The treatment length has been adjusted to 2 and 3 years in scenario analyses to examine the sensitivity of this assumption. After biologic treatment, patients are assumed to remain on conventional care until either the end of the

modelled time horizon or death.



Further information on the clinical data used in the model can be found in section 5.3.2 of the company submission.

The induction period uses a patient-weight-based dose of ustekinumab (approximately equivalent to 6mg/kg), delivered intravenously at baseline. For the maintenance phase, ustekinumab is delivered as a 90mg subcutaneous injection every 8 or 12 weeks. The base case assumes that 86% of patients in the conventional care failure population and 77% of patients in the TNF failure population start on the lower dose. Dosing regimens for infliximab, adalimumab and vedolizumab are assumed to be in line with their marketing authorisations and the model assumes that all patients start on the lowest dose.

Patient baseline characteristics for mean age, gender and weight, and proportions of patients in each weight category (for ustekinumab induction dosing), are based on mean values from pooled data taken from the UNITI-1 and UNITI-2 clinical study reports for the TNF failure and conventional care failure populations, respectively.

Following the treatment period (1 year in the base case) the biologic

maintenance phase ends and patients are switched to conventional care, on which they continue for the duration of the model (60 years in the base case) unless death occurs.

The company reported several limitations of the Targan *et al*. study, used for infliximab. Due to uncertainty stemming from this, and that the base case analysis uses CDAI-100 which is not reported for infliximab, infliximab is only considered in sensitivity analysis.

Efficacy inputs for delayed responders (i.e. patients who respond after the first maintenance dose) are taken from the clinical study reports and trial publications for ustekinumab and vedolizumab and from a conference abstract by Panaccione *et al. for adalimumab.* There is a lack of data for CDAI-70 response criteria; therefore, for all treatments, it is assumed that the proportion of patients achieving a CDAI-70 response is equal to the proportion of patients achieving a CDAI-100 response.

Rates of all-cause mortality were taken from the Office for National Statistics (ONS) life tables for England and Wales, 2012–2014. The company reported that a leading clinician in Crohn's disease confirmed that patients with Crohn's disease should not expect any differential mortality compared to the general population. Therefore, the model considers only all-cause mortality.

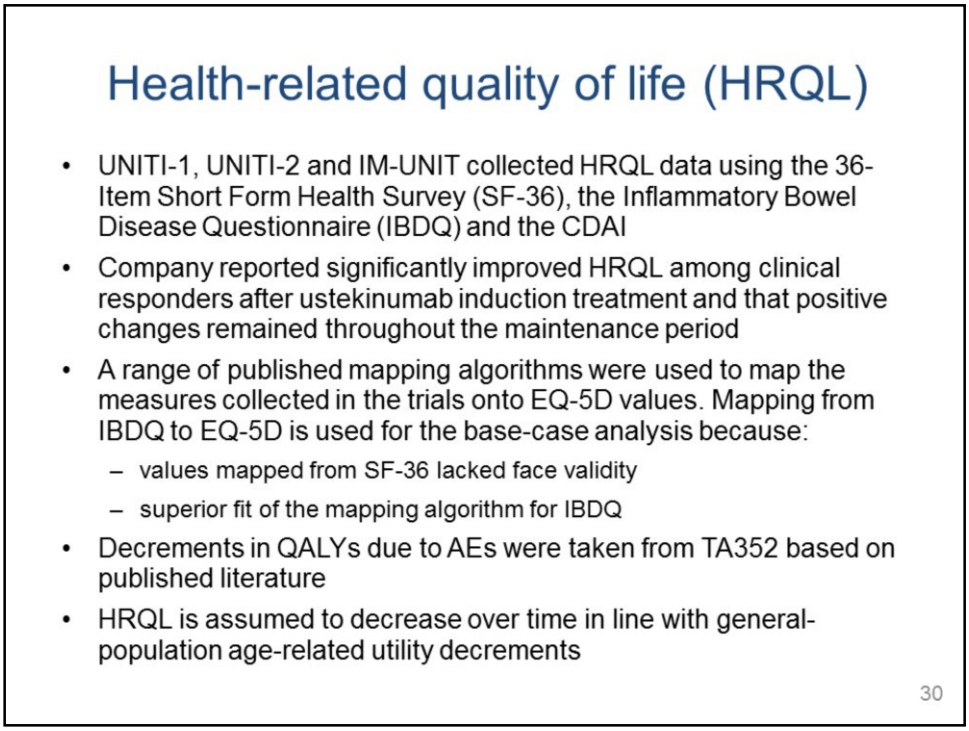
The cycle probability of patients discontinuing biologic treatment during the maintenance phase due to a lack of efficacy is built into the model. This was done using patient data from the maintenance trials of both ustekinumab (IM-UNITI) and comparators (ACCENT I for infliximab and GEMINI II for vedolizumab). Due to a lack of available data, adalimumab is assumed to have the same rate as infliximab as both share the same mode of action. Combined cycle probabilities for ustekinumab and vedolizumab are calculated using the proportion of the patients on the higher or lower dose of the treatment. The combined rate for infliximab is taken directly from the ACCENT I trial.

Adverse events and surgical complications

- AEs included in the model were based on expert clinical opinion and were: serious infection, tuberculosis, hypersensitivity, injection site reactions and lymphoma
- Individual AEs were extracted from the study publications as not reported in the NMA
- The rates for placebo were calculated as a weighted average of the placebo rates from all trials
- Rates were converted into a cycle rate using the exponential formula, taking into account the duration of each study
- Impact of assuming no effect of AEs is tested in scenario analyses
- Rates of surgical complications (wound infection, prolonged ileus/bowel obstruction, intra-abdominal abscess, anastomotic leak) were estimated from published sources and assumed to affect costs but not health-related quality of life

29

Further information on the adverse events and surgical complications incorporated in the model can be found in section 5.3.5 of the company submission.



Further information on health-related quality of life (HRQL) data incorporated in the model can be found in section 5.4 of the company submission.

The company reported that the EQ-5D utility values mapped from SF-36 were much lower than the EQ-5D utility values mapped from IBDQ and CDAI scores and those published in the work by Bodger *et al*. The EQ-5D utility values mapped from SF-36 further lack face validity compared with the UK population norms; the utility for patients in remission (0.54) is much lower than for those aged 75+ (0.73). Given this, the EQ-5D utility values mapped from SF-36 were not considered appropriate for use within the cost-effectiveness model. The EQ-5D utility values mapped from IBDQ and CDAI scores gave similar results to each other and both sets of results compare reasonably with the utility values presented by Bodger *et al*. Both of the mapping algorithms used were identified from the study by Buxton *et al.*; this study demonstrated that there is stronger correlation between IBDQ and EQ-5D (spearman correlation coefficient 0.76) than between CDAI and EQ-5D (spearman correlation coefficient -0.62) and that the fit of the mapping algorithm is superior for IBDQ compared with CDAI (R-squared of 0.45 versus 0.29). Given this and the similarity of results between using IBDQ and CDAI scores to map EQ-5D, the mapping from IBDQ to EQ-5D is preferred by the company for the base-case analysis. The ERG commented that, in addition to being a composite of items,

the IBDQ is a tool which is prone to recall bias as participants may not accurately remember their historical health status indicators.

Utility values used in company's model

Health state	Utility value*
Remission	0.800
Mild	0.680
Moderate to severe	0.550
Surgery	As for moderate to severe

*Mapped from the Inflammatory Bowel Disease Questionnaire (IBDQ) to EQ-5D

Decrements in QALYs due to adverse events*	
Serious infection	-0.52
Tuberculosis	-0.55
Malignancy (lymphoma)	-0.195
Acute hypersensitivity reactions	-0.11
Skin site reactions	-0.03

*Taken from TA352 based on published literature

31

A summary of the health-related quality-of-life data used in cost-effectiveness analysis is given in section 5.4.5 of the company submission. The tables in the slide are adapted from Table 52 of the company submission.

For the surgery health state, no trial-based utility values were available. To be able to incorporate a utility for the surgery health state in the base case, the same assumptions were used as in Bodger *et al.* whereby for 8 weeks in the surgery health state, it is assumed the first 2 weeks are spent with a utility equal to that of the moderate to severe health state, followed by 6 weeks of utility equal to the remission health state.

Scenario analyses are conducted in the model to test the impact of using CDAI mapping and of using health state utility values taken from Bodger *et al.* (shown in Table 47 of the company submission).

Company's base case deterministic results*

Conventional care failure population	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Ustekinumab	263,053	13.08	-	-	-
Conventional care	278,542	12.68	15,489	-0.4003	Dominated
Adalimumab	283,762	12.94	20,709	-0.1393	Dominated

TNF failure population	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Ustekinumab	288,088	12.98	-		
Conventional care	294,600	12.76	6,512	-0.2241	Dominated
Vedolizumab	302,820	12.85	14,732	-0.1345	Dominated

Tables 46 and 47, company response to clarification
*Ustekinumab also dominates other treatment options in the probabilistic analysis

32

Further detail on the company's base case can be found in the company submission, section 5.7. Some errors were identified by the company in tables 65 and 66 of the company submission. Updated results are provided in the company's response to clarification, tables 46 and 47.

Base-case results are presented for both the conventional care failure and TNF failure populations. Results are shown for the CDAI-100 response criteria and using list prices for all comparators. Vedolizumab has a confidential patient access scheme (PAS), and biosimilar prices are variable; however, as the PAS is confidential, the company has used list prices for all comparators.

The base case results show that ustekinumab dominates other treatments in both populations, that is, it has lower costs and greater QALYs. Influximab is not included in company base case analysis due to lack of CDAI-100 induction data. The conclusions of the probabilistic results are similar to the deterministic results with both analyses indicating that ustekinumab dominates other treatment options in both populations.

The company presents cost-effectiveness acceptability curves in section 5.8.1.4 of its submission. The results indicate that, at £30,000 per QALY

gained, ustekinumab has a 100% chance of being the most cost-effective treatment available in both the conventional care failure and TNF failure populations.

The company also presented deterministic sensitivity analysis (see section 5.8.2 of the company submission). The variables that had the biggest impact on results were duration of biologic treatment, several resource use frequencies for the moderate to severe health state, and induction efficacy. In addition, the company presented a series of scenario analyses (see section 5.8.3 of its submission). The company reported that most scenarios tested did not affect the incremental cost-effectiveness decision. Using the original health state costs from TA352 (from Bodger et al. 2009) resulted in ICERS for ustekinumab versus conventional care of £4,433 and £14,001 for the conventional care failure and TNF failure populations, respectively. The company reported that use of a 2-year and 3-year treatment duration for biologic therapy did not affect the decision for the conventional care population, but gave ICERs versus conventional care of £440 and £25,459, respectively, for the TNF failure population. Using IM-UNITI transition probabilities resulted in ICERs for ustekinumab versus conventional care of £56,516 and £59,956 for the same populations, respectively. The company reports that this scenario should be interpreted with extreme caution; the IM-UNITI placebo arm, which portrays conventional care in this scenario, is not a true placebo arm as patients had previously received and responded to ustekinumab in the induction phase and were then randomised to placebo in the maintenance phase. The effect of ustekinumab induction coupled with longer half-life could potentially explain a smaller difference in efficacy between ustekinumab and conventional care which can be reflected in the increased ICERs.

The company considered that a cost-minimisation approach may be more appropriate, as the ICER is subject to large differences in the sensitivity analysis due to the small QALY gains in the base case results. A cost-minimisation analysis was conducted, using only the acquisition and administration costs of each biologic treatment (derived directly from the cost-effectiveness model). Costs of health states and adverse events were excluded as under a cost-minimisation analysis, the biologic treatments are assumed to have equal efficacy and comparable safety profiles. The company excluded conventional care because biologic treatments and conventional care cannot be assumed to have equal efficacy.

The company reported that the results of the cost-minimisation analysis indicate that ustekinumab is cost-saving versus other biologic treatments for the conventional care failure and TNF failure populations, respectively, based on the list prices of the drugs (more detail is given in section 5.8.3.2 of the company submission).

Company's scenario analysis – including infliximab (using CDAI-100 induction data and assuming equal efficacy for adalimumab and infliximab)

Conventional care failure population	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Ustekinumab	263,053	13.0501	-	-	-
Conventional care	278,542	12.6500	15,489	-0.4001	Dominated
Infliximab – Inflectra	278,693	12.8208	15,640	-0.2292	Dominated
Infliximab – Remsima	278,693	12.8208	15,640	-0.2292	Dominated
Infliximab – Remicade	279,698	12.8208	16,645	-0.2292	Dominated
Adalimumab	283,762	12.9022	20,709	-0.1479	Dominated

Table 67, company submission

33

Further detail on the company's scenario analysis including infliximab can be found in the company submission, section 5.7.1.1. The table in the slide is adapted from table 67 in the company submission.

As previously noted, infliximab is not included in the company's base case due to lack of CDAI-100 induction efficacy data. However, it is included as a scenario analysis using the CDAI-100 outcome and assuming equal efficacy for adalimumab and infliximab. In this scenario ustekinumab continues to Dom-dinate the other treatment options.

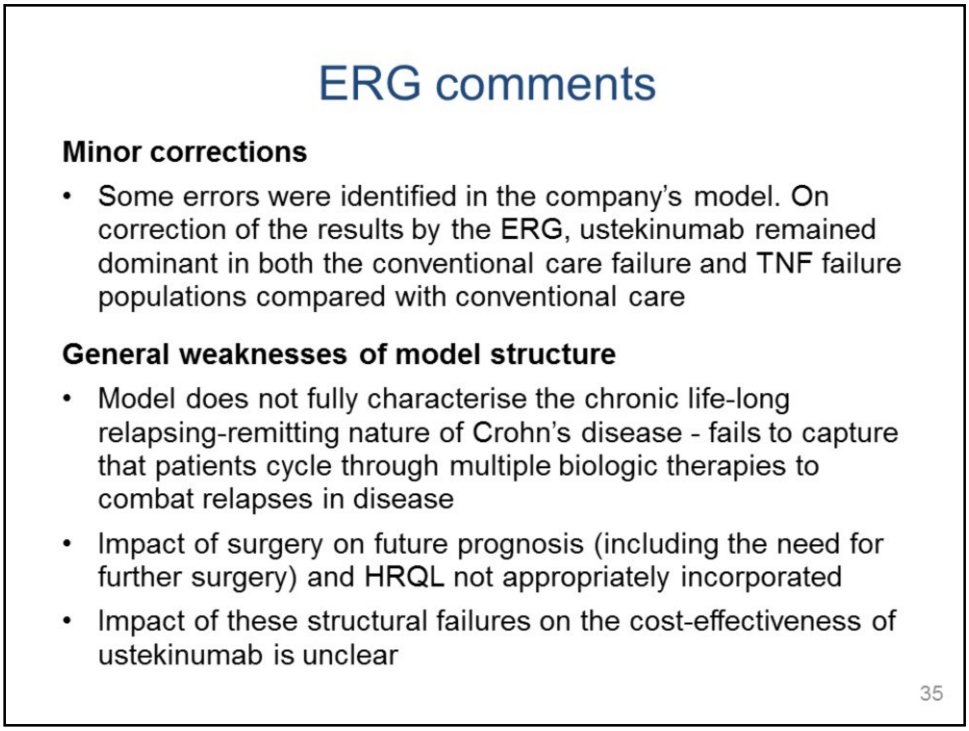
Company's scenario analysis – including infliximab (using CDAI-70 induction data)

Conventional care failure population	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER
Ustekinumab	264,420	13.0285			
Infliximab – Inflectra	264,476	13.1388	56	0.1103	£504
Infliximab – Remsima	264,476	13.1388	0	0.0000	Dominated
Infliximab – Remicade	265,930	13.1388	1454	0.0000	Dominated
Conventional care	278,219	12.6555	13,743	-0.4833	Dominated
Adalimumab	286,251	12.8766	21,776	-0.2622	Dominated

Table 68, company submission

34

Infliximab is included in a second scenario analysis using the CDAI-70 outcome. In this scenario, Inflectra is the most cost-effective treatment option. However, the company highlights that these results should be interpreted with caution given the limitations of the NMA outcomes for infliximab noted previously. The table in the slide is adapted from table 68 in the company submission.



Further details on the ERG's summary and critique of company's submitted economic evaluation are presented in section 5.2 of the ERG report (from page 96).

Corrections

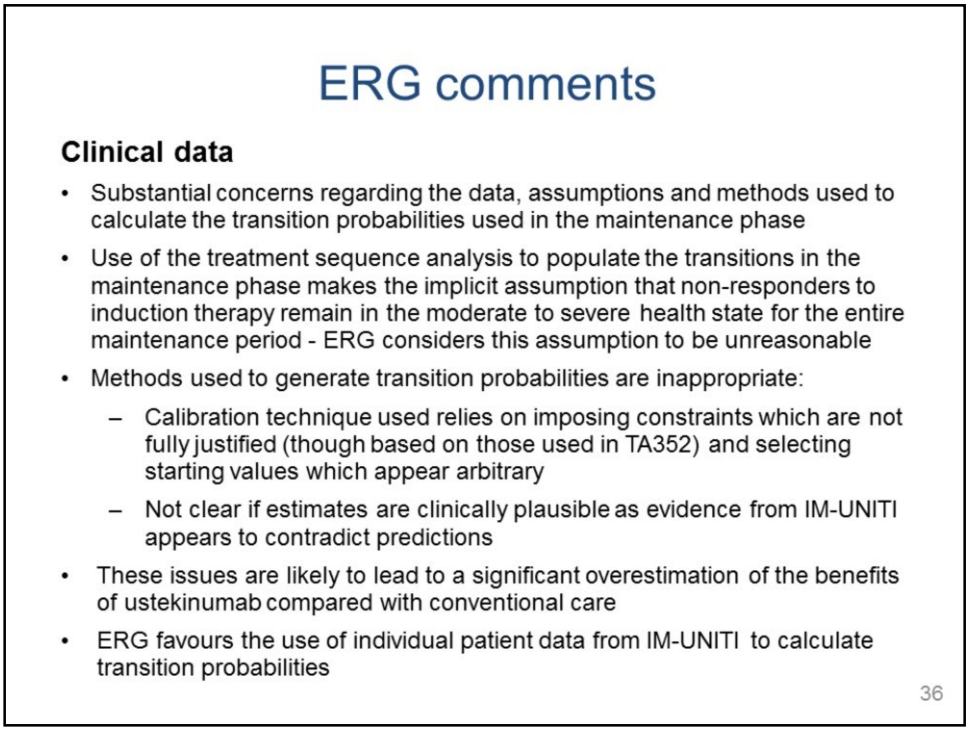
The ERG report states that the original economic model was corrected by company and also by the ERG during the clarification process. The ERG made further corrections after the clarification process. Details of the all errors are presented in section 5.2.12 of the ERG report. The results of the ERG's corrections to the company's base-case model are presented in Table 85 and Table 86 for the conventional care failure and TNF failure population, respectively. The results show very small differences in total QALYs after the correction and a small increase in total costs for all treatments, resulting in small increase in ICERs for all active treatments relative to conventional care in both population. Ustekinumab remains dominant in both conventional care failure and TNF failure populations.

Model structure

The ERG stated the model does not account for the fact that Crohn's disease is a relapsing condition. Biologic therapies do not represent a cure for Crohn's

and it is not thought that they fundamentally alter the course of the disease. As such, the aim of treatment with biologic therapies including ustekinumab is to induce and ideally maintain remission. If patients discontinue treatment, loss of remission is, however, considered to be inevitable and follow up therapy will be necessary at some time for all patients. Even on treatment, eventual loss of response is likely. As such it is common for patients to cycle through multiple biologic therapies as needed to combat relapses in disease. The model fails to capture these dynamics of Crohn's disease and the need for additional lines of therapy.

The ERG also stated that the model structure does not recognise that patients who receive surgery are likely to have a quite different prognosis and treatment pathway to patients receiving drug therapy. Specifically, the model while allowing for multiple surgeries over a patient's life-time does not consider the impact of surgery on the prospect of receiving future surgery or the long-term impact of surgery on HRQoL, for example where surgery involves resection (removal of inflamed area of the intestine). The ERG acknowledged that the company attempted to incorporate post-surgical remission health states into the model structure, but found that the data available to populate the transition probabilities produced unrealistic results.



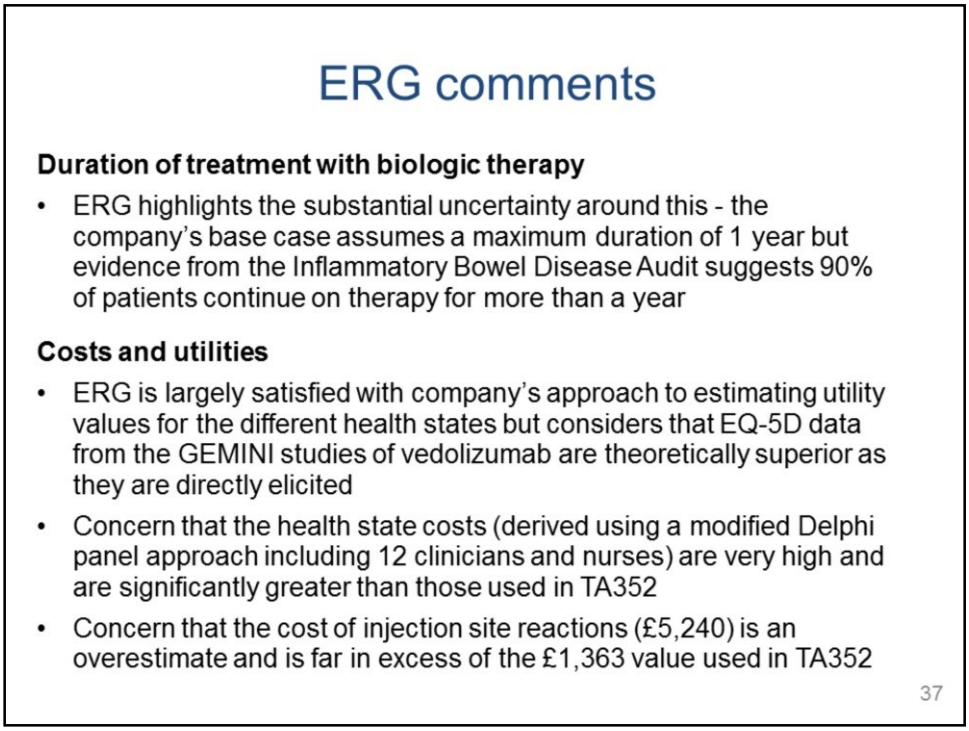
The ERG's concerns about the transition probabilities used in the maintenance phase are discussed on pages 114 to 18 of the ERG report.

The ERG commented that there is no reason to believe that non-responders to induction therapy remain in the moderate to severe health state for the entire maintenance period as patients will often spontaneously improve even while only receiving conventional care, as observed in the placebo arms of the induction trials. The impact of this implicit assumption is that it underestimates the likelihood that patients who are in the moderate to severe health state at the end of induction will move either to mild or remission health states during the course of the maintenance phase. During the maintenance phase this assumption will likely favour conventional care as we may expect that the carry over effects of biological induction therapy would mean relatively more moderate to severe patients would achieve response or remission. However, in the long-term the implications of this assumption are likely to favour biologic therapies as the conventional care transition probabilities are applied for the majority of periods in the model. If the conventional care transition probabilities underestimate the likelihood of moderate to severe patients moving to the mild or remission health states it acts to trap patients who fail to respond to treatment induction ensuring that they are very likely to remain in the moderate to severe health state. This will favour treatments with fewer patients in the

moderate to severe health state at the end of the maintenance phase and will overestimate their effectiveness i.e. biologic therapies. The ERG highlights that the impact of this assumption is potentially very significant and undermines the transition probabilities calculated by the company. It also states that data on the post-treatment outcomes of non-responders is very limited and there is no way to use the treatment sequence analysis in a way that avoids this issue.

The ERG commented that the use of a calibration technique to estimate the transition probabilities of patients in the maintenance phase of the model relies on imposing a series of constraints and selecting a series of starting values. The Excel solver function is then used to estimate transition probabilities that fit with the limited clinical data available. The constraints implied in this process are however, only partially justified, though based on those used in TA352, and the starting values are entirely arbitrary. Both the constraints imposed and starting values have a considerable impact on the estimated transition probabilities and as consequence the estimated cost-effectiveness of ustekinumab.

The ERG noted that the clinical evidence contradicts the predictions made by the transition probabilities. Data from the company submission suggest that approximately 60% of ustekinumab patients who achieve remission will retain that remission over the maintenance period. The estimated transition probabilities, however predict that over 90% will retain remission. The transition probabilities for conventional care patients are applied for a large proportion of the model time horizon and therefore have a very substantial influence on the results of the model. The calculated transition probabilities tends to overestimate the likelihood of staying in remission and staying in the moderate to severe health state. This tends to favour treatments in which patients do better in the first year as it extends the benefits of treatment into the future as patients are assumed to hold remission for a long time following discontinuation of treatment. This has a very significant impact on the ICER and will mean that the model drastically overestimates the benefits of biologic therapy.



Duration of treatment with biologic therapy (page 118 of the ERG report)

The ERG report highlights that, while the company's base-case analysis assumes a maximum duration of biologic treatment of 1 year, there is considerable evidence to suggest that in practice patients receive biologic treatment for a longer period of time. Acknowledging this issue the company present scenario analysis considering longer maximum durations of treatment. There is, however, no clinical data supporting the long-term effectiveness of biologic therapies. The company's model therefore assumes that patients transition using the same transition probabilities as were used in the maintenance period. This is likely to overestimate the effectiveness of biologic therapies as it is common for patients to lose response to therapy over time, for example due to the development of anti-bodies that prevent the drugs from working properly. These scenario analyses are therefore likely to overestimate the benefits of biologic therapy relative to conventional care.

Utilities (pages 126 to 131 of the ERG report)

The estimated utility values in the GEMINI studies were elicited directly from the EQ5D using pooled data from the GEMINI II and GEMINI III studies. The utility values from the GEMINI studies are, however, similar to those used in the company's base-case and therefore it is not expected to impact on

estimated QALYs greatly.

Costs (pages 135 to 139 of the ERG report)

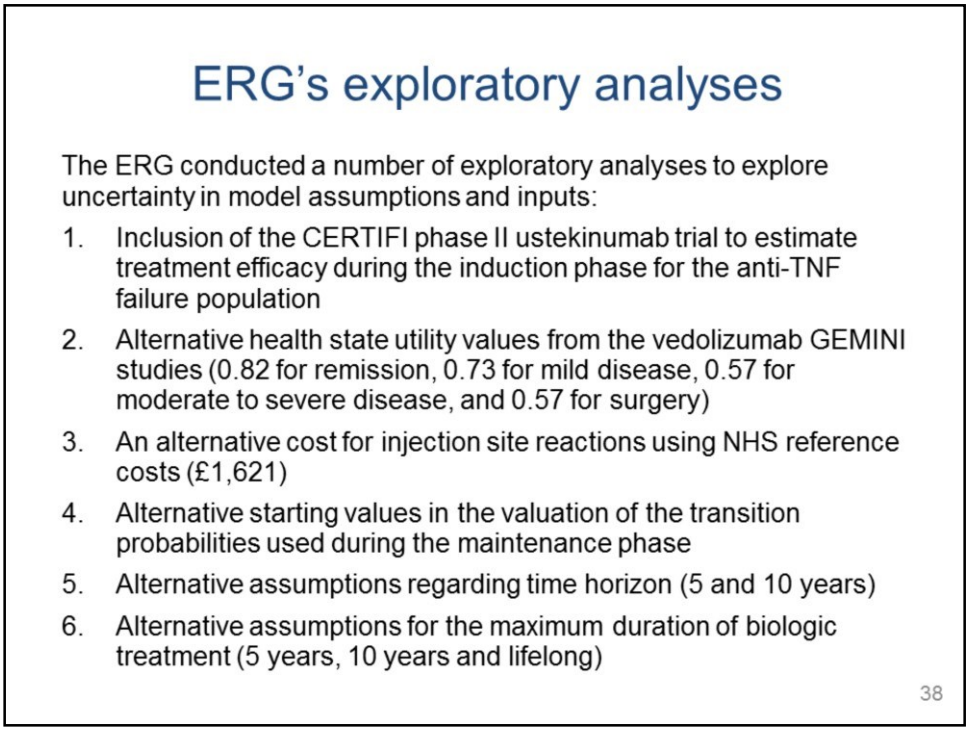
The health state costs associated with Crohn's disease included in the model were estimated based on an elicitation exercise of 12 clinicians. Details of the specific process used is presented in the company submission on pages 207 to 208. The resulting health state costs are summarised in Table 66 of the ERG report. The company also included scenario analyses based on the values from Bodger et al. 2009 (derived from a sample of 160 patients) used in TA352 (summarised in Table 67 of the ERG report). The ERG has no specific concerns about the process used to generate the health state costs, but does not consider them to be superior to those used in the ACD response of TA352 which were based on a survey of clinicians and nurses. Furthermore, the ERG notes that they are substantially higher than estimated in a number of recent costing studies. For example, a recent study looking at the cost associated with care of 100 patients before and after receiving infliximab estimated mean annual non-treatment costs prior to the initiation of infliximab to be £4,965 and post to be £2,214. This compares with estimated mean monitoring costs in the first year of the company's model (conventional care failure population) of £12,226 for convention care patients and £9,742 for infliximab patients. Another UK costing study of 72 matched patients compared the cost-effectiveness of adalimumab and infliximab. This study estimated annual non-treatment costs to be £3,103 for adalimumab and £1,724 for infliximab both substantially lower values than the predicted by the company's economic model.

The ERG has some concerns regarding the justification for the use of differential costs for biologic patients. Differential costs were not used in the previous technology appraisals of biologic therapies for Crohn's. Furthermore, advice from the clinical advisor to the ERG suggests that there was no clear reason to expect costs for patients receiving biologic therapy to be significantly different to those for patients receiving conventional care. In addition, the ERG notes that additional surgical costs are included in health state costs such that patients in all health states may undergo surgery independent of the separate surgery health state. The company also included a scenario analysis in their clarification response which excludes these additional surgery costs. The ERG consider this scenario to be more representative than the company's base-case due to the issue of double counting of surgery costs and because the surgery health state accounts for both the HRQoL impact of surgery as well as the costs and is therefore a superior way of accounting for the impact of

surgery.

In summary the ERG considers that the base-case health state costs are likely to overestimate the management and monitoring costs associated with Crohn's disease. The ERG therefore has a preference for the values used in the in TA352 base-case as these health state costs are more in-line with evidence from published UK costing studies.

The ERG considers the cost values used for adverse events to be largely appropriate but is concerned about the value used for injection site reactions. The value used in the company submission is far in excess of the £1,363 value used in TA352 and is likely to be an overestimate. This is unlikely to have a significant impact on the total costs associated with delivering ustekinumab, though may have greater impact on comparator costs particularly adalimumab for which skin reaction are more common. The ERG therefore presents an alternative analysis in Section 6 using more appropriate values from NHS reference costs.



Further detail can be found in the ERG report section 6.3, pages 161 to 172.

1. As previously stated the ERG was not satisfied with the company's justification for excluding CERTIFI trial.

2. The ERG identified an alternative source of utility values from TA352 which used data from GEMINI studies. The utility values were 0.82, 0.73, 0.57 and 0.57 for remission, mild, moderate to severe and surgery health states, respectively.

3. The ERG considered that the estimate of injection site reaction costs for adverse event too high in the company model. The ERG used a value based on a weighted average of the costs of treating skin disorders with and without interventions using NHS reference costs. This gives an alternative cost of treating for injection site reactions of £1621.

4. The ERG has significant concerns regarding the methods used to generate transition probabilities and the potential influence arbitrary starting values have on the transition probabilities generated. To illustrate the influence of

alternative starting values the ERG generated two sets of transition probabilities (based on starting values shown in Table 92 of the ERG report). The two sets of transition probabilities are presented in Appendix 10.2. of the ERG report.

5. The ERG stated that there is considerable uncertainty over the long-term benefits and costs of ustekinumab given the short duration of the clinical effectiveness data available (maximum 52 weeks) and the failure of the model structure to incorporate retreatment. Given this uncertainty, the ERG, considers it worth considering the impact of a shorter time horizon, which effectively imposes the assumption that costs and benefits are the same for the treatment and comparator arms after the time horizon. The ERG therefore presents scenario analysis considering the alternative time horizons of 5 and 10 years.

6. The ERG stated that a large proportion of people continue with biologics treatment beyond one year in current practice. The ERG therefore conducted exploratory analysis to assess the alternative assumption of 5 years, 10 years and lifelong maximum treatment durations for biologic therapy.

ERG's exploratory analyses - results

- Ustekinumab remained dominant or had an ICER lower than £8,200 per QALY gained versus conventional care in all scenarios and for both populations apart from when the duration of biologic treatment was assumed to be 5 years or higher:
  - 5 years: ICER £23,320 in the conventional care failure population and £70,728 in the TNF failure population
  - 10 years or lifelong: all ICERs above £65,000 per QALY
- Ustekinumab dominated other biologic therapies in all scenarios
- Some counterintuitive results: e.g. conventional care more effective (higher QALYs) than anti-TNFs and vedolizumab in some analyses. Shows substantial weakness in the modelling

39

The results of the ERG's exploratory analyses are presented on pages 163 to 173 of the ERG report.

ERG's preferred base case

- The ERG made the following amendments to the company's base-case:
  - Inclusion of CERTIFI to estimate efficacy of ustekinumab during induction phase for TNF failure population
  - Inclusion of alternative utility values from the vedolizumab GEMINI studies
  - Inclusion of an alternative cost of £1,621 applied for injection site reactions (from NHS reference costs)
  - Inclusion of IM-UNITI data to estimate maintenance phase efficacy
  - Health state costs based on those used in the TA352 original submission (from Bodger et al. (2009))
- Analyses assumed a response definition of CDAI-100 and CDAI-70
- Analyses assumed a maximum treatment duration for biologic therapy of 1 year but the ERG also explored the impact of longer maximum treatment durations (resulting in higher ICERs for all biologics vs conventional care)

40

For further details of the ERG's preferred base case, see ERG report section 6.4, pages 173 to 179.

The health state costs from Bodger et al. 2009 are presented in Table 67 of the ERG report: £1,469 for remission, £4,194 for mild disease, and £6,551 for severe disease.

The ERG considers this alternative base-case to be at least as plausible as the company's base-case.

ERG's preferred base case deterministic results: conventional care failure population (CDAI-100)*

Company base case (corrected)				ERG preferred base case			
	Total costs (£)	Total QALY	ICER (£)		Total costs (£)	Total QALY	ICER (£)
Ustekinumab	263,292	13.08	-	Conventional care	107,150	13.11	-
Conventional care	278,542	12.68	Dominated	Ustekinumab	114,670	13.18	109,279
Infliximab-Inflectra	278,730	12.85	Dominated	Infliximab-Inflectra	116,756	13.17	Dominated
Infliximab-Remsima	278,730	12.85	Dominated	Infliximab-Remsima	116,756	13.17	Dominated
Infliximab-Remicade	279,739	12.85	Dominated	Infliximab-Remicade	117,767	13.17	Dominated
Adalimumab	283,714	12.94	Dominated	Adalimumab	119,479	13.19	1,133,179

Table 107 ERG report
*Probabilistic analysis showed ICERs minimally different from deterministic analysis

41

Results in this slide are shown for the conventional care failure population using the CDAI-100 response criteria.

The ICER estimated by the ERG for ustekinumab compared with conventional care is £109,279 per QALY gained. None of the biological treatments are cost effective compared with conventional care.

ERG's preferred base case deterministic results: conventional care failure population (CDAI-70)*

Company base case (corrected)				ERG preferred base case			
	Total costs (£)	Total QALY	ICER (£)		Total costs (£)	Total QALY	ICER (£)
Ustekinumab	263,292	13.08	-	Conventional care	107,097	13.12	-
Conventional care	278,542	12,68	Dominated	Ustekinumab	114,782	13.18	111,878
Infliximab-Inflectra	278,730	12.85	Dominated	Infliximab-Inflectra	120,188	13.19	705,040
Infliximab-Remsima	278,730	12.85	Dominated	Infliximab-Remsima	120,838	13.22	22,466
Infliximab-Remicade	279,739	12.85	Dominated	Infliximab-Remicade	120,838	13.22	Dominated
Adalimumab	283,714	12.94	Dominated	Adalimumab	122,331	13.22	Dominated

Table 107 ERG report

*Probabilistic analysis showed ICERs minimally different from deterministic analysis

42

Results in this slide are shown for the conventional care failure population using the CDAI-70 response criteria. The ICER estimated by the ERG for ustekinumab compared with conventional care is £111,878 per QALY gained.

ERG's preferred base case deterministic results: TNF failure population (CDAI-100)

Company base case (corrected)				ERG preferred base case			
	Total costs (£)	Total QALY	ICER (£)		Total costs (£)	Total QALY	ICER (£)
Ustekinumab	287,780	12.99	-	Conventional care	123,303	12.46	-
Conventional care	294,600	12.76	Dominated	Ustekinumab	129,531	12.52	110,967
Vedolizumab	302,258	12.85	Dominated	Vedolizumab	136,581	12.49	Dominated

Table 108 ERG report
*Probabilistic analysis showed ICERs minimally different from deterministic analysis

43

Results in this slide are shown for the TNF failure population using the CDAI-100 response criteria.

The ICER estimated by the ERG for ustekinumab compared with conventional care is £110,967 per QALY gained. Vedolizumab is dominated by ustekinumab.

ERG's preferred base case deterministic results: TNF failure population (CDAI-70)

Company base case (corrected)				ERG preferred base case			
	Total costs (£)	Total QALY	ICER (£)		Total costs (£)	Total QALY	ICER (£)
Ustekinumab	287,780	12.99	-	Conventional care	123,259	12.46	-
Conventional care	294,600	12.76	Dominated	Ustekinumab	129,792	12.52	110,507
Vedolizumab	302,258	12.85	Dominated	Vedolizumab	137,322	12.49	Dominated

Table 108 ERG report

*Probabilistic analysis showed ICERS minimally different from deterministic analysis

44

Results in this slide are shown for the TNF failure population using the CDAI-70 response criteria.

The ICER estimated by the ERG for ustekinumab compared with conventional care is £110, 507 per QALY gained. Vedolizumab is dominated by ustekinumab.

Innovation and equalities

- The company considers ustekinumab to be innovative because it:
  - is a new biologic treatment option with a distinct mechanism of action
  - addresses a current unmet clinical need by providing an additional treatment option
  - induces and maintains clinical response/remission and thus improves health-related quality of life, while providing a favourable benefit/risk profile
  - has a reduced administration burden compared to current biologic treatment options (less frequent dosing, maintenance therapy is administered in the home setting). The positive impact this can have on minimising the interruption of patients' daily living, including work activities, may not be fully captured in the cost-effectiveness modelling
  - minimises periods of high disease activity, which could have a positive impact on economic loss associated with absence from work and/or reduced work productivity
- The company did not identify any potential equality issues

45

Further information on the innovative aspects of ustekinumab, as reported by the company, is given in section 2.5 (page 36) of the company submission.

Key issues: cost effectiveness

- The ERG raised concerns about the structure of the company 's model. What is the commi ttee's view of the company 's modelling approach?
- What is the committee 's view of the ICERs estimated by the company and the ERG and their robustness:
  - for the conventional care failure population?
  - for the TNF failure population?
- Which assumptions does the committee consider to be most plausible?
- Does the committee agree with the company that cost minimisation is an appropriate approach?
- Does the committee consider ustekinumab to be an innovative therapy?

Authors

- **Helen Tucker**
- Technical Lead
- **Zoe Charles**

  Technical Adviser
- with input from the Lead Team (Rachel Hobson, Stephen Sharp and Pam Rees)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ustekinumab within its marketing authorisation for treating moderately to severely active Crohn's disease in people who are intolerant of, or whose disease has not responded or is resistant to either conventional therapy or a tumour necrosis factor-alpha inhibitor.

Background

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract (gut) that may affect any part of the gut from the mouth to the anus. People with Crohn's disease have recurrent attacks, with acute exacerbations ('flares') in between periods of remission or less active disease. These flares may affect any part of the gut and are defined by location (terminal ileal, colonic, ileocolic, upper gastrointestinal), or by the pattern of the disease (inflammatory, fistulising, or stricturing).

The clinical features of Crohn's disease are variable and are determined partly by the site of the disease. Common symptoms include diarrhoea, abdominal pain, extreme tiredness, unintended weight loss and blood and mucus in stools. Less common symptoms include fever, nausea, vomiting, arthritis, inflammation and irritation of the eyes, mouth ulcers and areas of painful, red and swollen skin.

Crohn's disease can be complicated by the development of strictures (a narrowing of the intestine), obstructions, fistulae and perianal disease. Other complications include acute dilation, perforation and massive haemorrhage, and carcinoma of the small bowel or colon.

There are currently at least 115,000 people in the UK with Crohn's disease.[1] The incidence of Crohn's disease is greatest in people aged between 16 and 30 years. However, it may affect people of any age.[2]

Crohn's disease is not medically or surgically curable. Treatment aims to control manifestations of Crohn's disease to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects. Clinical management depends on disease activity, site, behaviour of disease, response to previous treatments, side-effect profiles of treatments and extra-intestinal manifestations, such as uveitis and arthritis.

NICE clinical guideline 152 recommends monotherapy with a corticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. Budesonide or 5-aminosalicylates are considered for some people who decline, cannot tolerate or in whom a conventional corticosteroid is contraindicated. When 2 or more inflammatory exacerbations are experienced in a 12-month period, azathioprine, mercaptopurine and methotrexate may be considered as add-on treatments to conventional corticosteroids or budesonide to induce remission of Crohn's disease.

NICE technology appraisal 187 recommends infliximab and adalimumab as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. At the time of NICE technology appraisal 187, marketing authorisations for infliximab and adalimumab did not include treating adults with moderately active Crohn's disease and so moderately active disease is not covered by that guidance. The marketing authorisations for infliximab and adalimumab have subsequently been expanded to include treating people with both moderately and severely active disease that has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments).

NICE technology appraisal 352 recommends vedolizumab as an option for treating moderately to severely active Crohn's disease if a tumour necrosis factor‑alpha inhibitor has failed, cannot be tolerated or is contraindicated.

In addition to pharmacological treatment, between 50 and 80% of people with Crohn's disease will require surgery during the course of their disease. The main reasons for surgery are strictures causing obstructive symptoms, lack of response to medical therapy, and complications such as fistulae and perianal disease.

The technology

Ustekinumab (Stelara, Janssen) is a humanised IgG_1 monoclonal antibody derived from a newly engineered cell line. It is targeted against the p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23), which is expressed in certain white blood cells which cause bowel tissue to become inflamed. It is administered by intravenous infusion.

Ustekinumab does not currently have a marketing authorisation in the UK for treating Crohn's disease. However, in September 2016, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending that ustekinumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were

intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Intervention(s)	Ustekinumab
Population(s)	People with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-alpha inhibitor, or who are intolerant to either of them.
Comparators	• Conventional therapy (which can include drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) • Tumour necrosis factor-alpha inhibitors (infliximab and adalimumab) • Vedolizumab
Outcomes	The outcome measures to be considered include: • disease activity (remission, response, relapse) • mucosal healing • surgery • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability and cost of biosimilars should be taken into consideration. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows, the following subgroups may be considered: • People who have not previously received a tumour necrosis factor-alpha inhibitor; • People for whom at least 1 tumour necrosis factor-alpha inhibitor has failed; • People for whom tumour necrosis factor-alpha inhibitors are not suitable because of intolerance or contraindication. • Location of Crohn's disease (Ileal, colonic and perianal)
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (2015). NICE Technology Appraisal 352. Review date August 2018. 'Adalimumab and infliximab for the treatment of Crohn's disease (2010). NICE Technology Appraisal 187. Guidance on static list Related Guidelines: 'Crohn's disease: management' (2012). NICE guideline 152. Review date 2017. Related Interventional Procedures: 'Extracorporeal photopheresis for Crohn's disease' (2009). NICE interventional procedure 288. Related NICE Pathways: Crohn´s disease overview (2012) NICE Pathway http://pathways.nice.org.uk/pathways/crohns-disease
Related National Policy	Department of Health, Manual for Prescribed Specialised Services 2013/14, Jan 2014. Chapter 101 Severe intestinal failure service (adults). https://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf

References

1 Crohn's and Colitis UK (2015) What is Crohn's disease? Accessed October 2015.
2. NHS Choices. (2015) Crohn's disease: Overview. Accessed October 2015.

APPENDIX C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy ID843

Provisional matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Janssen (ustekinumab) Patient/carer groups • Colostomy Association • Crohn's and Colitis UK • For Crohns • IA: Ileostomy and Internal Pouch Support Group • Muslim Council of Britain • Ostomy Lifestyle Centre • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Coloproctology of Great Britain and Ireland • Association of Surgeons of Great Britain and Ireland • British Geriatrics Society • British Institute of Radiology • British Society of Gastroenterology • Primary Care Society for Gastroenterology • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons of England • Royal Pharmaceutical Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • AbbVie (adalimumab) • Accord Healthcare UK (methotrexate) • Allergan (azathioprine, prednisolone) • Alliance Pharmaceuticals (prednisolone) • Almirall (balsalazide) • Amdipharm Mercury Company (hydrocortisone, methotrexate) • Aspen Pharma (azathioprine, mercaptopurine) • AstraZeneca UK (budesonide) • Kent Pharmaceuticals (methylprednisolone) • Dr Falk Pharma UK (budesonide) • Ferring Pharmaceuticals (mesalazine) • Focus (prednisolone)

APPENDIX C

Consultees	**Commentators (no right to submit or appeal)**
• Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS England • NHS Leeds West CCG • NHS West London CCG • Welsh Government	• Hameln (methotrexate) • Hospira UK (infliximab, methotrexate) • Interpharm (prednisolone) • Merck Sharp & Dohme (infliximab) • Medac GmbH (methotrexate) • Napp (infliximab) • Nova Laboratories (mercaptopurine) • Orion Pharma UK (methotrexate) • Pfizer (hydrocortisone, methylprednisolone, methotrexate, sulfasalazine) • Rosemont (methotrexate, sulfasalazine) • Sandoz (azathioprine, methotrexate) • Takeda UK (vedolizumab) • Tillotts Pharma (mesalazine) • Warner Chilcott UK (mesalazine) <u>Relevant research groups</u> • Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group • CORE - The Digestive Disorders Foundation • MRC Clinical Trials Unit • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical experts and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland;; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ustekinumab for previously treated moderate to severe active Crohn's disease [ID843]

Company evidence submission

November 2016

File name	Version	Contains confidential information	Date
		Yes	**24 November 2016**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables and figures

1 Executive summary

Ustekinumab (Stelara®) is a human monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin-12 (IL-12) and interleukin-23 (IL-23). It is available as a 45 mg and 90 mg solution for injection in a pre-filled syringe and as a 130 mg concentrate for solution for infusion; it is currently licensed by the European Medicines Agency (EMA) and recommended by NICE as a treatment option for adults with moderate to severe plaque psoriasis (PsO) and active psoriatic arthritis (PsA).

Crohn's disease (CD) is a chronic, progressive inflammatory condition that affects different parts of the gastrointestinal (GI) tract and is clinically characterised by fluctuating periods of high and low disease activity. Disproportionally affecting young adults with age-specific incidence peaking at between 15 to 30 years of age, CD often affects people in their most formative and productive years. In the absence of a cure, management of CD is a life-long requirement and during the course of their disease, patients are faced with numerous choices regarding the best treatment approach. The three most important attributes of medical therapy to CD patients are reported to be achievement of lasting remission, frequency of medical administration, and how quickly the patient achieves therapeutic response.

A pivotal randomised controlled trial (RCT) programme, consisting of two Phase III induction studies (UNITI-1 and UNITI-2), and a follow-on Phase III maintenance study (IM-UNITI) examined and demonstrated the efficacy and safety of ustekinumab for the treatment of moderately to severely active CD across a range of outcomes. Based on the robust RCT results, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 15 September 2016 recommending an extension of ustekinumab's license indication to active CD. Following positive opinion, the European Commission (EC) granted a marketing authorisation on 11 November 2016.

The licensed indication for ustekinumab is anticipated to state that Stelara is indicated *"for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies"*. Differently to previous approved indications,

ustekinumab for CD is to be administered via intravenous (IV) infusion at Week 0 followed by a subcutaneous (SC) injection at Week 8 and then every 12 weeks thereafter (or every 8 weeks in the case of dose escalation). The annual acquisition cost of ustekinumab at list price and based on the licensed dosing is £15,029 in the initial year and, on average, £9,339 p.a. in the following years. [redacted]

Currently, two biologic drugs collectively referred to as tumour necrosis factor (TNF) α inhibitors (infliximab and adalimumab) have marketing authorisations and are recommended by NICE as treatment options for moderately to severely active CD in patients whose disease has not responded to, or who are intolerant of or have contraindications to, conventional therapy. Additionally, vedolizumab, a humanised IgG1 monoclonal antibody against α4β7-Integrin, has a marketing authorisation and is recommended by NICE as a treatment option for moderately to severely active CD in whom a TNFα inhibitor has failed, cannot be tolerated or is contraindicated. Along with non-biologic 'conventional therapy' consisting of corticosteroids and/or immunosuppressants, TNFα inhibitor drugs and vedolizumab are the standard of care for the relevant patient population and are therefore suitable comparators for ustekinumab in this technology appraisal. Considering the chronic and heterogenous nature of CD, this restricted treatment choice represents a considerable unmet medical need. Indeed, many patients do not attain clinical benefit and/or tolerate therapy in current practice, with over 4,000 patients estimated to have failed all available therapies in England. Secondary failure, where patients initially respond to therapy but subsequently lose response, is a particular concern in CD management.

Ustekinumab provides an additional treatment option for patients with moderately to severely active CD with a novel mechanism of action (that may target the underlying condition of CD) that can induce and maintain clinical response/remission and thus improve patient health-related quality of life (HRQL), while providing a favourable benefit/risk profile. Single dose induction through IV infusion induces rapid onset of clinical response/ remission, and SC injection effectively maintains clinical response/remission. Ustekinumab is associated with an extended half-life such that standard dosing during the maintenance phase is recommended every 12 weeks

compared to existing biologics, which require dosing every two to eight weeks. In addition, ustekinumab is available in the form of a pre-filled syringe for SC maintenance dosing and can be administered in the home care setting. This reduces the administrative burden associated with current biologics, two of which require IV administration in the hospital setting. Ustekinumab therefore provides the three most important attributes of medical therapy to CD patients and addresses a current unmet medical need. The significant clinical benefit ustekinumab brings in comparison with existing therapies was recently acknowledged by the CHMP who granted an extended marketing protection period in this new therapeutic indication based on a major contribution to patient care. *"…considering the high number of primary and secondary non response to TNF antagonist therapies in the treatment of Crohn's disease and the different mechanism of action of this compound Stelara is considered to provide both a treatment alternative as well as a response different from other treatments in a substantial part of the targeted population. "*

"In the pivotal induction studies with Stelara clinical response and remission were significant as early as week 3 and continued to improve through week 8. Vedolizumab pivotal trials showed significance for remission at Week 10, however it did not reach significance at the earlier timepoint of Week 6. Lastly vedolizumab require intravenous administration every 8 weeks during maintenance whereas Stelara is administered s.c. with possible self-administration (i.e. no administration in hospital or clinic needed) can be considered to contribute to the significant clinical benefit compared to vedolizumab."

"Thus, overall, it is considered that Stelara provides a significant clinical benefit in comparison with existing therapies based on a major contribution to patient care."

In the UNITI trial programme that provides data up to 2 years, ustekinumab demonstrated a significant improvement in clinical response and remission in patients with moderately to severely active CD who have failed, or are contraindicated to, conventional therapy or TNFα inhibitor therapy versus conventional therapy (represented by a placebo control group with concomitant corticosteroid and/or immunosuppressant drug use). In the induction trials, UNITI-1 and UNITI-2, ustekinumab treated groups achieved significantly greater proportion of CDAI-100 responders than the placebo group. In TNFα inhibitor therapy failure population (UNITI-1) ustekinumab achieved 33.7% (~6 mg/kg) and 34.3% (130 mg)

of patients in response vs 21.5% of placebo; p=0.003 and p=0.002. In conventional care failure population (UNITI-2) ustekinumab achieved 55.5% (~6 mg/kg) and 51.7% (130 mg) of patients in response vs 28.7% of placebo. In the maintenance phase, IM-UNITI, a significantly greater proportion of patients were in clinical remission (CDAI < 150) at 1-year, 48.8% (q12w) and 53.1% (q8w) ustekinumab groups than 35.9% in the placebo group; p=0.040 and p=0.005, respectively. [redacted]

Ustekinumab was also associated with significant improvements in HRQL and was associated with significant improvements in objective measures of inflammation (including serum and faecal biomarkers) and endoscopic response. Importantly, ustekinumab was generally well tolerated, with very low discontinuation rates due to adverse events (AEs) and low rates of serious adverse events (SAEs) reported across trials. The safety profile observed in CD trials was generally in line with that observed in other indications (PsO and PsA), for which 5 years of data registry provide conclusive evidence of the favourable long-term safety profile of ustekinumab.

Due to well-accepted complexities with comparing biologic treatments in a head-to-head trial design, a network meta-analyses (NMA) approach has been adopted to provide comparative efficacy estimates for ustekinumab versus alternative biologics. A series of NMA were performed to investigate induction and maintenance phases of therapy in patients who had failed conventional therapy (conventional care failure subpopulation) or who had failed, or were intolerant to, TNFα inhibitor therapy (TNF failure subpopulation).

In induction phase analysis, the likelihood of being in clinical remission/response was higher with ustekinumab treatment than vedolizumab in the conventional care failure subpopulation, and similar with ustekinumab and vedolizumab treatment in the TNF failure subpopulation; the likelihood was also similar with ustekinumab and adalimumab treatment in both subpopulations. Although infliximab was associated with the highest chance of being in clinical response/remission in induction phase analysis, these results should be interpreted with caution due to several concerns of bias (see Section 1.3). In treatment sequence analysis that combined data from induction and maintenance phases of therapy, the likelihood of being in clinical

remission/response at 1 year was higher with ustekinumab treatment than with adalimumab or vedolizumab in both subpopulations (conventional care failure and TNF failure). Infliximab was associated with the highest chance of being in clinical remission at 1 year in the conventional care subpopulation (data not available for clinical response), but again, results should be interpreted with caution due to concerns of bias.

The economic modelling technique used in previous appraisals for active CD (TA187 and TA352) is a combination of a short-term decision tree and a long-term Markov model. In line with these appraisals, a *de novo* model was developed to estimate the cost effectiveness of ustekinumab versus conventional therapy or TNFα inhibitor therapy in the conventional care failure subpopulation, and the cost effectiveness of ustekinumab versus conventional therapy or vedolizumab in the TNF failure subpopulation. The base-case results indicate that ustekinumab dominates conventional therapy and adalimumab in the conventional care failure subpopulation, and dominates conventional therapy and vedolizumab in the TNF failure subpopulation, obtaining larger QALY gains at a lower cost.

The incremental quality-adjusted life year (QALY) gains in CD tend to be small, ranging between, 0.13 and 0.40; therefore, incremental cost-effectiveness ratios (ICERs) can be rather sensitive to small changes in costs adding to the uncertainty in the results. An alternative and perhaps a better way to assess drugs such as ustekinumab would be to use a cost minimisation analysis versus anti-TNF and vedolizumab, which are similar in efficacy and price. [redacted]

In conclusion, ustekinumab provides a highly effective and cost-effective treatment option for patients living with moderately to severely active CD, which represents a further therapeutic advancement in the CD arena and should be considered a noteworthy step-change for the continued management of this chronic, progressive condition.

1.1 Statement of decision problem

The decision problem addressed in this submission matches that described in the final scope, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-α inhibitor, or who are intolerant to either of them.	People with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-α inhibitor, or who are intolerant to either of them.	Not applicable
Intervention	Ustekinumab	Ustekinumab	Not applicable
Comparator(s)	• Conventional therapy (which can include drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) • Tumour necrosis factor-α inhibitors (infliximab and adalimumab) • Vedolizumab	• Conventional therapy (which can include drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) • Tumour necrosis factor-α inhibitors (infliximab and adalimumab) • Vedolizumab	Not applicable
Outcomes	The outcome measures to be considered include: • disease activity (remission, response, relapse) • mucosal healing • surgery • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • disease activity (remission, response, relapse) • mucosal healing • surgery • adverse effects of treatment • health-related quality of life	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability and cost of biosimilars should be taken into consideration. The availability of any patient access schemes for the intervention or comparator technologies will be considered.	The model estimates cost effectiveness in terms of incremental cost per quality-adjusted life year. The model uses a lifetime time horizon (60 years) as Crohn's disease is a chronic condition and patients are diagnosed at a young age. Costs are considered from an NHS and Personal Social Services perspective. Biosimilars are considered as separate comparators within the economic analysis (scenario analysis only). [redacted] We are not privy to confidential simple patient access schemes and thus we have used list prices for all comparators.	Not applicable
Subgroups to be considered	If evidence allows, the following subgroups may be considered: • People who have not previously received a tumour necrosis factor-α inhibitor • People for whom at least 1 tumour necrosis factor-α inhibitor has failed • People for whom tumour necrosis factor-α inhibitors are not suitable because of intolerance or contraindication • Location of Crohn's disease (ileal, colonic and perianal)	Clinical evidence is provided for the named subgroups as follows: • People who have not previously received a tumour necrosis factor-α inhibitor • People for whom at least 1 tumour necrosis factor-α inhibitor has failed • People for whom tumour necrosis factor-α inhibitors are not suitable because of intolerance or contraindication • Location of Crohn's disease (ileal, colonic and perianal)	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		Subgroups are not considered in the economic model outside of those relevant to treatment decisions in clinical practice; i.e. treatment history in line with the UNITI induction trial criteria which provide data for: • People who have not previously received a tumour necrosis factor-α inhibitor • People for whom at least 1 tumour necrosis factor-α inhibitor has failed • People for whom tumour necrosis factor-α inhibitors are not suitable because of intolerance or contraindication	
Special considerations including issues related to equity or equality	None	None	Not applicable

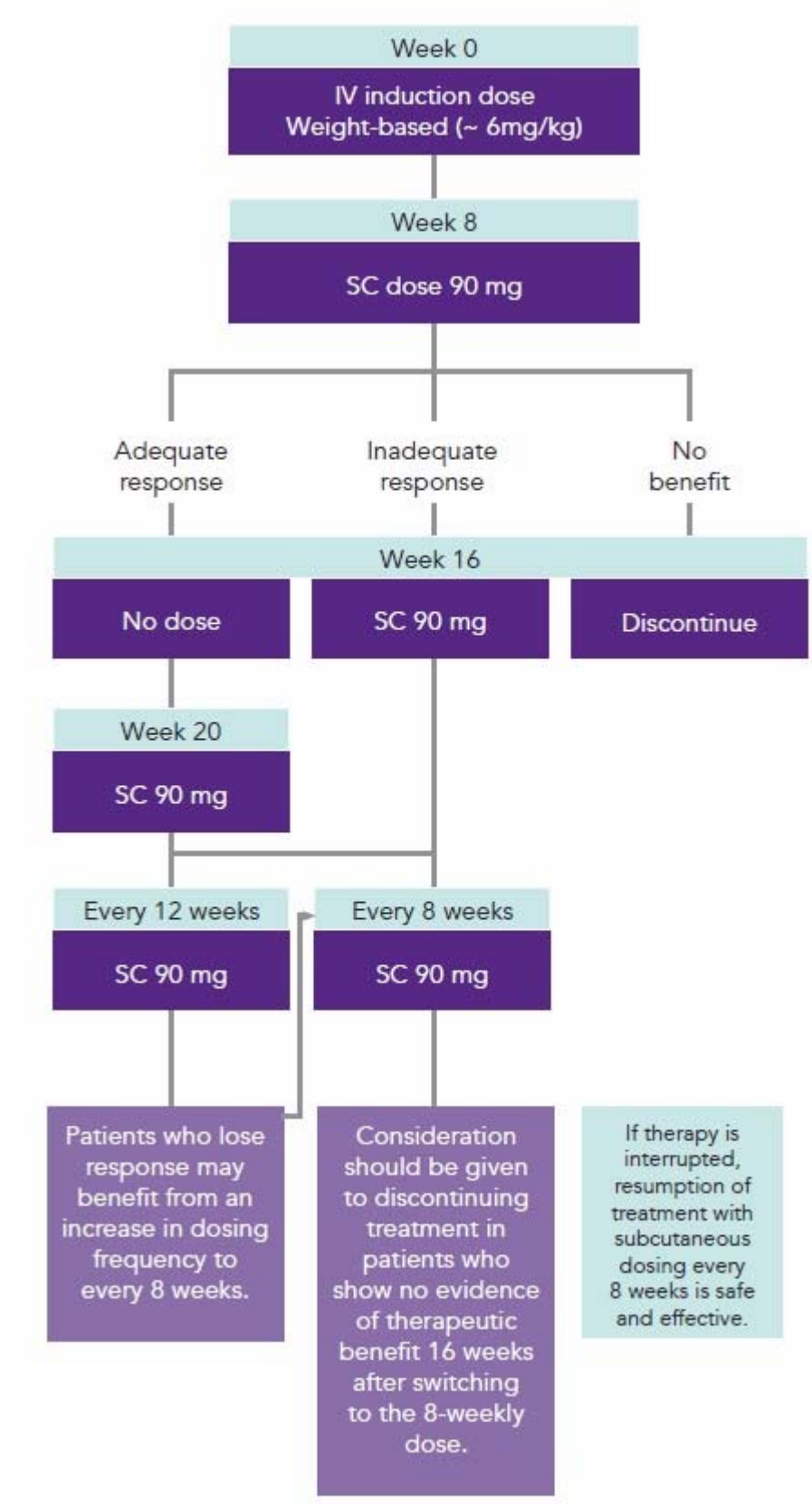
1.2 Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2; the dosing schedule for ustekinumab is depicted in Figure 1.

Table 2: Technology being appraised

<table>
<tr><td>UK approved name</td><td>Ustekinumab</td></tr>
<tr><td>Brand name</td><td>Stelara</td></tr>
<tr><td>Marketing authorisation status</td><td>Positive opinion from the CHMP was received on 15 September 2016.
Marketing authorisation was received on 11 November 2016.</td></tr>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics</td><td>Stelara is indicated “for the treatment of adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies”</td></tr>
<tr><td>Method of administration and dosage</td><td>Induction IV infusion solution is to be composed of the number of vials as specified below, which aligns to a dose of approximately 6mg/kg:
<table>
<tr><th>Body weight</th><th>Dose</th><th>Number of 130mg vials</th></tr>
<tr><td>≤55kg</td><td>260mg</td><td>2</td></tr>
<tr><td>>55kg to ≤85kg</td><td>390mg</td><td>3</td></tr>
<tr><td>>85kg</td><td>520mg</td><td>4</td></tr>
</table>
Maintenance SC injection solution is dosed at 90mg.
All patients should receive an IV induction dose followed by a maintenance SC dose at Week 8. After this, dosing every 12 weeks is recommended.
Patients who have not shown adequate response 8 weeks after the first SC dose (Week 16) may receive a second SC dose at this time.
Patients who lose response on maintenance dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks; patients may subsequently be dosed every 8 or 12 weeks according to clinical judgement.
Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by Week 16 or 16 weeks after switching to the 8-weekly dose.
If therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.</td></tr>
<tr><td colspan="2">Key: CHMP, Committee for Human Medicinal Products; IV, intravenous; SC, subcutaneous.</td></tr>
</table>

Figure 1: Ustekinumab dosing schedule



Key: SC, subcutaneous; IV, intravenous.

1.3 Summary of the clinical effectiveness analysis

A comprehensive clinical trial programme supports the use of ustekinumab for the treatment of patients with moderately to severely active CD, providing data up to 2 years. This clinical trial programme includes three pivotal RCTs that provide evidence of the potential clinical effectiveness of induction and maintenance therapy with ustekinumab in patients that have failed either conventional care and/or TNFα inhibitor therapy (or are contraindicated to TNFα inhibitor therapy). A summary of this trial programme is provided below:

UNITI-1

- Phase III, multicentre, double-blind RCT comparing the clinical efficacy and safety of ustekinumab induction therapy (weight-based dosing equivalent to ~6mg/kg or 130mg) versus placebo in adult patients with moderately to severely active CD who have failed, or are contraindicated to, TNFα inhibitor therapy. Concomitant corticosteroid and/or immunosuppressant drugs were permitted, representing clinical practice and allowing the placebo group to act as a proxy for, and thus provide a comparison to, conventional therapy.
- Primary efficacy endpoint analysis demonstrated that a significantly greater proportion of patients were in clinical response (defined as a 100-point response based on the Crohn's Disease Activity Index [CDAI]) at Week 6 in both the ~6 mg/kg (33.7%) and 130 mg (34.3%) ustekinumab groups than in the placebo group (21.5%); p=0.003 and p=0.002, respectively. Onset of clinical response was rapid, observed as early as Week 3 post induction.
- Secondary efficacy endpoint analysis demonstrated that a significantly greater proportion of patients were in clinical remission (defined as CDAI <150) at Week 8 in both the ~6 mg/kg (20.9%) and 130 mg (15.9%) ustekinumab groups than in the placebo group (7.3%); p<0.001 and p=0.003, respectively.

UNITI-2

- Phase III, multicentre, double-blind RCT comparing the clinical efficacy and safety of ustekinumab induction therapy (weight-based dosing equivalent to ~6mg/kg or 130mg) versus placebo in adult patients with moderately to

severely active CD who have failed conventional therapy. Concomitant corticosteroid and/or immunosuppressant drugs were permitted, representing clinical practice and allowing the placebo group to act as a proxy for, and thus provide a comparison to, conventional therapy.

- Primary efficacy endpoint analysis demonstrated that a significantly greater proportion of patients were in clinical response (defined as a 100-point response based on the CDAI) at Week 6 in both the ~6 mg/kg (55.5%) and 130 mg (51.7%) ustekinumab groups than in the placebo group (28.7%); p<0.001 for both comparisons. Onset of clinical response was rapid, observed as early as Week 3 post induction.
- Secondary efficacy endpoint analysis demonstrated that a significantly greater proportion of patients were in clinical remission (defined as CDAI <150) at Week 8 in both the ~6 mg/kg (40.2%) and 130 mg (30.6%) ustekinumab groups than in the placebo group (19.6%); p<0.001 and p=0.009, respectively.
- The observed differences between ustekinumab groups and placebo are larger in the conventional care failure population (UNITI-2) compared to TNFα inhibitor therapy (UNITI-1), as patients are at a less advanced stage of disease.

IM-UNITI

- Phase III, multicentre, double-blind RCT comparing the clinical efficacy and safety of ustekinumab maintenance therapy (dosing every 12 weeks [q12w] or every 8 weeks [q8w]) versus placebo in adult patients with moderately to severely active CD who have failed, or are contraindicated to, conventional therapy or TNFα inhibitor therapy and who had responded to ustekinumab induction treatment as part of the UNITI-1 or UNITI-2 trials. Concomitant corticosteroid and/or immunosuppressant drugs were permitted, representing clinical practice and allowing the placebo group to act as a proxy for, and thus provide a comparison to, conventional therapy.
- Primary efficacy endpoint analysis demonstrated that a significantly greater proportion of patients were in clinical remission (defined as CDAI <150) at Week 44 (1-year post treatment initiation) in both the q12w (48.8%) and q8w

(53.1%) ustekinumab groups than in the placebo group (35.9%); p=0.040 and p=0.005, respectively.

- Secondary efficacy endpoint analysis demonstrated that a significantly greater proportion of patients were in clinical response (defined as a 100-point response based on the CDAI) at Week 44 in both the q12w (58.1%) and q8w (59.4%) ustekinumab groups than in the placebo group (44.3%); p=0.033 and p=0.018, respectively.

[redacted]

A greater proportion of patients in both ustekinumab groups of all trials also demonstrated a clinically meaningful improvement in disease-specific HRQL, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ). This difference was shown to be statistically significant in both induction trials, and in the q8w dosing group of the maintenance trial. In contrast to vedolizumab, ustekinumab was also efficacious in reducing both serum- (C-reactive protein [CRP]) and faecal- (calprotectin and lactoferrin) based biomarkers of inflammation. In addition, ustekinumab was associated with a significantly greater improvement in mucosal healing compared with placebo, and a greater proportion of patients achieved a minimally important clinical difference (defined as ≥3 point improvement in Simplified Endoscopic Activity Score for Crohn's Disease [SES-CD] score) as measured by the SES-CD tool; and ustekinumab treated patients were significantly more likely to achieve clinically meaningful endoscopic improvement.

Importantly, ustekinumab was also shown to be generally well tolerated, rates of AEs comparable to placebo were reported across trials, with low discontinuation rates due to AEs and low rates of SAEs. The safety profile observed in CD trials was generally in line with that observed in other indications, for which 5 years of data registry provide conclusive evidence of the favourable long-term safety profile of ustekinumab.

In the absence of head-to-head data for biologic treatments, the clinical benefit of ustekinumab versus alternative biologics has been estimated using a NMA

approach. A systematic literature review identified 11 placebo controlled-trials that were included in the NMA: 3 for ustekinumab (UNITI-1, UNITI-2 and IM-UNITI); 4 for adalimumab (CHARM, CLASSIC I, GAIN and Watanabe); 2 for infliximab (ACCENT I and Targan *et al.*); and 2 for vedolizumab (GEMINI II and GEMINI III). NMA were separately performed for induction trials and maintenance trials (as part of treatment sequence analysis); and for patients who had failed conventional therapy and for those who had failed, or are contraindicated to TNFα inhibitor therapy. A treatment sequence approach designed to account for trial heterogeneity of placebo groups was adopted for maintenance NMA that utilised induction and maintenance trial data.

The NMA synthesised endpoints of most relevance to trial assessments of clinical efficacy and the cost-effectiveness modelling, defined as CDAI-70-point response, CDAI ≥100-point response and clinical remission (CDAI <150); results are presented as odds ratios (OR) and credible intervals (CrI). In induction phase analysis of the TNF failure subpopulation, for whom vedolizumab is the relevant comparator based on current UK practice, ustekinumab was associated with a similar probability of reaching CDAI-100 response (56%, OR [CrI]: 1.05 [0.59, 1.85]) and a high probability of reaching clinical remission (85%, OR [CrI]: 1.53 [0.69, 3.39]). In induction phase analysis of the conventional care failure subpopulation, for whom TNFα inhibitor treatment is the relevant comparator based on current UK practice, ustekinumab was associated with a high probability of reaching CDAI-100 response (80%, OR [CrI]: 1.39 [0.64, 2.97]) and a similar probability of reaching clinical remission (60%, OR [CrI]: 0.44, 2.82]) compared to adalimumab standard induction dose. CDAI-100 data were not available for infliximab; however, this treatment was associated with the highest chance of being in clinical response, based on CDAI-70 data post induction. These results should be interpreted with caution due to several concerns of bias, including low patient numbers (n=52), missing data in the placebo control group (that were classed as treatment failures), and inverse dose relationships observed in the infliximab group of the induction treatment trial providing data for this treatment.

In treatment sequence analysis that combined data from induction and maintenance phases of therapy, the likelihood of being in clinical remission/response at 1 year was higher with ustekinumab treatment than with adalimumab or vedolizumab in both subpopulations. In the TNF failure subpopulation, ustekinumab was associated

with a high probability of achieving CDAI-100 response (95%, OR [CrI]: 1.77 [0.91, 3.45]) or clinical remission (80%, OR [CrI]: 1.35 [0.66, 2.73]) compared to vedolizumab at 1 year. In the conventional care failure subpopulation, ustekinumab was associated with a high probability of achieving CDAI-100 response (86%, OR [CrI]: 1.58 [0.68, 3.62]) or clinical remission (69%, OR [CrI]: 1.26 [0.50, 3.07]) compared to adalimumab standard dose at 1 year. Infliximab was associated with the highest chance of being in clinical remission at 1 year in the conventional care subpopulation (data not available for clinical response), but results should be interpreted with caution due to the aforementioned concerns of bias.

1.4 Summary of the cost-effectiveness analysis

The model uses a structure by Bodger *et al*., previously used in TA187 and TA352.[1-3] The structure consists of a short-term induction phase estimated by a decision tree, followed by a longer-term maintenance phase, represented by a Markov structure. The induction phase length is variable for all treatments, to reflect variation in induction trial length. The maintenance phase consists of four mutually-exclusive health states, defining progression in terms of CDAI score: Remission (CDAI <150), Mild (CDAI 150 - <220), Moderate to severe (CDAI 220-600), and Surgery. The maintenance phase for biologic treatments is assumed to last for one year in the base case, after which patients are assumed to switch to disease management via conventional care.

The base case results indicate ustekinumab dominates conventional care and adalimumab in the conventional care failure population, and dominates conventional care and vedolizumab in the TNF failure population (Table 3 and Table 4, respectively). Infliximab was excluded from the base case as CDAI-100 response was not reported; however, it is included in the sensitivity analysis using CDAI-70 response. The deterministic sensitivity analysis demonstrated that the most influential parameters in the comparison with conventional care were duration of treatment, resource use units for the moderate to severe state, and induction efficacy. Versus biologic treatments (vedolizumab and adalimumab) the most influential parameters were the OR for response and remission following induction treatment, duration of treatment, rate of surgery and resource use units for the moderate to severe state. Results of the probabilistic sensitivity analysis indicate the

base case ICERs are robust and that the probability of ustekinumab being the most cost-effective treatment at a willingness to pay (WTP) threshold of £30,000 per QALY is 100% in both the conventional care failure and TNF failure populations. Overall, the model indicates that when ustekinumab is provided under the confidential pricing agreement with the CMU, ustekinumab results in a higher number of QALYs compared with other treatments, and is cost-saving to the NHS.

Alternatively, using a cost minimisation approach, ustekinumab is cost saving in the TNF failure population compared to vedolizumab at list price. In the conventional care failure population, the cost of ustekinumab is similar to branded anti TNF α treatments (infliximab and adalimumab) at the recommended doses and is cost saving at the escalated doses.

Table 3: Incremental cost-effectiveness results – Conventional care failure population

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus Conventional Care	ICER
Ustekinumab	£263,053	43.0941	13.0501				Dominant	
Conventional care	£278,542	43.0941	12.6500	£15,489	0.0000	-0.4001	-	Dominated
Adalimumab	£283,762	43.0941	12.9022	£20,709	0.0000	-0.1479	£20,701	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.								

Table 4: Incremental cost-effectiveness results – TNF failure population

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus Conventional Care	Incremental analysis
Ustekinumab	£288,088	44.9817	12.9521				Dominant	
Conventional care	£294,600	44.9817	12.7280	£6,512	0.0000	-0.2241	-	Dominated
Vedolizumab	£302,820	44.9817	12.8179	£14,732	0.0000	-0.1342	£91,454	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.								

2 The technology

2.1 Description of the technology

Brand name: Stelara®

UK approved name: Ustekinumab

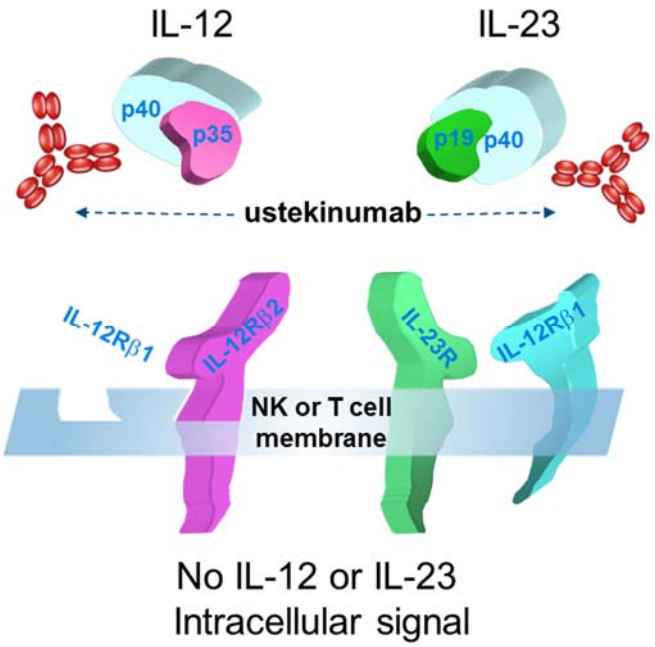
Therapeutic class: Interleukin 12/23 inhibitor

Mechanism of action:

Ustekinumab is a fully human IgG1κ monoclonal antibody (mAb) that binds with high affinity and specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23.

Both IL-12 and IL-23 participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, and IL-23 induces the T helper 17 (Th17) pathway. Ustekinumab inhibits the intracellular signalling of IL-12 and IL-23 by blocking p40 binding to the IL-12 receptor β1 chain expressed on the surface of immune cells, as depicted in Figure 2.

Figure 2: Mechanism of action of ustekinumab



Key: IL, interleukin; NK, natural killer.
Source: Sandborn *et al*. 2016.[4, 5]

Several factors provide a strong rationale for inhibiting these cytokines in Crohn's disease (CD), as summarised below:

- Abnormal regulation of IL-12 and IL-23 has been associated with numerous immune mediated diseases, including CD, in which intestinal antigen-presenting cells secrete increased levels of both cytokines.[6, 7]
- Multiple lines of evidence suggest that part of CD pathogenesis is IL-12/IL-23-mediated induction of Th1 and Th17 cells.[7-9]
- Significant associations have been found between CD and genetic polymorphisms in the genes encoding the IL-23 receptor and the IL-12/IL-23 p40 protein.[10-13]
- Both IL-12 and IL-23 stimulate tumour necrosis factor (TNF) production, resulting in the intestinal inflammation and epithelial cell injury typical of CD (see Section 3).
- Anti-IL-12/IL-23p40 antibodies administered in rodent models of colitis improved clinical and histopathologic changes.[14, 15]

2.2 Marketing authorisation/CE marking and health technology assessment

The indication for ustekinumab of interest to this appraisal is:

"for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies".

This indication is based on the results of the UNITI trial programme, consisting of two Phase III induction studies and a follow-on Phase III maintenance study that encompassed a broad range of biologic-eligible patients with CD, from those who were TNFα antagonist naïve, previously failing only conventional therapy (immunomodulators and/or steroids), to those who had previously failed two or more TNFα antagonists (see Section 4).

Marketing authorisation for this application was submitted to the European Medicines Agency (EMA) in November 2015, and a positive opinion from the Committee for

Human Medicinal Products (CHMP) was received on 15 September 2016. Following positive opinion, the European Commission (EC) granted a marketing authorisation on 11 November 2016. The European Public Assessment Report (EPAR) is due to be released by the EMA this week but an internal copy is provided for early sight in Appendix 1. At the same time of positive opinion, the CHMP recommended an extended (11-year) marketing protection period in accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004 as it considered that *"Stelara provides a significant clinical benefit in comparison with existing therapies based on a major contribution to patient care."* A copy of this recommendation is also provided in Appendix 1.

The summary of product characteristics (SmPC) submitted with the application is also provided in Appendix 1. The only contraindication listed in this SmPC alongside hypersensitivity to the active substance or excipients is clinically important, active infection as ustekinumab may have the potential to increase the risk of infections and reactivate latent infections.

Ustekinumab (Stelara®) already has marketing authorisation in Europe and elsewhere for the treatment of adult and adolescent (age 12 years or older) patients with moderate to severe plaque psoriasis, and for the treatment of adult patients with psoriatic arthritis. NICE currently recommends ustekinumab as a treatment option within its marketing authorisation for adult patients with moderate to severe plaque psoriasis or psoriatic arthritis, and the adolescent psoriasis indication is the subject of an ongoing multiple technology appraisal (MTA).

Regarding UK health technology assessment (HTA), it is anticipated that Janssen-Cilag Ltd. will submit ustekinumab for the treatment of CD to the Scottish Medicines Consortium (SMC) early 2017.

2.3 Administration and costs of the technology

Administration details and costs of ustekinumab are summarised in Table 5.

Table 5: Costs of the technology being appraised

	Cost / detail	**Source**
Pharmaceutical formulation	Induction: concentrate for solution for infusion Maintenance: solution for injection	SmPC

<table>
<tr><th></th><th>Cost / detail</th><th>Source</th></tr>
<tr><td>Acquisition cost (excluding VAT)</td><td>130mg vial concentrate for solution for infusion: £2,147.00
90mg vial solution for injection: £2,147.00
[redacted]</td><td>MIMS

Manufacturer</td></tr>
<tr><td>Method of administration</td><td>Induction: intravenous infusion
Maintenance: subcutaneous injection</td><td>SmPC</td></tr>
<tr><td>Doses</td><td>Induction infusion solution is to be composed of the number of vials, as specified below, which aligns to a dose of approximately 6mg/kg:
<table>
<tr><th>Body weight</th><th>Dose</th><th>Number of 130mg vials</th></tr>
<tr><td>≤55kg</td><td>260mg</td><td>2</td></tr>
<tr><td>>55kg to ≤85kg</td><td>390mg</td><td>3</td></tr>
<tr><td>>85kg</td><td>520mg</td><td>4</td></tr>
</table>
Maintenance injection solution is dosed at 90mg</td><td>SmPC</td></tr>
<tr><td>Dosing frequency</td><td>All patients should receive an IV induction dose followed by a maintenance SC dose at Week 8. After this, dosing every 12 weeks is recommended.
Patients who have not shown adequate response 8 weeks after the first SC dose (Week 16) may receive a second SC dose at this time.
Patients who lose response on maintenance dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks; patients may subsequently be dosed every 8 or 12 weeks according to clinical judgement.
Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by week 16 or 16 weeks after switching to the 8-weekly dose.
If therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.
The dosing schedule for ustekinumab is depicted in Figure 1.</td><td>SmPC</td></tr>
<tr><td>Average length of a course of treatment</td><td>Modelling based on a 52-week course in line with current biologic treatment recommendations and the formal induction and maintenance portions of the UNITI trial programme</td><td>UNITI trial programme</td></tr>
</table>

	Cost / detail	Source
Average cost of a course of treatment	**LIST PRICE:** **For induction year:** The annual treatment cost ustekinumab is £15,029 **For maintenance Year 2 and onwards:** The annual treatment cost ustekinumab is £9,339 [redacted]	UNITI trial programme
Anticipated average interval between courses of treatments	Patients whose disease relapses after treatment is stopped should have the option to start treatment again in line with current recommendations for biological therapy	NICE pathway
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	During maintenance therapy, dose escalation from 12-week to 8-week dosing is permitted for patients who lose response. Patients may subsequently be dosed every 12 or 8 weeks based on clinical judgement	SmPC
Anticipated care setting	Induction: hospital setting Maintenance: home setting Patients may self-inject if a physician determines that this is appropriate	SmPC
Key: CMU, Commercial Medicines Unit; MIMS, Monthly Index of Medical Specialities; SmPC, summary of product characteristics.		

[redacted]

2.4 Changes in service provision and management

No additional tests or investigations are needed for treatment eligibility, outside of those required for the diagnosis of moderately to severely active CD in need of further treatment (following conventional and/or TNFα antagonist therapy).

Ustekinumab is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of CD. Induction treatment must be administered through IV infusion. Hospital units already have the staffing and infrastructure needed for the IV administration of biologic drugs; ustekinumab would utilise this existing resource. Maintenance treatment is administered through SC injection. Janssen funds a homecare service, already in place for existing ustekinumab indications, where the SC injection is delivered to patients at home with an optional service of nurse administration. The homecare service with nurse administration is available for the entire maintenance phase without additional resource burden to the NHS for the administration of ustekinumab during maintenance treatment. After proper training, patients or their caregivers may inject ustekinumab without the assistance of a health care professional (HCP), if a physician determines that it is appropriate.

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection and the treatment plan changed in the case of active TB. Treatment of latent TB infection should be initiated prior to administering ustekinumab; anti-TB therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients should be monitored closely for signs and symptoms of active TB during and after treatment. Patients should also be monitored for early signs of cancer as immunosuppressants like ustekinumab have the potential to increase the risk of malignancy.

Concomitant therapies are not specified in the marketing authorisation for ustekinumab. Patients may receive conventional therapy (immunosuppressants and/or corticosteroids) alongside ustekinumab treatment as this was permitted in the UNITI clinical trial programme, and concomitant use of conventional therapy did not appear to influence the safety or efficacy of ustekinumab. Such concomitant use of

conventional therapy is common to all biologic treatments, and in line with the current pathway of care in UK practice (see Section 3.3).

All resource requirements associated with ustekinumab treatment are fully accounted for in the economic modelling presented in Section 5.

2.5 Innovation

CD is a chronic, progressive condition characterised by fluctuating periods of high and low disease activity. CD is disproportionally diagnosed in young adults and thus often affects people in their most formative and productive years. Moreover, in the absence of a cure, management of CD is a life-long requirement, but there are few treatment options available in current practice, and those that are available are associated with limitations such that many patients do not attain clinical benefit and/or tolerate therapy (see Section 3). It is estimated that over 4,000 patients in England and Wales may have failed all available therapies in current practice.[16, 17] Secondary failure, where patients initially respond to therapy but subsequently lose response, is a particular concern in CD management.

Ustekinumab offers a new biologic treatment option with a distinct mechanism of action to current biologics that provides a further therapeutic advancement for CD management. Although most of the health-related benefits demonstrated in the pivotal clinical trial programme (see Section 4) will be captured in the quality-adjusted life year (QALY) calculation, it should be acknowledged that ustekinumab addresses a current unmet medical need by providing an additional treatment option for patients with moderately to severely active CD with a novel mechanism of action (that may target the underlying condition of CD) that can induce and maintain clinical response/remission and thus improve patient health-related quality of life (HRQL), while providing a favourable benefit/risk profile. This gives clinicians and patients further ammunition to minimise periods of high disease activity, which, in addition to QALY captured health-related benefits, could also have a positive impact on economic loss associated with absence from work and/or reduced work productivity that will not be captured in the cost-effectiveness modelling presented in Section 5.

Ustekinumab is also associated with an extended half-life such that standard maintenance dosing is recommended every 12 weeks, which is four or five times per year. This represents a reduced administration burden compared to current biologic

treatment options, for which standard maintenance dosing is recommended every 2 weeks, 26 times per year to 8 weeks, six or seven times per year. In addition, the maintenance therapy is also administered in the home setting, compared to infusion treatments, infliximab or vedolizumab, which are administered intravenously in the hospital setting. Although the practical benefits of this dosing schedule will be captured in the cost-effectiveness modelling, the positive impact this can have on minimising the interruption of patients' daily living, including work activities, may not be fully captured. Indeed, frequency of medical administration, alongside the achievement of lasting remission and how quickly the patient achieves therapeutic response, are reported to be the three most important attributes of medical therapy to CD patients[18]; ustekinumab provides each of these attributes.

The significant clinical benefit ustekinumab brings in comparison with existing therapies was recently acknowledged by the CHMP who granted an extended marketing protection period in this new therapeutic indication based on a major contribution to patient care. As part of their assessment, the CHMP recognised the clinical unmet medical need due to limitations of current treatments (see Section 3.6) and how ustekinumab addresses this need, stating:

"…considering the high number of primary and secondary non response to TNF antagonist therapies in the treatment of Crohn's disease and the different mechanism of action of this compound Stelara is considered to provide both a treatment alternative as well as a response different from other treatments in a substantial part of the targeted population."

"In the pivotal induction studies with Stelara clinical response and remission were significant as early as week 3 and continued to improve through week 8. Vedolizumab pivotal trials showed significance for remission at Week 10, however it did not reach significance at the earlier timepoint of Week 6. The notion of a slower onset of efficacy with vedolizumab does not only support Stelara as a treatment alternative but showing a response different from vedolizumab in the target population. Lastly vedolizumab require intravenous administration every 8 weeks during maintenance whereas Stelara is administered s.c. with possible self-administration (i.e. no administration in hospital or clinic needed) can be considered to contribute to the significant clinical benefit compared to vedolizumab."

"Thus, overall, it is considered that Stelara provides a significant clinical benefit in comparison with existing therapies based on a major contribution to patient care."

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

CD is an immune-mediated condition that causes inflammation of the gastrointestinal (GI) system.[19, 20] Together with ulcerative colitis (UC), CD is a key component of inflammatory bowel disease (IBD). CD can affect any section of the GI tract from the mouth to the anus, and inflamed areas can range in size and volume.

CD is a chronic disease characterised by fluctuating periods of high and low disease activity. At diagnosis, approximately 80% of patients are estimated to have high disease activity; of all patients with CD, approximately 40% are estimated to have moderately to severely active disease at any time post-diagnosis.[21-25] Due to its heterogeneous phenotype, the clinical features of CD are variable, and disease activity is assessed against a number of clinical factors, including disease-related symptoms, HRQL, objective signs of disease and laboratory parameters.[26, 27]

Common measures of disease activity are summarised in Table 6.

Table 6: Assessments of disease activity in Crohn's

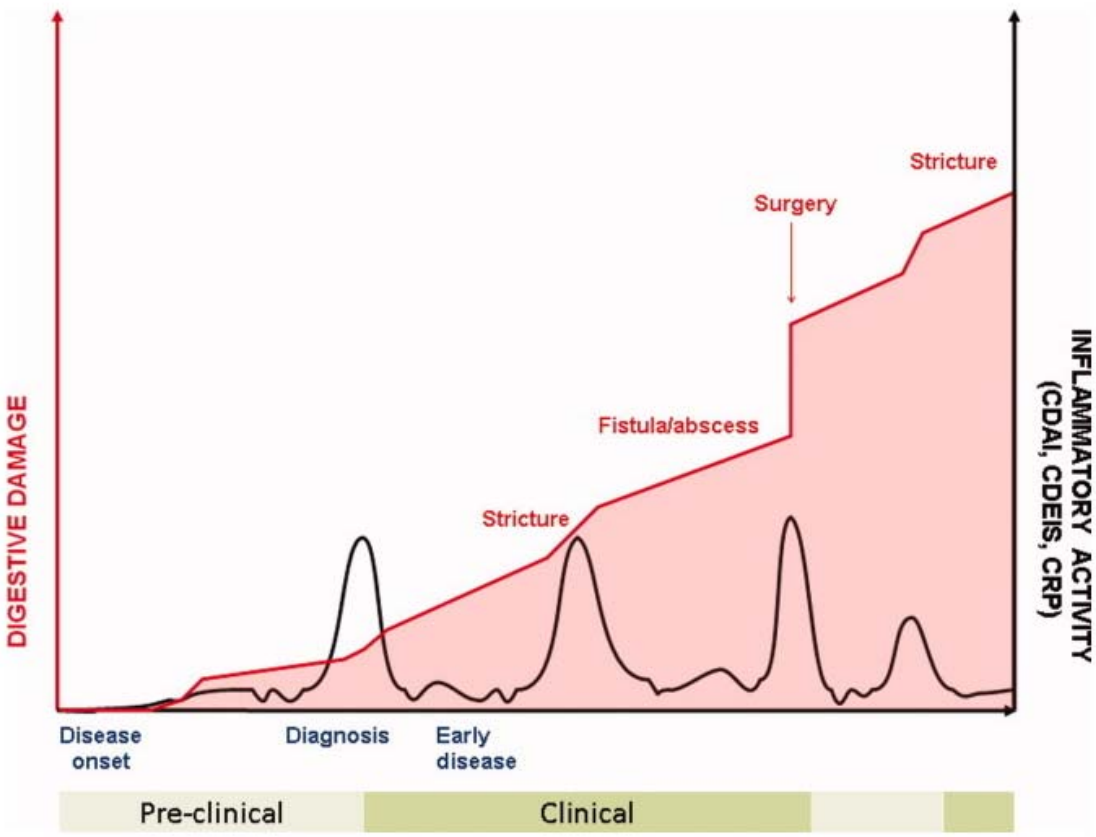
Assessment	Description
CDAI	Measurement of clinical, biochemical and physical parameters of disease activity each week, including domains related to the general wellbeing of the patient, abdominal pain, abdominal mass, extra-intestinal symptoms, haematocrit and weight. Generates a score between 0-600 with higher scores representing more severe disease activity. A CDAI score of less than 150 is considered to be remission, a score greater than 220 is considered to define moderate to severe disease, and a score greater than 300 is considered to be severe disease.[a] Widely accepted and validated method for assessing disease activity, most used in clinical trials.
CDEIS	Measurement of endoscopic disease activity that assesses severity based on GI tract ulcerations and surface involvement.
SES-CD	Measurement of endoscopic disease activity that assesses the size of mucosal ulcers, the ulcerated surface, the endoscopic extension and the presence of stenosis.

Assessment	Description
	The SES-CD was developed as an alternative to the CDEIS. It is simpler to use and therefore more suited to a routine use in clinical practice. During validation, SES-CD showed a strong correlation with CDEIS and was also shown to correlate with clinical parameters and serum levels of CRP.
HBI	Simpler version of the CDAI measuring clinical parameters of disease activity each day, including domains related to the general wellbeing of the patient, abdominal pain, abdominal mass and presence of complications. Generates a score between 0-15, with higher scores representing more severe disease activity.
IBDQ	HRQL tool measuring clinical parameters of disease activity and patient quality of life. Questionnaire includes 32-items across four domains: bowel function, emotional status, systemic symptoms and social function. Generates a score between 32-224, with higher scores representing better HRQL. Shows excellent correlation with CDAI and has been mapped to EQ-5D and SF-6D utility values. Widely accepted and validated method for assessing HRQL, most used in clinical trials. A short version (SIBDQ) containing 10-items is sometimes used in clinical practice.
Biomarkers	CRP is a non-specific biomarker of inflammation, infection and tissue injury, considered to be a reliable measure of disease activity, which can easily be used as a follow-up measure. Faecal biomarkers including fCal and lactoferrin can accurately measure intestinal inflammation, showing good correlation with endoscopic and histological scores. In clinical trials, fCal has been used as a surrogate for mucosal healing with a recommended cut-off of 250µg/g for predicting CDEIS ≤3.
Imaging	Imaging techniques are used to objectively examine the GI tract in clinical practice and can reveal some of the more severe complications of CD. US is commonly used to examine the terminal ileum and colon of patients and can reveal bowel wall thickness and stiffness, loss of stratification, strictures, and loss of haustra coli. CT scans are also commonly used to examine luminal and extraluminal structures, and MRI can be used to assess mural and mucosal characteristics of the GI tract.
Key: CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; CT, computed tomography; EQ-5D, EuroQol-5 Dimension; fCal, faecal calprotectin; GI, gastrointestinal; HBI, Harvey Bradshaw Index; HRQL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; SF-36, Short Form-36; US, ultrasound. **Notes**: [a]. further details on calculating CDAI scores are provided in Appendix 10.	

Longitudinal studies conducted prior to the introduction of disease modifying agents report that the natural course of CD is progressive, with a worsening of digestive damage and shortening of remission periods over time.[28-37] This is well depicted by Pariente *et al*.[28], as presented in Figure 3. Although patients may therefore have

activity-free intervals during long periods of remission, management of CD is a life-long requirement, and monitoring disease activity is of paramount importance, not only to assess the control and progression of patients in clinical practice but also to measure treatment effect and to adjust the therapeutic management.

Figure 3: Progression of digestive damage and inflammatory activity in a theoretical patient with Crohn's disease



Key: CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein.
Source: Pariente *et al*. 2011.[28]

CD disproportionately affects young adults, with age-specific incidence peaking at between 15 to 30 years of age.[38-40] Cases appear to be evenly split between males and females, but CD is more common in White people than in Hispanic and Asian people, and there is a greater incidence observed in the Jewish population.[38] Studies have shown that individuals emigrating from low prevalent regions (e.g. Asia) to higher prevalent countries (e.g. England) are at increased risk for developing IBD[41], which suggests an environmental influence.

There is no single known cause of CD; rather, its pathology involves a complex interplay between genetic, microbial, immunomodulatory and environmental factors.[42] A recent genome-wide meta-analysis in CD confirmed that 71 susceptible gene loci are associated with the development of the disease[43]; specifically, polymorphisms in the genes encoding the IL-23 receptor and the IL-12/IL-23 p40 protein have been significantly associated with CD.[10, 11, 13, 44] A large number of environmental factors potentially associated with CD have been studied, including urbanisation, stress, breast feeding, hygiene, water quality, diet and other socioeconomic factors, but the most studied and strongest identified environmental risk factor for developing CD is smoking.[45-51] Events that could disrupt the intestinal mucosa have also been suggested as potential risk factors for the development of CD[42]; this could be linked to increased uptake of bacteria and reduced regulation of the intestinal microbial composition with dysbiosis (an abnormal ratio of beneficial and aggressive bacterial species) common in CD.[42, 52, 53] Immunomodulation is a key element involved in the pathology of CD. In general terms, immune cell activation triggers cascades of various signalling factors (including TNF and IL-12 p40), resulting in an inflammatory response.[25, 54] While initial inflammatory responses in CD are driven by the innate immune system, the adaptive immune system is believed to be responsible for the mediation and perpetuation of these responses. CD patients are believed to have an imbalance between Th1 and Th17 cells that are responsible for the defence of the intestinal mucosa.[19]

3.2 Effect of disease on patients, carers and society

Patients with disease activity experience a variety of disease-related symptoms and complications, all of which affect normal living.

Clinical manifestations of CD are often cryptic and general, which can make early diagnosis challenging.[20] Disease-related symptoms are variable, determined partly by the site of the disease, but common symptoms include chronic diarrhoea, abdominal cramps and weight loss.[20, 55, 56] Additional, non-specific symptoms of CD can include malaise, fever, anaemia, cachexia and anorexia.[20, 55, 56] During periods of high disease activity, increased intestinal loss and malabsorption results in up to 85% of patients with CD experiencing malnutrition.[57]

Complications associated with worsening digestive damage include strictures, bowel fistulas and abscesses[58] (as depicted in Figure 3). In a recent study following 16,902 patients with CD, the proportion of patients with stricturing or penetrating disease was less than 30% at diagnosis but increased to 43% at 5 years, 56% at 10 years and 74% at 30 years.[29] Such complications often require multiple surgeries and cumulatively can lead to short gut syndrome.[58] Studies suggest that over a life-time, between 70-90% of patients with CD will have undergone at least 1 major intra-abdominal surgery[15, 59-61]; by the same time point, 35% of patients will have required two such operations, and 20% will have required at least three.[15]

Patients may also experience extraintestinal manifestations (EIM) over the course of the disease, with EIM estimated to affect around 40% of patients with CD.[62] EIM typically involves the musculoskeletal, skin, ocular and hepatobiliary systems of the body, with specific EIM including aphthous mouth ulcers, pyoderma gangrenosum, erythema nodosum, uveitis and arthritis.[20, 56, 62]

This substantial morbidity has a profound impact on many dimensions of patient quality of life, including an increased risk for clinical depression.[63, 64] Quality of life is particularly impaired during active disease stages, where patients may face several bowel movements a day, and abdominal pain; and may also feel tired due to alterations in sleep patterns, due to pain or food malabsorption. Indeed, formal assessment of HRQL report state of disease activity and magnitude of disease activity are predictive of HRQL impairment.[65-80] The Inflammatory Bowel Disease Questionnaire (IBDQ) is the most prominent disease-specific HRQL tool used in studies of CD.[81-83] Associations between impaired HRQL, symptom severity, stress, depression, fatigue and employment with worsening disease activity according to the IBDQ suggest that prolonged remission could have a substantial benefit on patient quality of life.[75, 84] Similarly, a recent analysis of SF-36 scores in patients with CD revealed significant burden of disease, which was more significant in patients with higher disease activity.[85] Indeed, the state of clinical remission (Crohn's Disease Activity Index [CDAI] <150) has been associated with a substantial improvement in HRQL, as measured by both disease-specific and generic instruments.[75] While not as extensively investigated, we can also expect a high carer burden in CD considering the debilitating nature of this disease. Alongside the physical burden of care, there is likely to be a mental impact of disease on carers themselves; this may

be particularly prominent for parents of patients diagnosed in their teenage years given the chronic and progressive nature of CD.

Aside from the direct economic burden captured in the cost-effectiveness modelling (see Section 5), it is also important to consider the wider economic burden of CD. The proportion of direct costs is estimated to be 21% to 26% of the total cost of disease in Europe, reflecting the high economic burden of other factors in CD.[86] In part at least, this is likely due to the young age of this patient population at diagnosis and the chronic nature of the disease; that is, CD disproportionally affects young adults during their prime working years. Absenteeism, presenteeism, activity loss and work productivity can all be substantially impaired in patients with CD, with impairments driven by disease severity.[87] Direct costs are also seen to be driven by disease severity, particularly severe CD requiring surgical intervention[86, 88]; direct costs have also been shown to be dependent on time spent in remission.[71] Therefore, while medical therapy is expensive, early and effective treatment (induction and maintenance of remission) should offset large direct and indirect costs from more severely active CD.

3.3 Clinical pathway of care

CD is not medically or surgically curable. Treatment aims are therefore to control manifestations of active disease to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects (AEs); due to the heterogenous nature of CD, treatment choices are often reliant on clinical judgement and patient preference.[55, 89] The three most important attributes of medical therapy to CD patients are reported to be achievement of lasting remission, frequency of medical administration, and how quickly the patient achieves therapeutic response.[18]

The NICE pathway for active CD[90] recommends that drug treatment to induce remission in patients with a first presentation or a single inflammatory exacerbation of CD within a 12-month period is monotherapy with a conventional glucocorticosteroid (or budenoside or 5-ASA in people who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated). Add-on treatment with an immunosuppressant should be considered in patients with two or more inflammatory exacerbations in a 12-month period, or in patients for whom the glucocorticosteroid monotherapy dose cannot be tapered. Immunosuppressant

monotherapy is also recommended to maintain remission for patients in whom glucocorticosteroid treatment has successfully induced remission.

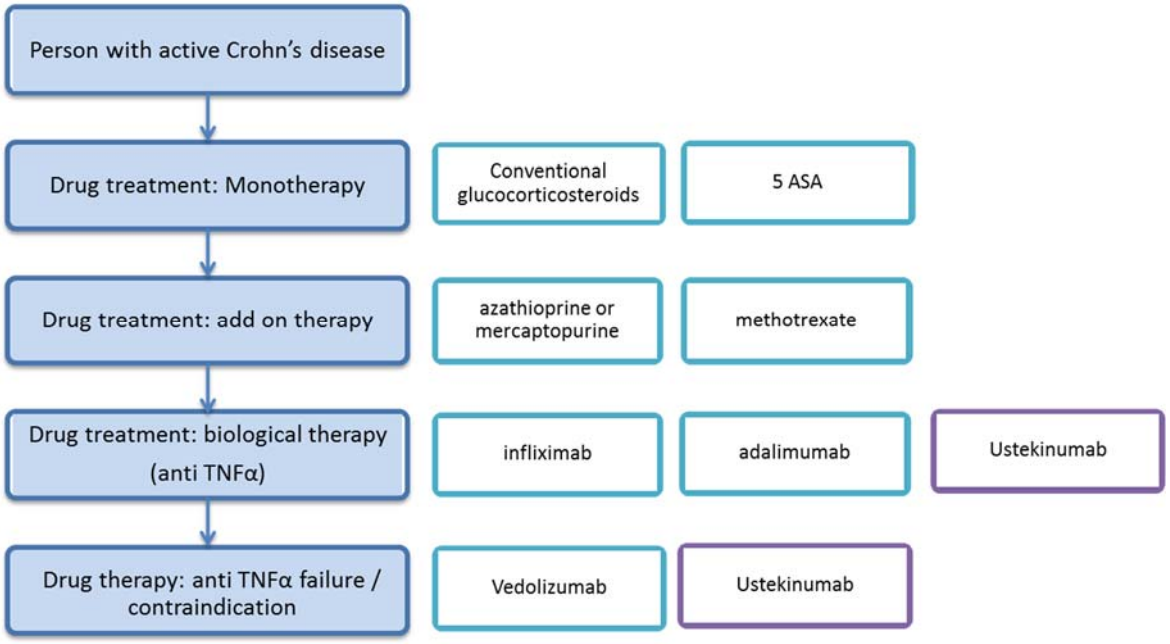
Biologic treatment in the form of the TNFα inhibitors, infliximab or adalimumab, is recommended for adults with moderately to severely active CD whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatment), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure, or until 12 months after the start of treatment (whichever is shorter). People should then have their disease reassessed to determine whether ongoing treatment is clinically appropriate, with treatment continued only if there is clear evidence of ongoing active disease. Patients whose disease relapses after treatment is stopped have the option to start treatment again.

TNFα inhibitor treatment is normally started with the less expensive drug, but this may vary for individual patients because of differences in the licensed indications, method of administration and treatment schedules, as summarised in Table 7. Patients who have no response to their primary TNFα inhibitor therapy (primary failure) are unlikely to be treated with the other, whereas patients who have an initial response to primary therapy may be switched to the alternative TNFα inhibitor option on loss of response (secondary failure), unless the likely cause of loss of response is antibody development against the drug.

Biologic treatment in the form of the IgG_1 monoclonal antibody against α4β7-integrin, vedolizumab, is recommended for adults with moderately to severely active CD in whom a TNFα inhibitor has failed (i.e. the disease has responded inadequately or has lost response to treatment), or in whom a TNFα inhibitor cannot be tolerated or is contraindicated. The licensed indication, method of administration and treatment schedule for vedolizumab are summarised in Table 7. Treatment should only continue if there is clear evidence of ongoing clinical benefit, and for people in complete remission at 12 months, vedolizumab should be stopped with the option to resume treatment if there is a relapse. Patients who have not shown a response by Week 10 may benefit from an additional dose, but if no evidence of therapeutic benefit is observed by Week 14, no patient should continue treatment.

In line with NICE recommendations, the clinical pathway of care for CD is depicted in Figure 4. Ustekinumab offers a new biologic treatment option for patients who have moderately to severely active CD who have failed, or are contraindicated to conventional therapy and/or TNFα inhibitor therapy. Ustekinumab therefore fits into this clinical pathway of care at the positions highlighted (Figure 4) and offers an alternative treatment to TNFα inhibitor therapy and vedolizumab, or the continuation of conventional therapy. Although not explicitly depicted within this pathway, it should also be acknowledged that during biologic treatment, patients may still receive conventional therapy for additional symptom control. Due to concerns of toxicity associated with corticosteroids in particular (see Section 3.6), reduction of concomitant use of such treatments is also important to the overall treatment aims in CD.

Figure 4: NICE clinical pathway adapted to show proposed place in the pathway of ustekinumab



Source: Adapted from NICE Clinical Guideline 125 (2012 updated 2016)[90]

Table 7: Summary of biologic treatment characteristics

Product	Indication	Dosing	Treatment continuation	Care setting
Infliximab	For the treatment of: Moderately to severely active CD in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Fistulising, active CD in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.	Induction: 5mg/kg given as an IV infusion followed by an additional 5mg/kg IV infusion at Week 2. Maintenance: 5mg/kg given as an IV infusion at Week 6, with subsequent dosing every 8 weeks thereafter.	Patients who do not respond to induction dosing should discontinue treatment. Patients who respond to induction dosing should receive maintenance dosing until treatment failure, or until 12 months at which point treatment discontinuation should be considered.	Hospital
Adalimumab	For the treatment of: Moderately to severely active CD in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.	Induction: 80mg given as a SC injection followed by a 40mg SC dose at Week 2; or 160mg given as a SC injection followed by an 80mg SC dose at Week 2 if there is a need for a more rapid response that warrants an increased risk for AE. Maintenance: 40mg given as a SC injection every 2 weeks, or every 1 week for patients with a decrease in response who may benefit from dose escalation.	Patients who do not respond to induction dosing may benefit from continued maintenance dosing through Week 12, but continued therapy should be carefully reconsidered in a patient not responding within this time period. Patients who respond to induction dosing should receive maintenance dosing until treatment failure, or until 12 months at which point consideration should be given treatment discontinuation.	Hospital/ Home

Vedolizumab	For the treatment of: Moderately to severely active CD in adult patients who have not responded despite a full and adequate course of therapy with a TNF-α inhibitor or who are intolerant to or have medical contraindications for such therapies.	Induction: 300mg given as an IV infusion at Weeks 0, 2 and 6 weeks. Patients who have not shown a response may benefit from another dose at Week 10. Maintenance: After induction, patients should be treated with 300mg given as an IV infusion every 8 weeks from Week 14.	Patients who have not responded to treatment by Week 14 should discontinue treatment. Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to 300mg every 4 weeks.	Hospital
Key: CD, Crohn's disease; IV, intravenous; SC, subcutaneous. **Source:** Entyvio SmPC[91]; Humira SmPC[92]; Remicade SmPC.[93]				

3.4 Life expectancy and patient population

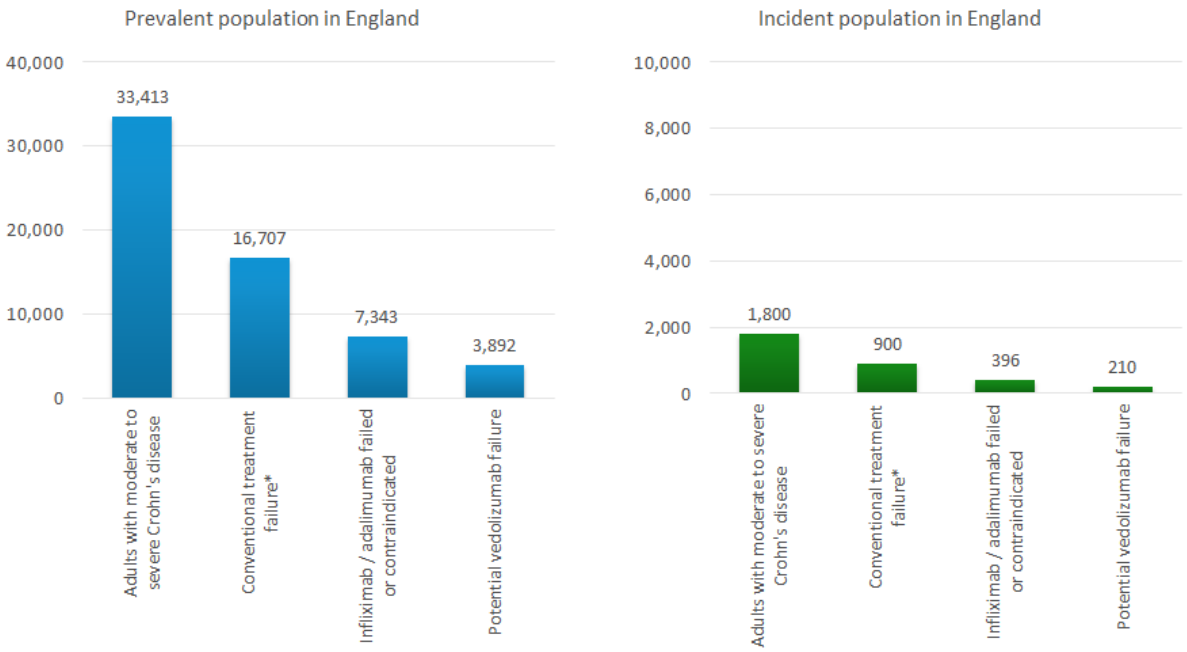
Life expectancy is relatively unaffected by CD, and epidemiological studies suggest that overall mortality rates for patients with IBD in England are similar to those of the general population.[94] The key consideration for patients and carers is therefore how to manage disease and minimise the impact of CD on patient quality of life.

The leading UK charity for CD and UC, Crohn's and Colitis UK, estimates that there are currently at least 115,000 people in the UK with CD.[95] This is reasonably aligned with epidemiology estimates for CD from cohort studies conducted within the last 20 years that report incidence rates of 5.9 to 8 per 100,000 people in England[96, 97], and prevalence rates of 130 to 185 per 100,000 people.[98-100]

Of all patients with CD, approximately 40% are estimated to have moderately to severely active disease at any time post diagnosis. Therefore, approximately 46,000 patients with CD are estimated to need treatment for moderately to severely active disease. Ustekinumab will not be considered for all of these patients; however, given the cyclic treatment pathway; as a result of the relapsing and remitting nature of disease, it is difficult to further break down estimates for the eligible patient population.

In the most recent technology appraisal conducted by NICE in CD, cost estimates for vedolizumab were based on patient numbers depicted in Figure 5, which breaks down patient numbers by treatment history. According to these estimates, 17,607 patients in England were considered to have failed conventional therapy, and an additional 7,739 patients were considered to have failed TNFα inhibitor therapy.[16, 17] Considering the proportion of responders to vedolizumab at the end of maintenance of GEMINI II trial[17], it is estimated that over 4,000 may have failed also vedolizumab. Further details on patient population are provided in Appendix 1.

Figure 5: Patient population estimates broken down by treatment history



Key: CD, Crohn's disease; TNF, tumour necrosis factor.
Source: Adapted from NICE costing report TA352[16] and Sandborn *et al*. 2013.[17]

3.5 Relevant NICE guidance and clinical guidelines

NICE guidance and additional clinical guidelines of relevance to this appraisal are summarised in Table 8.

Table 8: Relevant NICE guidance and clinical guidelines

Organisation	Title	Date	Summary
NICE guidance			
NICE clinical guideline CG152	Crohn's disease: management[90]	2016	• Conventional corticosteroids should be offered to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period • Budesonide or 5-ASA should be considered in patients with one or more of distal ileal, ileaocaecal or right-sided colonic disease in whom conventional glucocorticosteroids are contraindicated • Azathioprine or mercaptopurine should be considered add-on treatment to glucocorticosteroids or budesonide if there are ≥2 inflammatory exacerbations in a 12-month period or the glucocorticosteroid dose cannot be tapered - MTX should be considered to induce remission in people who cannot tolerate azathioprine or mercaptopurine • Azathioprine or mercaptopurine are recommended to induce remission in both patients who had previously received these treatments and treatment naïve patients • Conventional glucocorticosteroids or budesonide should not be offered to maintain remission • Azathioprine or mercaptopurine should be offered to maintain remission after surgery in patients with adverse prognostic factors • 5-ASA treatment should be considered to maintain remission after surgery
NICE technology appraisal No. 187	Infliximab and adalimumab for the treatment of Crohn's disease[2]	2010	• Infliximab and adalimumab are recommended as treatment options for adults with severe active CD whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy • Infliximab is also recommended as a treatment option for people with active fistulising CD whose disease has not responded to conventional therapy or who are intolerant of or have contraindications to conventional therapy

Organisation	Title	Date	Summary
			- Treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary • Infliximab is also recommended for the treatment of people aged 6–17 years with severe active CD whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy
NICE technology appraisal No. 352	Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy[3]	2015	• Vedolizumab is recommended as an option for treatment moderately to severely active CD if a TNFα inhibitor has failed or cannot be tolerated or is contraindicated - At 12 months, patients should be reassessed to determine whether treatment should continue
Clinical guidelines			
WGO	Inflammatory Bowel Disease[101]	2015	• SCS can be used to induce remission in patients with a first presentation or a single inflammatory exacerbation of CD within a 12-month period; they should not be used for maintenance of remission • Mild CD should be treated with sulfasalazine or other 5-ASA for colonic disease only; metronidazole or ciprofloxacin for perineal disease; budesonide for ileal and/or right colon disease • Moderate CD should be treated with oral corticosteroids, AZA or 6-MP, MTX, or anti-TNF • Severe CD should be treated with systemic corticosteroids (SCS), subcutaneous or intramuscular methotrexate, intravenous infliximab or subcutaneous adalimumab or subcutaneous certolizumab • Corticosteroid-resistant or dependent CD should be treated with AZA or 6-MP or anti-TNF but preferably with a combination of AZA and 6-MP - Vedolizumab therapy is another alternative in moderate or severe disease - Budesonide is an option for patients with distal ileal, ileocecal or right-sided CD is a first presentation or a single inflammatory exacerbation within a 12-month period; this should not be used in severe CD or exacerbations • Quiescent CD should be treated with AZA or 6-MP or MTX

Organisation	Title	Date	Summary
			• Perianal CD should be treated with oral antibiotics, AZA or 6-MP, intravenous infliximab or subcutaneous adalimumab • Thiopurines can be used for maintaining remission in patients induced on corticosteroids • Use of calcineurin inhibitors should be reserved for special circumstances • Infliximab and adalimumab show better clinical response, remission and mucosal healing than placebo with no increase in AE • Infliximab, adalimumab and certolizumab are effective in maintaining remission of CD induced by anti-TNF agents
IOIBD	Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target[102]	2015	• Resolution of abdominal pain and normalisation of bowel habit should be the target - Resolution of clinical symptoms and inflammation are goals of treatment that define the term "remission" • Absence of ulceration is the target of endoscopic therapy; histologic remission is not a target of therapy • Biomarkers such as CRP and faecal calprotectin are not treatment targets because there is insufficient evidence to recommend this. However, failure of normalisation of these biomarkers should prompt further endoscopic evaluation • The primary PRO should be resolution of abdominal pain and normalisation of bowel habit
BSG	Guidelines for the management of inflammatory bowel disease in adults[103]	2011	• For moderately active CD, SCS or budesonide is recommended • At first presentation of CD or in the case of a single flare-up in the past 12 months, conventional SCS is preferred with budesonide or 5-ASA an alternative. SCS or budesonide should be considered with add on therapy of 6-MP, AZA or MTX • For severely active CS in patients who have failed conventional OCS, infliximab or adalimumab use is recommended - Infliximab is also recommended for CD patients with severe fistulising disease
ECCO	European Evidence-based consensus on the diagnosis and management of	2016	• Oral budesonide is the preferred treatment for patients with mildly active localised ileocaecal Crohn's disease

Organisation	Title	Date	Summary
	Crohn's disease 2016: Part 1: Diagnosis and medical management[104]		• Patients with moderately active localised ileocaecal CD should be treated with budesonide or with SCS. An anti-TNF-based strategy should be used in patients' refractory or intolerant to SCS. In patients refractory to SCS and/or anti-TNFs, vedolizumab is an appropriate alternative • SCS should be used for initial treatment in patients with severely active localised ileocaecal CD, or those with active colonic CD. For those who relapse, an anti-TNF-based strategy is appropriate. For patients refractory to SCS and/or anti-TNF, vedolizumab is appropriate • Surgery is a reasonable alternative for patients refractory to conventional medical treatment with severely active localised ileocaecal CD • For some patients, with moderately or severely active localised ileocaecal CD who have infrequently relapsing disease, restarting SCS with an immunomodulator may be appropriate • SCS should also be used for initial treatment in patients with extensive small bowel disease, but early use of anti-TNFs should also be evaluated. For patients with severe disease who have relapsed, an anti-TNF-based strategy is appropriate • Patients who have clinical features suggesting a poor prognosis appear the most suitable for early introduction of immunosuppressive therapy. Early anti-TNF therapy should be initiated in patients with high disease activity and features indicating a poor prognosis • Mild oesophageal or gastroduodenal CD may be treated with a proton pump inhibitor only. More severe or refractory disease requires additional systemic corticosteroids or an anti-TNF-based strategy. Dilatation or surgery are appropriate for symptomatic strictures • Patients with objective evidence of active CD refractory to corticosteroids should be treatment with an anti-TNF-based strategy, although surgical options should also be considered and discussed at an early stage

Key: 5-ASA, 5-aminosalicylic acid; 6-MP, mercaptopurine; AZA, azathioprine; CD, Crohn's disease; CRP, C-reactive protein; MTX, methotrexate; NICE, National Institute of Health and Care Excellence; OCS, oral corticosteroids; PRO, patient-reported outcome; SCS, systemic corticosteroids; TNF, tumour necrosis factor.

3.6 Issues relating to clinical practice

Considering the need for long-term disease management in CD, there are few treatment options in current clinical practice. Furthermore, treatment options that are available are associated with several limitations, as summarised below:

- Many current treatment strategies target symptom control, and do not appear to significantly alter the natural course of the disease[102]
- Corticosteroids are associated with significant toxicity including AEs of arterial hypertension, infection and loss of bone mineral density that limit their long-term use[105-110]; long-term use of corticosteroids can also result in steroid dependency and resistance[106, 111-114]
- Immunosuppressants are associated with potentially severe AEs including hepatoxicity, marrow suppression and hepatic fibrosis[115-121] and have limited effectiveness with regard to response induction[122]
- Although TNFα inhibitor agents demonstrate significantly higher efficacy than conventional therapy, 20-40% of patients fail to respond to TNFα inhibitor therapy (primary failure), and a large proportion of patients (estimated at up to 60%) experience loss of response over time (secondary failure) (see Section 5.3.3).[123-125]
    - This observation is consistent with evidence reported across a number of other indications, including plaque psoriasis (PsO) and psoriatic arthritis (PsA)[126-130]
- TNFα inhibitor therapy is associated with a high administration burden consisting of SC injection every 1 to 2 weeks in the case of adalimumab[92] and IV infusion (conducted in the hospital setting) three times in the first 8 weeks and every 8 weeks thereafter in the case of infliximab[93]
- The only treatment available for patients who fail, or are contraindicated to, TNFα inhibitor therapy is vedolizumab, but many patients do not respond to such treatment (CDAI-100 clinical response rate of 31% at induction), and it has no proven effect of objective measures of inflammation[17, 131]

- Vedolizumab also has a high administration burden consisting of IV infusion (conducted in the hospital setting) three times in the first 6 weeks and every 8 weeks thereafter[91]
- It is estimated that over 4,000 patients in England and Wales have failed all available therapies in current practice.[16, 17]

There is a clear unmet medical need for additional treatment options with new mechanisms of action (that may target the underlying condition of CD) that can induce and maintain clinical response/remission and thus improve patient HRQL, while providing a favourable benefit/risk profile and a minimally invasive dosing schedule.

3.7 Equality

No equality issues related to the use of ustekinumab have been identified or are foreseen.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

A systematic literature review (SLR) was designed to identify all relevant studies of clinical data related to moderately to severely active CD. This SLR was conducted in accordance with NICE guidelines. The searches for clinical, safety and HRQL endpoints were originally run in July 2015 and were updated in October 2016.

Details of the search strategy used for clinical effectiveness searches are provided in Appendix 2.

4.1.2 Study selection

Titles and abstracts (where available) were reviewed by two independent reviewers. Articles that were identified as potentially relevant during the first phase of the screening were then retrieved and reviewed in full and assessed for inclusion according to the list of pre-specified inclusion/exclusion criteria, presented in Table 9. Any discrepancy was resolved through discussion and/or involvement of a third reviewer.

Table 9: Eligibility criteria applied to systematic search results

	Inclusion criteria	Exclusion criteria
Population	Patients with active moderate to severe Crohn's disease	Patients with mild disease Patients with other conditions Healthy volunteers
Interventions	All biologic therapies licensed for Crohn's, including: • ustekinumab (Stelara®) • infliximab (Remicade®) • adalimumab (Humira®) • vedolizumab (Entyvio®) • certolizumab (Cimzia®) • natalizumab (Tysabri®)	Non-biologic therapies
Comparators	Any study that compared a biologic therapy of interest with any other treatment, including placebo, no treatment or another active therapy was included	-

	Inclusion criteria	Exclusion criteria
Outcomes	The outcome measures to be considered for the SLR are: • Efficacy endpoints including: - CDAI - C-reactive protein - Faecal lactoferrin and calprotectin - Mucosal healing/Endoscopic improvement - Fistula closure • Safety endpoints: - Infections & serious infections - Grade III & IV adverse events - Hospitalisations/Surgery - Discontinuations/Withdrawals Dose escalations • Quality of life/other measures: - IBDQ - WPAI - SF-36 - EQ-5D	Pharmacokinetics
Study type	Randomised controlled trials of any design	Non-randomised trials Non-controlled trials Observational studies
Restrictions	Date: none Language: English abstract	-
Key: CDAI, Crohn's Disease Activity Index; EQ-5D, EuroQol-5 Dimension; IBDQ, Inflammatory Bowel Disease Questionnaire; SF-36, Short Form-36; SLR, systematic literature review; WPAI, Work Productivity and Activity Impairment. **Notes:** Abstracts and contents that had been reported in another publication were excluded. It should be noted that this criterion was only be applied if the numerical values are the same in the full publication.		

Data were extracted from the included full text article by one reviewer, and all extracted data verified against the original source paper by a second reviewer. Any query raised during the quality check was resolved through discussion and/or involvement of a third reviewer.

4.1.3 Search results

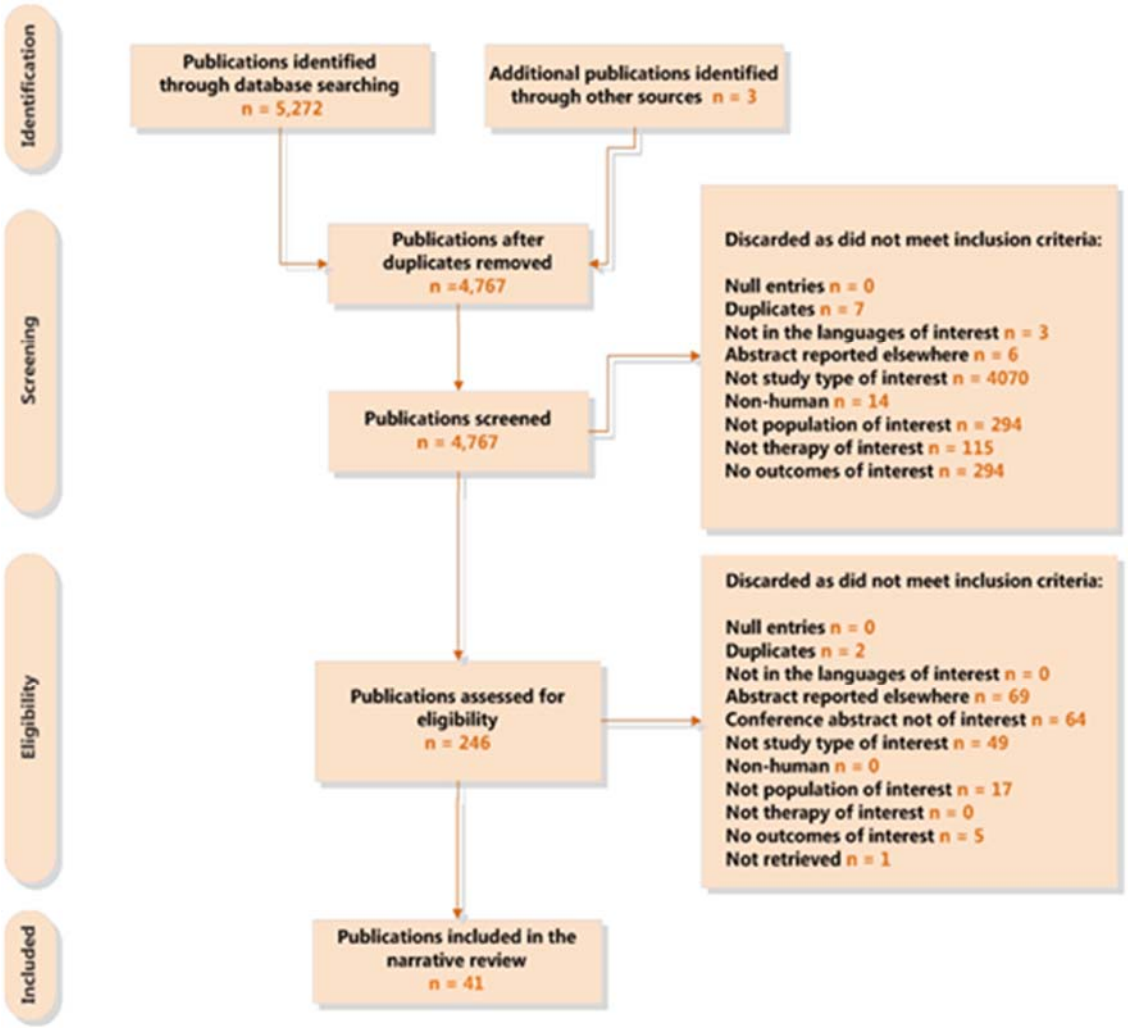
Initial electronic database searches and website searches were conducted on 3rd July 2015. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the initial review is presented in Figure 6.

A total of 5,272 citations were captured from the electronic database searches, and 3 additional publications were identified through manual searches. After removal of duplicates, there were 4,767 citations remaining. The screening of titles and abstracts led to the review of 246 publications to assess their eligibility for inclusion.

After exclusion of publications that did not meet the selection criteria, 41 publications reporting the results of 31 different clinical trials were included in the narrative synthesis (Figure 6).

Records of the 246 citations obtained in full and reasons for inclusion/exclusion against the eligibility criteria are available as a separate document that can be provided on request.

Figure 6: PRISMA flow diagram of the systematic search process (July 2015)



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Searches were updated in October 2016. In total, 75 publications for eight trials were identified; three of which had not been identified in the previous review. Details of this search update, including a PRISMA flow diagram and a text summary showing the number of studies included and excluded at each stage of the review update, are provided in Appendix 2.

4.2 List of relevant randomised controlled trials

The three pivotal, regulatory Phase III randomised controlled trials (RCTs) that provide data for ustekinumab in CD are the 8-week induction trials: UNITI-1 and UNITI-2, and the 44-week maintenance trial IM-UNITI. These trials are summarised in Table 10.

UNITI-1 provides evidence on the clinical benefits of ustekinumab versus placebo for patients with moderately to severely active CD who have failed or are intolerant to TNFα inhibitor therapy, and UNITI-2 provides evidence on the clinical benefits of ustekinumab versus placebo for patients with moderately to severely active CD who have failed conventional therapy. IM-UNITI provides evidence on the clinical benefits of longer-term treatment with ustekinumab versus placebo for both patient groups.

Prior to the UNITI trial programme, ustekinumab for the management of CD was investigated in the Phase II RCT, CERTIFI (Table 10). A summary of the CERTIFI study and its main efficacy results are presented in Appendix 3. This study is not presented in detail within the main body of this submission, as the focus is on the Phase III data, on which marketing authorisation was granted and on which the cost-effectiveness modelling has been based. The CERTIFI study does not provide comparable evidence to these data in the respect that patients received a 1, 3 or 6 mg/kg induction dose, rather than the vial-based dose approximating to 6mg/kg as per licence terms.[132] However, broadly speaking, the results from this Phase II study supported those from the Phase III trial programme.

Table 10: List of relevant RCTs

Trial name (NCT number)	Population	Intervention	Comparator	Primary study reference
UNITI-1 (NCT01369329)	Adult patients with moderately to severely active CD who have failed or are intolerant to TNFα inhibitor therapy	Ustekinumab 130mg IV (n=245) Ustekinumab ~6mg/kg IV (n=249)	Placebo (n=247)	Feagan *et al*. 2016[133]
UNITI-2 (NCT01369342)	Adult patients with moderately to severely active CD who have failed conventional therapy	Ustekinumab 130mg IV (n=209) Ustekinumab ~6mg/kg IV (n=209)	Placebo (n=210)	Feagan *et al*. 2016[133]
IM-UNITI (NCT01369355)	Adult patients with moderately to severely active CD induced into clinical response with ustekinumab in the induction studies UNITI-1 or UNITI-2[a]	Ustekinumab 90mg SC q12w (n=132) Ustekinumab 90mg SC q8w (n=132)	Placebo (n=133)	Feagan *et al*. 2016[133]

CERTIFI (NCT00771667)	Adult patients with moderately to severely active CD that was resistant to TNFα inhibitor therapy	Ustekinumab 1mg/kg (n=131) Ustekinumab 3mg/kg (n=132) Ustekinumab 6mg/kg (n=131)	Placebo (n=132)	Sandborn *et al*. 2012[132]
Key: CSR, clinical study report; IV, intravenous; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; TNF, tumour necrosis factor. **Notes:** [a], patients randomised to placebo in UNITI-1 and UNITI-2 and patients who did not show a clinical response to ustekinumab at 8 weeks were also eligible for non-randomised maintenance dosing after completion of the induction studies.				

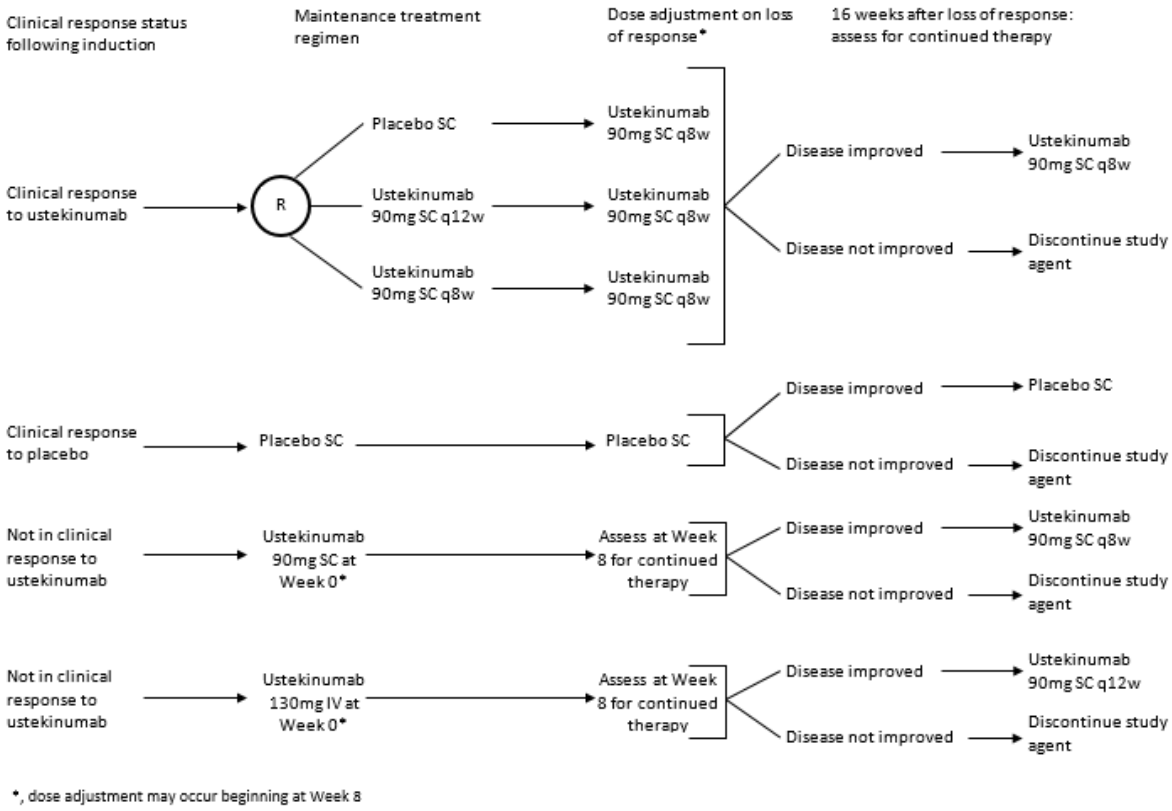
4.3 Summary of methodology of the relevant randomised controlled trials

Details of the methodology of the two induction trials, UNITI-1 and UNITI-2, and the subsequent maintenance trial, IM-UNITI, are presented in Table 11.

The design of the induction studies was essentially identical except for the trial populations. In UNITI-1, patients had received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of CD, and either did not respond, responded initially but since lost response, or were intolerant to the medication (according to strict predefined failure criteria as specified in the protocol). In UNITI-2, patients had failed conventional therapy of corticosteroids and/or immunomodulators and/or corticosteroids, including patients who were corticosteroid dependent. Patients in UNITI-2 could have been exposed to TNFα inhibitor therapy previously but must not have met the failure criteria specified for UNITI-1. Patients were randomised in a 1:1:1 ratio to receive a single IV administration of ustekinumab 130mg, ustekinumab weight-based dosing equivalent to approximately 6mg/kg or placebo. Throughout both studies, patients were permitted to receive concomitant CD medications (including corticosteroids), but the dosage was to remain stable without initiation or increase through Week 8. Therefore, although placebo-controlled in design, the UNITI trial programme provides head-to-head data for ustekinumab versus conventional therapy, relevant to this appraisal.

In the IM-UNITI study, patients with a clinical response to ustekinumab in either of the two induction trials (UNITI-1, UNITI-2) at Week 8 were randomised to receive subcutaneous (SC) administrations of ustekinumab 90mg every 12 weeks (q12w), ustekinumab 90mg every 8 weeks (q8w), or placebo up to Week 44 (52 weeks after induction). In an advancement to previous maintenance trials, all other patients enrolled in UNITI-1 and UNITI-2 could also be included in IM-UNITI, as depicted in Figure 7.

Figure 7: Study populations of IM-UNITI



Key: IV, intravenous; R, randomisation; SC, subcutaneous; q8w, every 8 weeks; q12w, every 12 weeks.
Notes: to maintain the blind for the non-randomised patients, both IV and SC administrations were given to all patients not in clinical response following induction.
Source: IM-UNITI CSR.[134]

Alongside the UNITI trial programme, an endoscopic substudy was conducted at participating sites to assess improvements in the appearance of the mucosa during endoscopy (ileocolonoscopy) in patients who consented to the substudy.

To evaluate the long-term persistence (safety and efficacy) of ustekinumab in CD (and to avoid interruptions in ustekinumab treatment), patients who completed the

safety and efficacy evaluation at Week 44 of IM-UNITI and who, in the opinion of the investigator, may benefit from continued treatment, were offered the opportunity to participate in a study extension starting at Week 44 through Week 272 (remaining on the same study agent and dosing regimen being received at the end of IM-UNITI). The first data cut of this study extension has recently become available (two weeks prior to submission), providing data up to Week 92.

Table 11: Summary of UNITI-1, UNITI-2 and IM-UNITI methodology

Study	UNITI-1	UNITI-2	IM-UNITI
Location	177 locations worldwide: Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, Iceland, Ireland, Israel, Japan, Korea, Netherlands, New Zealand, Poland, Serbia, South Africa, Spain, UK, USA.	226 study locations worldwide: Australia, Belgium, Brazil, Bulgaria, Canada, Croatia, France, Germany, Hungary, Iceland, Israel, Japan, Korea, Netherlands, New Zealand, Poland, Russian Federation, Serbia, South Africa, Spain, UK, USA.	220 study locations worldwide: Australia, Belgium, Brazil, Bulgaria, Canada, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Iceland, Ireland, Israel, Japan, Korea, Netherlands, New Zealand, Poland, Russia, Serbia, South Africa, Spain, UK, USA.
Trial design	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study. Randomisation was stratified by study region, CDAI score, and initial response to TNFα inhibitor therapy.	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study. Randomisation was stratified by study region and CDAI score.	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study. Randomisation was stratified by clinical remission (yes/no) and ustekinumab induction dose.
Eligibility criteria for participants	Inclusion criteria included: • Man or woman ≥18 years of age. • CD or fistulising CD of at least 3 months duration, with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography histology, and/or endoscopy • Active CD, defined as a baseline CDAI score of ≥220 and ≤450. • Have received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of CD, AND	Inclusion criteria included: • Man or woman ≥18 years of age. • CD or fistulising CD of at least 3 months' duration, with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography histology, and/or endoscopy • Active CD, defined as: - A baseline CDAI score of ≥220 and ≤450, AND - An abnormal CRP (>0.3mg/L) at screening, OR - Calprotectin >250mg/kg at screening, OR	Patients were taken from the two induction trials: UNITI-1 and UNITI-2. Patients who achieved clinical response on ustekinumab were included in the randomised portion of this trial that made up the primary study population. Other patients from the induction trials (i.e. responders to placebo and non-responders) could also be included in the study, but were not included in the randomised portion of the trial.

Study	UNITI-1	UNITI-2	IM-UNITI
	- Did not respond initially (i.e. primary non-responders), OR - Responded initially but then lost response with continued therapy (i.e. secondary non-responders), OR - Were intolerant to the medication. • Adhere to the requirements for concomitant medication for the treatment of CD. Exclusion criteria were: • Has complications of CD such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with ustekinumab. • Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to baseline, or 8 weeks prior to baseline for intra-abdominal abscesses, provided that there is no anticipated need for any further surgery. Patients with active fistulas may be included	- Endoscopy with evidence of active CD during the current disease flare (defined as ulcerations in the ileum and/or colon). The endoscopy must have occurred within 3 months prior to baseline. • Meet the following requirements for prior or current medications for CD: - Has failed conventional therapy: - Is currently receiving corticosteroids and/or immunomodulators (i.e. AZA, MTX, or 6-MP) at adequate therapeutic doses, OR - Has a history of failure to respond to or tolerate an adequate course of corticosteroids and/or immunomodulators (i.e. AZA, MTX, or 6-MP), OR - Is corticosteroid dependent or has had a history of corticosteroid dependency • Has not previously demonstrated inadequate response or intolerance to 1 or more TNFα inhibitor therapies (i.e. infliximab, adalimumab, or certolizumab pegol)	

Study	UNITI-1	UNITI-2	IM-UNITI
	if there is no anticipation of a need for surgery and there are currently no abscesses identified. • Has had any kind of bowel resection within 6 months or any other intra-abdominal surgery within 3 months prior to baseline. • Has a draining (i.e. functioning) stoma or ostomy. • Current or recent use of other immunosuppressive therapies. • Signs and symptoms of ongoing infections, history of serious infections, history of transplantations, cancer or other complications. • Pregnant or breastfeeding women	• Adhere to the requirements for concomitant medication for the treatment of CD. Exclusion criteria were the same as those listed for UNITI-1.	
Settings and location where the data were collected	Samples were tested at a central laboratory and post-baseline test results were not to be released to the investigators. The Sponsor or its designee assayed samples under conditions in which the identification of the patient and treatment assignment were blinded. An independent DMC was used to monitor patient safety.	Samples were tested at a central laboratory and post-baseline test results were not to be released to the investigators. The Sponsor or its designee assayed samples under conditions in which the identification of the patient and treatment assignment were blinded. An independent DMC was used to monitor patient safety.	Samples were tested at a central laboratory and post-baseline test results were not to be released to the investigators. The Sponsor or its designee assayed samples under conditions in which the identification of the patient and treatment assignment were blinded. An independent DMC was used to monitor patient safety.
Trial drugs	**Ustekinumab 130mg:** patients received a fixed IV dose of 130mg of ustekinumab at Week 0	**Ustekinumab 130mg:** patients received a fixed IV dose of 130mg of ustekinumab at Week 0	**Ustekinumab 90mg q12w:** patients received an SC dose every 12 weeks

Study	UNITI-1	UNITI-2	IM-UNITI
	Ustekinumab ~6mg/kg: patients received 1 of 3 IV doses of ustekinumab, based on their weight, to approximate a dose of 6mg/kg. The exact doses were: • Ustekinumab 260mg (weight ≤55kg) • Ustekinumab 390mg (weight >55kg and ≤85kg) • Ustekinumab 520mg (weight >85kg) **Placebo:** patients received a matching IV placebo	**Ustekinumab ~6mg/kg:** patients received 1 of 3 IV doses of ustekinumab, based on their weight, to approximate a dose of 6mg/kg. The exact doses were: • Ustekinumab 260mg (weight ≤55kg) • Ustekinumab 390mg (weight >55kg and ≤85kg) • Ustekinumab 520mg (weight >85kg) **Placebo:** patients received a matching IV placebo	**Ustekinumab 90mg q8w:** patients received an SC dose every 8 weeks **Placebo:** patients received a matching SC placebo Patients who lost response were eligible to move to the ustekinumab 90mg SC q8w dose (patients already on this schedule continued on it). Patients who showed no improvement 16 weeks after dose adjustment were discontinued from the study and considered as treatment failures (responders continued at this dose). **Non-randomised patients:** Patients in clinical response to placebo in the induction trials continued to receive placebo in IM-UNITI. Patients not in clinical response to IV placebo induction received ustekinumab 130mg IV administration at Week 0. Patients who achieved clinical response at Week 8 initiated ustekinumab 90mg SC at Week 8 and then q12w thereafter through Week 32; otherwise they were discontinued from further study agent administration. Patients who were not in clinical response to ustekinumab IV induction received ustekinumab 90mg SC at Week 0 of this maintenance study. Patients who achieved clinical response at Week 8 continued to

Study	UNITI-1	UNITI-2	IM-UNITI
			receive ustekinumab 90 mg SC q8w through Week 40; otherwise they were discontinued from further study agent administration.
Permitted and disallowed concomitant medication	The following medications were permitted provided dosing had been stable for at least 3 weeks prior to baseline, unless otherwise specified: • Oral 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) providing patients had been taking them for ≥12 weeks, and dosing had been stable dose for at least 4 weeks prior to baseline • Oral corticosteroids (e.g. prednisone, budesonide) at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide • Antibiotics being used as a primary treatment for CD. Patients were not to initiate treatment with any of the following concomitant CD-specific therapies: • Oral or rectal 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) • Oral, parenteral or rectal corticosteroids	The following medications were permitted provided dosing had been stable for at least 3 weeks prior to baseline, unless otherwise specified: • Oral 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) providing patients had been taking them for ≥12 weeks, and dosing had been stable dose for at least 4 weeks prior to baseline • Oral corticosteroids (e.g. prednisone, budesonide) at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide • Antibiotics being used as a primary treatment for CD. Patients were not to initiate treatment with any of the following concomitant CD-specific therapies: • Oral or rectal 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) • Oral, parenteral or rectal corticosteroids	The following medications were permitted provided dosing had been stable for at least 3 weeks prior to baseline, unless otherwise specified: • Oral 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) providing patients had been taking them for ≥12 weeks, and dosing had been stable dose for at least 4 weeks prior to baseline • Oral corticosteroids (e.g. prednisone, budesonide) at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide • Antibiotics being used as a primary treatment for CD. With the exception of corticosteroids for which tapering was recommended, dosing of concomitant medications was to remain stable through Week 44. Patients were not to initiate treatment with any of the following concomitant CD-specific therapies: • Oral or rectal 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX)

Study	UNITI-1	UNITI-2	IM-UNITI
	• Antibiotics as a primary treatment for CD • Total parenteral nutrition as a primary treatment for CD The following medications were prohibited: • Immunomodulatory agents other than 6-MP/AZA or MTX • Immunomodulatory biologic agents (including but not limited to natalizumab, abatacept) • Experimental CD medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG 827)	• Antibiotics as a primary treatment for CD • Total parenteral nutrition as a primary treatment for CD The following medications were prohibited: • Immunomodulatory agents other than 6-MP/AZA or MTX • Immunomodulatory biologic agents (including but not limited to natalizumab, abatacept) • Experimental CD medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG 827)	• Oral, parenteral or rectal corticosteroids • Antibiotics as a primary treatment for CD • Total parenteral nutrition as a primary treatment for CD The following medications were prohibited: • Immunomodulatory agents other than 6-MP/AZA or MTX • Immunomodulatory biologic agents (including but not limited to natalizumab, abatacept) • Experimental CD medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG 827)
Primary outcome	The primary endpoint was clinical response at Week 6, defined as a reduction from baseline in the CDAI score ≥100 points. Patients with a baseline CDAI score ≥ 220 to ≤ 248 points were considered to be in clinical response if a CDAI score <150 was attained.	The primary endpoint was clinical response at Week 6, defined as a reduction from baseline in the CDAI score ≥100 points. Patients with a baseline CDAI score ≥ 220 to ≤ 248 points were considered to be in clinical response if a CDAI score <150 was attained.	The primary endpoint was clinical remission at Week 44, defined as a CDAI score <150 points. Safety of the two maintenance regimens of ustekinumab was also considered a primary endpoint.
Major secondary outcomes	Secondary endpoints included: • Clinical remission at Week 8, defined as a CDAI score <150 points • Clinical response at Week 8	Secondary endpoints included: • Clinical remission at Week 8, defined as a CDAI score <150 points • Clinical response at Week 8	Secondary endpoints included: • Clinical response at Week 44 • Clinical remission at Week 44 for patients in clinical remission to ustekinumab at Week 0

Study	UNITI-1	UNITI-2	IM-UNITI
	• CDAI ≥70-point response at Week 6 • CDAI ≥70-point response at Week 3 Safety assessments were based on reported AEs, clinical laboratory test results, vital sign measurements, physical examinations, ECG findings and TB testing.	• CDAI ≥70-point response at Week 6 • CDAI ≥70-point response at Week 3 Safety assessments were based on reported AEs, clinical laboratory test results, vital sign measurements, physical examinations, ECG findings and TB testing.	• Corticosteroid-free remission at Week 44 • Clinical remission at Week 44 in the subset of patients who were refractory or intolerant to TNFα inhibitor therapy i.e. patients from UNITI-1 Safety assessments were based on reported AEs, clinical laboratory test results, vital sign measurements, physical examinations, ECG findings and TB testing.
Other outcomes	Other endpoints included: • Clinical response/remission over time • Inflammatory biomarkers - serum CRP - faecal calprotectin - faecal lactoferrin • IBD-specific and general HRQL measures - IBDQ - SF-36 • Medical resource utilisation and health economics • Relationship between efficacy and pharmacokinetics • Relationship between efficacy and antibodies to ustekinumab status	Other endpoints included: • Clinical response/remission over time • Inflammatory biomarkers - serum CRP - faecal calprotectin - faecal lactoferrin • IBD-specific and general HRQL measures - IBDQ - SF-36 • Medical resource utilisation and health economics • Relationship between efficacy and pharmacokinetics • Relationship between efficacy and antibodies to ustekinumab status	Other endpoints included: • Change in the CDAI score and the CDAI component scores • Corticosteroid endpoints and fistula response • Analyses to assess the effect of dose adjustment • Inflammatory biomarkers - serum CRP - faecal calprotectin - faecal lactoferrin • IBD-specific and general HRQL measures - IBDQ - SF-36 • Medical resource utilisation and health economics

Study	UNITI-1	UNITI-2	IM-UNITI
	Mucosal healing was also assessed by ileocolonoscopy in patients at participating sites who consented to inclusion in the endoscopic substudy.	Mucosal healing was also assessed by ileocolonoscopy in patients at participating sites who consented to inclusion in the endoscopic substudy.	• Relationship between efficacy and pharmacokinetics • Relationship between efficacy and antibodies to ustekinumab status Mucosal healing was also assessed by ileocolonoscopy in patients at participating sites who consented to inclusion in the endoscopic substudy.
Pre-planned subgroups	To evaluate the consistency of the efficacy of the primary endpoint over demographic, baseline disease characteristics, CD medication history, concomitant CD medication use at baseline, centre location, and initial response to TNFα inhibitor therapy. Subgroup analyses were planned when the number of patients in the subgroups permitted.	To evaluate the consistency of the efficacy of the primary endpoint over demographic, baseline disease characteristics, CD medication history, concomitant CD medication use at baseline, centre location, and initial response to TNFα inhibitor therapy. Subgroup analyses were planned when the number of patients in the subgroups permitted.	To evaluate the consistency of the efficacy of the primary endpoint over demographic, induction baseline disease characteristics, CD medication history (including TNFα inhibitor therapy), CD medication use at induction baseline, and centre location. Subgroup analyses were planned when the number of patients in the subgroups permitted.

Key: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; CDAI, Crohn's disease activity index; CRP, C-reactive protein; eCRF, electronic case report form; HRQL, health-related quality of life; IBD, irritable bowel disease; IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; MTX, methotrexate; OR, odds ratio; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; SF-36, 36-item short form health questionnaire; TNF, tumour necrosis factor.
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]; IM-UNITI CSR.[134]

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The hypothesis and associated statistical analysis methods adopted for primary endpoint analyses in the UNITI trial programme are presented in Table 12.

UNITI-1 and UNITI-2 were initiated in June 2011, and IM-UNITI was initiated in September 2011. [redacted] All efficacy analyses were carried out based on the intent-to-treat (ITT) principle and included all randomised patients (excluding patients randomised prior to study restart). Safety analyses were carried out in the Treated population, which consisted of all randomised patients who received at least one dose of study drug with patients analysed according to the actual treatment received.

For all studies, two database locks and no interim analyses were planned. In UNITI-1 and UNITI-2, the first database lock occurred after all patients had completed the Week 8 visit or discontinued from the study before Week 8; the second database lock occurred after all patients who did not enter the maintenance study (IM-UNITI) had completed their final safety visit (20 weeks after the administration of study agent) or discontinued from the study. In IM-UNITI, the first database lock occurred after all patients had completed the Week 44 visit or discontinued from the study before Week 44. The second database lock will occur after all patients have completed their final safety visit at Week 272 or discontinued from the study.

Table 12: Summary of statistical analyses UNITI-1, UNITI-2 and IM-UNITI

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
UNITI-1	The study was considered to be positive if the ustekinumab high dose group was significantly different from the placebo group for the primary endpoint.	Efficacy analyses included all patients randomised at Week 0, excluding 28 patients randomised prior to the study restart. Efficacy analyses were based on the ITT principle. The proportion of patients in clinical response at Week 6 was compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided CMH chi-square test, stratified by study region (Asia, Eastern Europe, or rest of world), CDAI score (≤300 or >300), and initial response to TNF antagonist therapy (yes or no), at a significance level of 0.05. A fixed sequence testing procedure was used to control the overall Type 1 error rate at the 0.05 level of significance. Specifically, the ustekinumab high dose group (~6 mg/kg) was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab high dose group was significantly different from	Assuming a 25% clinical response rate at Week 6 in the placebo group and a 40% rate in the ustekinumab high dose group, 205 patients per treatment group were predicted to yield an overall power of 90%, at a significance level of 0.05 (2-sided). The power for detecting a significant difference between the ustekinumab high dose group and placebo was also examined for the first major secondary endpoint of clinical remission at Week 8. Assuming a 10% clinical remission rate at Week 8 in the placebo group, and a rate of 20% in the ustekinumab high-dose group, 205 patients per treatment group were predicted to yield an overall power of 81%, at a significance level of 0.05 (2-sided).	All randomised patients were included in the efficacy analyses. Treatment failure rules were applied to determine each patient's final response status, and these rules overrode the CDAI score, such that if a patient had one of the following events before Week 6, they were considered a treatment failure, regardless of their actual CDAI score: • CD-related surgery (with the exception of drainage of an abscess or seton placement) that was thought to be a result of a lack of efficacy of study agent • Pre-specified changes in concomitant CD medication The CDAI score was calculated for a visit only if 4 or more of the 8 components were available at that visit. When at least 4 of the 8 components were available, any missing components were imputed by carrying forward the last non-missing component, with the exception of a missing haematocrit value. For missing baseline haematocrit values, the haematocrit value obtained closest to and before the date of the Week 0 infusion was used. For all other visits, the haematocrit value obtained closest to the date of the visit was used, provided that it was obtained within 7 days of the visit. If the laboratory value was not

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		the placebo group, then the ustekinumab low dose group (130mg) was compared with the placebo group at the 2-sided 0.05 level of significance.	To increase the power to detect a significant difference for the clinical remission endpoint, the sample size for the key efficacy analyses was increased to 225 patients per treatment group (total sample size of 675), which provides 85% power for the clinical remission endpoint.	available within the ±7-day window, then the closest previous haematocrit value was carried forward. If the CDAI score could not be calculated (i.e. <4 components available) at a visit, the CDAI score was considered missing. Patients with a missing CDAI score at Week 6 were considered to not have achieved clinical response at Week 6.
UNITI-2	The study was considered to be positive if the ustekinumab high dose group was significantly different from the placebo group for the primary endpoint.	Efficacy analyses included all patients randomised at Week 0, excluding 12 patients randomised prior to the study restart. Efficacy analyses were based on the ITT principle. The proportion of patients in clinical response at Week 6 was compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided CMH chi-square test, stratified by study region (Asia, Eastern Europe, or rest of world) and CDAI score (≤300 or >300), at a significance level of 0.05. A fixed sequence testing procedure was used to control the overall Type 1 error rate at	Assuming a 33% clinical response rate at Week 6 in the placebo group and 50% in the ustekinumab high dose group, 200 patients per treatment group will yield an overall power above 90%, at a significance level of 0.05 (2-sided). The power for detecting a significant difference between the ustekinumab high dose group and placebo was also examined for the first major secondary endpoint of clinical remission at Week 8. Assuming a 12% clinical remission rate at	All randomised patients were included in the efficacy analyses. Treatment failure rules were applied to determine each patient's final response status, and these rules overrode the CDAI score, such that if a patient had one of the following events before Week 6, they were considered a treatment failure, regardless of their actual CDAI score: • CD-related surgery (with the exception of drainage of an abscess or seton placement) that was thought to be a result of a lack of efficacy of study agent • Pre-specified changes in concomitant CD medication The CDAI score was calculated for a visit only if 4 or more of the 8 components were available at that visit. When at least 4 of the 8 components were available, any missing

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		the 0.05 level of significance. Specifically, the ustekinumab high dose group (~6 mg/kg) was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab high dose group was significantly different from the placebo group, then the ustekinumab low dose group (130mg) was compared with the placebo group at the 2-sided 0.05 level of significance.	Week 8 in the placebo group, and a rate of 25% in the ustekinumab high dose group, 200 patients per treatment group was predicted to yield an overall power above 90% for the first major secondary endpoint of clinical remission at Week 8, at a significance level of 0.05 (2-sided).	components were imputed by carrying forward the last non-missing component, with the exception of a missing haematocrit value. For missing baseline haematocrit values, the haematocrit value obtained closest to and before the date of the Week 0 infusion was used. For all other visits, the haematocrit value obtained closest to the date of the visit was used, provided that it was obtained within 7 days of the visit. If the laboratory value was not available within the ±7-day window, then the closest previous haematocrit value was carried forward. If the CDAI score could not be calculated (i.e. <4 components available) at a visit, the CDAI score was considered missing. Patients with a missing CDAI score at Week 6 were considered to not have achieved clinical response at Week 6.
IM-UNITI	Ustekinumab maintenance therapy is superior to placebo in patients with moderately to severely active CD induced into clinical response with ustekinumab in the induction studies, as	Primary study analyses included all patients randomised at Week 0, excluding 9 patients randomised prior to the study restart. Efficacy analyses were based on the ITT principle. The proportion of patients in clinical remission at Week 44 was compared between each of the ustekinumab treatment groups and the placebo group	Assuming a 15% clinical remission rate at Week 44 in the placebo group and 35% in the 90 mg q8w ustekinumab group, 100 patients per treatment group were predicted to yield power above 90%, at a significance level of 0.05 (2-sided). Assuming clinical response rates of 35%	All randomised patients were included in the efficacy analyses. Treatment failure rules were applied to determine each patient's final remission status, and these rules overrode the CDAI score, such that if a patient had one of the following events before Week 44, they were considered a treatment failure, regardless of their actual CDAI score: • CD-related surgery (with the exception of drainage of an abscess or seton

Study	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	measured by the proportion of patients who are in clinical remission at Week 44	using a 2-sided CMH chi-square test, stratified by clinical remission status at Week 0 (yes or no) and ustekinumab induction dose (130 mg or weight-range-based doses approximating ustekinumab 6 mg/kg) at a significance level of 0.05. To control the overall Type 1 error rate, the primary endpoint was tested in a fixed sequence. Specifically, the ustekinumab 90 mg SC q8w group was first compared with the placebo group at the 2-sided 0.05 level of significance. If the ustekinumab 90 mg SC q8w group was significantly different from the placebo group, then the ustekinumab 90 mg SC q12w group was compared with the placebo group at the 2-sided 0.05 level of significance.	and 40% in the 2 ustekinumab dose groups in UNITI-1, and clinical response rates of 45% and 50% in the UNITI-2 study, and an assumption of 10% drop-out rate, approximately 322 responders (approximately 107 per treatment group) were predicted to enter into the maintenance study.	placement) that was thought to be a result of a lack of efficacy of study agent • Discontinuation of study agent due to lack of efficacy or due to an AE of worsening CD • Loss of clinical response, defined as a CDAI score ≥220 points AND a ≥100 point increase from the Week 0 CDAI score • Pre-specified changes in concomitant CD medication In addition, patients who did not return for evaluation or had insufficient data to assess their clinical remission status at Week 44 (i.e. <4 components of the CDAI are available) were also considered to not have achieved clinical remission. To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint were conducted using different missing data approaches, including observed case and last observation carried forward.

Key: CD, Crohn's disease; CDAI, Crohn's disease activity index; CMH, Cochran-Mantel-Haenszel; ITT, intent-to-treat; SC, subcutaneous; TNF, tumour necrosis factor; q8w, every 8 weeks; q12w, every 12 weeks.
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]; IM-UNITI CSR.[134]

4.5 Participant flow in the relevant randomised controlled trials

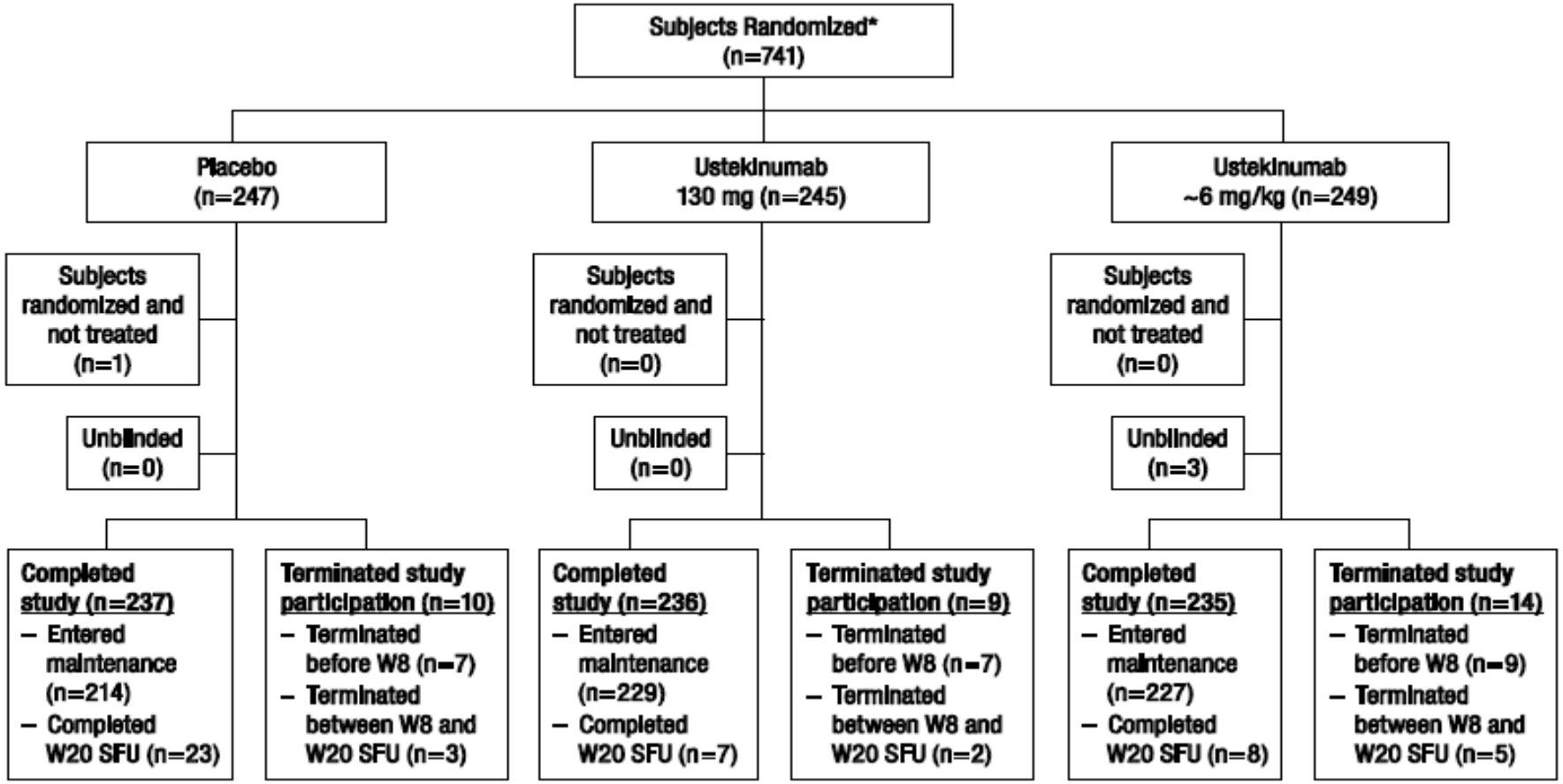
4.5.1 Patient disposition

The CONSORT flow chart for patient disposition in UNITI-1 and UNITI-2 are presented in Figure 8 and Figure 9, respectively.

The CONSORT flow chart patient disposition of the primary study population in IM-UNITI is presented in Figure 10 (patients randomised to maintenance treatment).

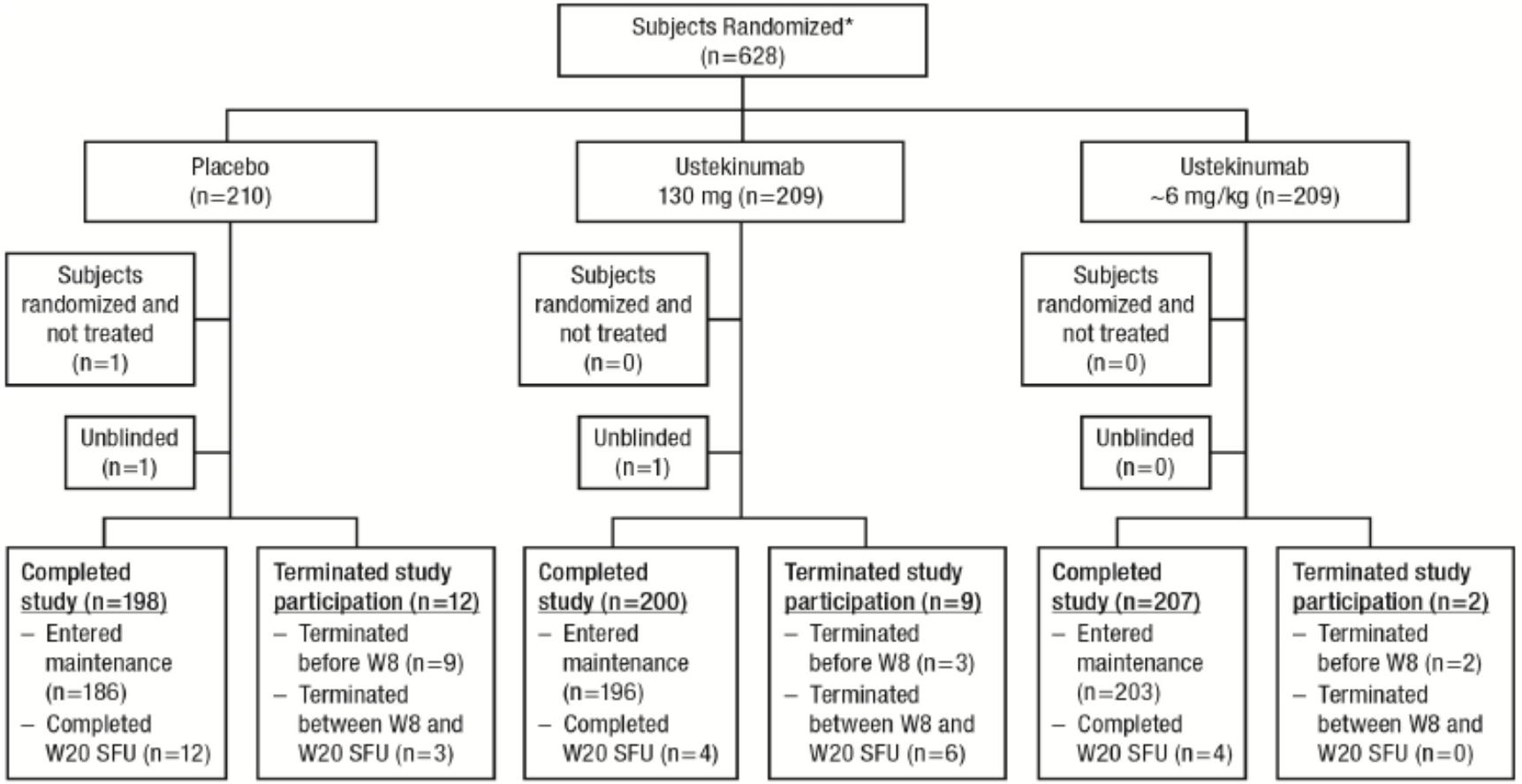
The CONSORT flow chart for patients not randomised to treatment (i.e. patients who responded to placebo and non-responders in the induction trials) in IM-UNITI is presented in Figure 11.

Figure 8: Consort diagram of patient disposition in UNITI-1



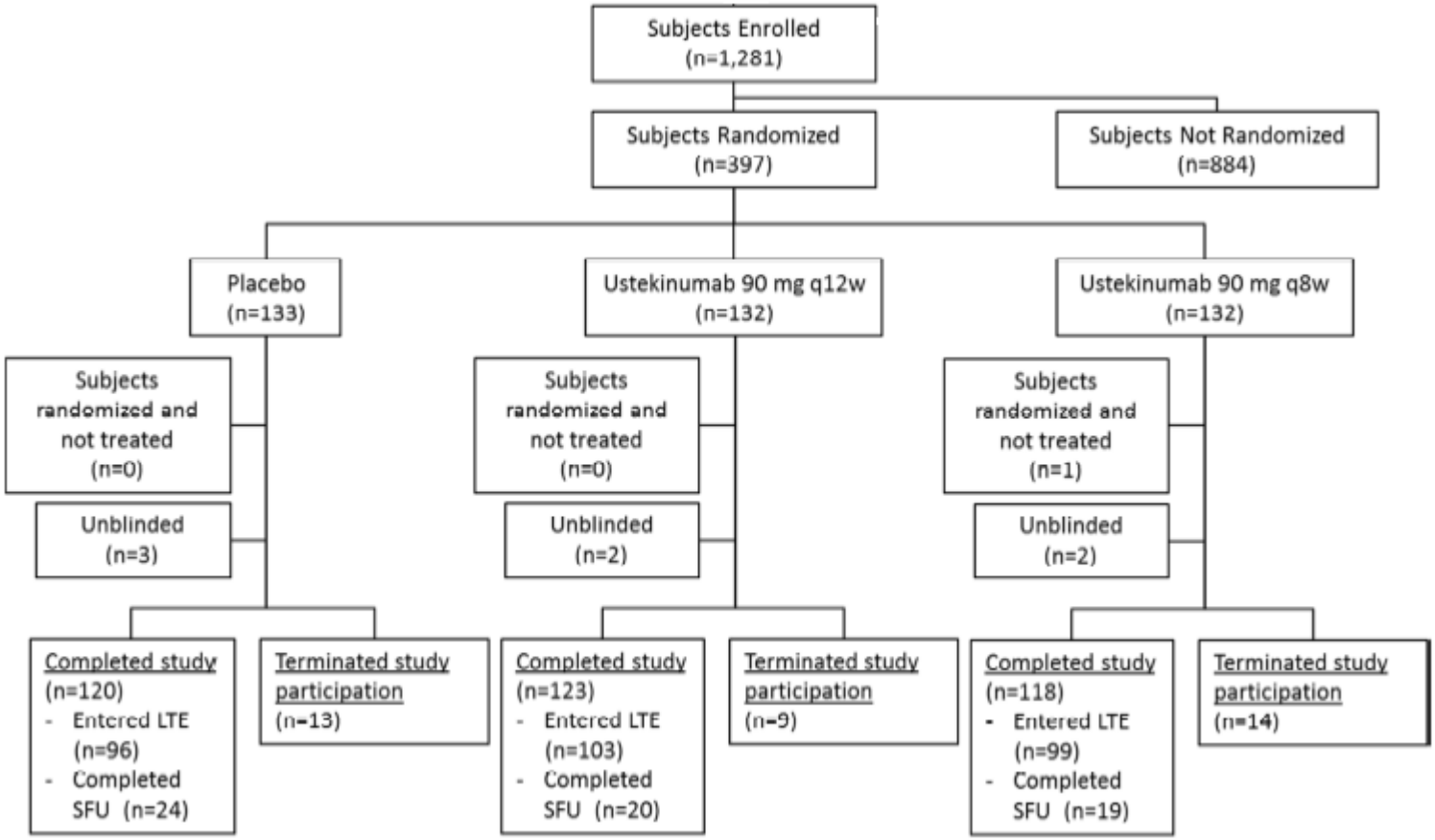
Key: SFU, safety follow-up.
Notes: *, Excludes patients randomised before study restart.
Source: UNITI-1 CSR[135]

Figure 9: Consort diagram of patient disposition in UNITI-2



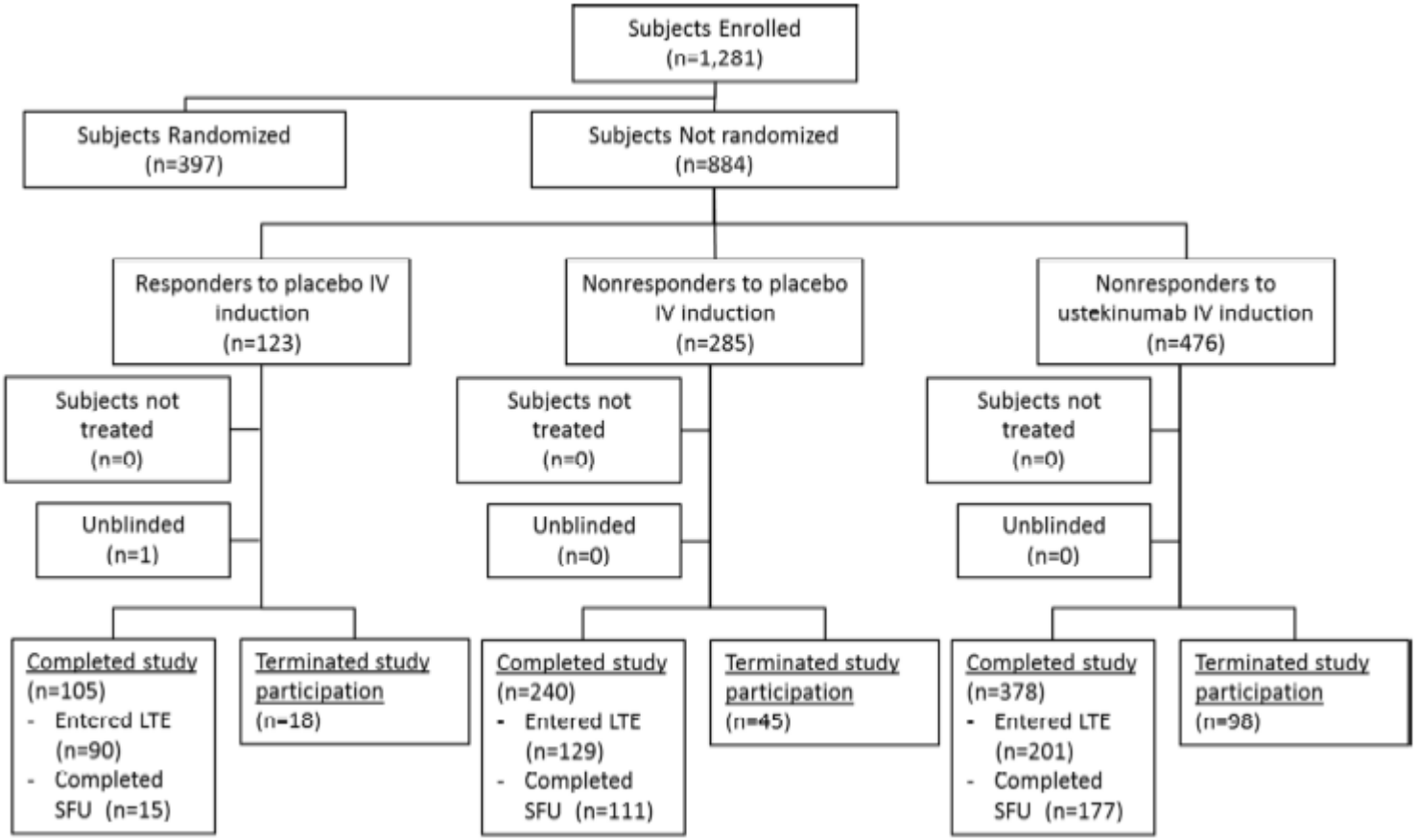
Key: SFU, safety follow-up.
Notes: *, Excludes patients randomised before study restart.
Source: UNITI-2 CSR[136]

Figure 10: Consort diagram of patient disposition in IM-UNITI (randomised patients)



Key: LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SFU, safety follow-up.
Source: IM-UNITI CSR[134]

Figure 11: Consort diagram of patient disposition in IM-UNITI (non-randomised patients)



Key: IV, intravenous; LTE, long-term extension; SFU, safety follow-up.
Source: IM-UNITI-CSR.[134]

4.5.2 Baseline characteristics

Baseline demographics and clinical characteristics of patients were well balanced between treatment groups and were generally similar across studies, as summarised in Table 13.

All study populations were representative of patients presenting with moderately to severely active CD in clinical practice. Differences that were observed between patients enrolled in UNITI-1 and UNITI-2 were reflective of the differences in trial eligibility criteria. Half of all patients in UNITI-1 had failed 2 or more TNFα inhibitor therapies. As we would therefore expect *a priori*, given this extensive treatment history, patients in UNITI-1 had more severe (median CDAI of 317 vs 292.5) and long-standing (10.1 vs 6.4 years) disease compared with patients in UNITI-2, as well as a modestly higher proportion of concomitant corticosteroid use at baseline (45.9% vs 39.3%).

Baseline characteristics data for randomised patients in IM-UNITI are provided for their disease at the start of induction therapy. Baseline characteristics data at the start of the maintenance therapy are provided in Appendix 4.

Table 13: Baseline characteristics of patients randomised in ustekinumab RCTs

	UNITI-1			UNITI-2			IM-UNITI		
Treatment	Ustekinumab		Placebo	Ustekinumab		Placebo	Ustekinumab 90mg		Placebo
Dose/schedule	130mg	~6mg/kg		130mg	~6mg/kg		q12w	q8w	
Randomised patients	245	249	247	209	209	210	132	132	133
Demographic characteristics									
Sex, male, n (%)	98 (40.0)	101 (40.6)	118 (47.8)	104 (49.8)	90 (43.1)	99 (47.1)	59 (44.4)	56 (42.4)	58 (43.9)
Age, years, mean (SD)	37.4 (11.8)	37.3 (12.5)	37.3 (11.8)	39.1 (13.8)	38.4 (13.1)	40.2 (13.1)	37.9 (13.2)	38.6 (13.7)	39.5 (12.7)
Weight, kg, mean (SD)	68.4 (17.4)	69.5 (19.5)	71.5 (17.7)	74.4 (21.3)	71.9 (18.8)	74.0 (19.9)	70.6 (16.9)	70.0 (19.6)	72.3 (17.3)
Crohn's disease characteristics									
Disease duration, years, mean (SD)	11.8 (8.3)	12.7 (9.2)	12.1 (8.4)	8.7 (8.5)	8.7 (8.4)	10.4 (9.8)	10.3 (8.7)	9.5 (8.7)	10.6 (9.5)
CDAI score, mean (SD)	321.0 (64.7)	327.6 (62.0)	319.0 (59.7)	304.1 (57.0)	302.2 (58.9)	302.2 (61.7)	320.4 (66.7)	313.1 (58.0)	319.1 (60.8)
C-reactive protein, mg/L, median	10.4	9.9	8.5	7.4	7.8	8.5	8.8	9.1	9.6
Faecal calprotectin, mg/kg, median	399.9	530.2	515.8	519.6	523.2	415.5	536.5	567.5	587.4
GI areas involved, n (%)									
Total	245	249	246	208	209	210	132	132	133
Ileum only	38 (15.5)	37 (14.9)	28 (11.4)	53 (25.5)	49 (23.4)	44 (21.0)	26 (19.7)	19 (14.4)	19 (14.3)
Colon only	36 (14.7)	40 (16.1)	48 (19.5)	44 (21.2)	43 (20.6)	37 (17.6)	23 (17.4)	29 (22.0)	28 (21.1)
Ileum and colon	171 (69.8)	171 (68.7)	166 (67.5)	109 (52.4)	117 (56.0)	129 (61.4)	83 (62.9)	84 (63.6)	86 (64.7)
Proximal GI tract	57 (23.3)	54 (21.7)	45 (18.3)	34 (16.3)	29 (13.9)	32 (15.2)	18 (!3.6)	19 (!4.4)	28 (21.1)
Perianal GI tract	107 (43.7)	107 (43.0)	107 (43.5)	60 (28.8)	61 (29.2)	57 (27.1)	39 (29.5)	46 (34.8)	43 (32.3)

	UNITI-1			UNITI-2			IM-UNITI		
Medications for Crohn's disease taken at baseline, n (%)									
One or more medications	178 (72.7)	174 (69.9)	185 (74.9)	161 (77.0)	170 (81.3)	158 (75.2)	106 (80.3)	108 (81.8)	101 (75.9)
Immunosuppressant	74 (30.2)	78 (31.3)	81 (32.8)	74 (35.4)	72 (34.4)	73 (34.8)	52 (39.4)	44 (33.3)	47 (35.3)
Aminosalicylate	50 (20.4)	50 (20.1)	54 (21.9)	89 (42.6)	93 (44.5)	89 (42.4)	47 (35.6)	49 (37.1)	46 (34.6)
Glucocorticoid	121 (49.4)	108 (43.4)	111 (44.9)	80 (38.3)	92 (44.0)	75 (35.7)	58 (43.9)	64 (48.5)	59 (44.4)
History of disease refractory to treatment with TNF antagonist, n (%)	243 (99.2)	246 (98.8)	246 (99.6)	NA	NA	NA	59 (44.7)	58 (43.9)	61 (45.9)
No history of TNF antagonist treatment, n (%)	NA	NA	NA	152 (72.7)	144 (68.9)	131 (62.4)	53 (40.2)	52 (39.4)	52 (39.1)
History of TNF antagonist treatment failure, n (%):									
Patients who received 1 drug	124 (50.6)	120 (48.2)	112 (45.3)	NA	NA	NA	NA	NA	NA
Patients who received 2 or 3 drugs	119 (48.6)	126 (50.6)	134 (54.3)	NA	NA	NA	NA	NA	NA
Primary non-response	70 (28.6)	72 (28.9)	74 (30.0)	NA	NA	NA	NA	NA	NA
Secondary non-response	173 (70.6)	171 (68.7)	170 (68.8)	NA	NA	NA	NA	NA	NA
Unacceptable side effects	78 (31.8)	105 (42.2)	87 (35.2)	NA	NA	NA	NA	NA	NA

Key: CDAI, Crohn's disease activity index; GI, gastrointestinal; NA, not applicable; SD, standard deviation; TNF, tumour necrosis factor.
Source: Feagen *et al*. 2016.[133]

4.6 Quality assessment of the relevant randomised controlled trials

All three trials were conducted in accordance with good clinical practice (GCP) guidelines with a single protocol to promote consistency across sites, and with measures taken to minimise bias.

The accuracy and reliability of the clinical study data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the Sponsor. In addition, an independent Data Monitoring Committee (DMC) was established with the responsibility of safeguarding the interests of study participants.

Randomisation in the trials was successfully carried out such that baseline characteristics of patients randomised were well balanced across treatment groups. There were few drop-outs in the trials, and patient withdrawals were accounted for with pre-defined, standard censoring methods. Patients and investigators remained blinded throughout the study, and all outcome assessments were conducted in accordance with trial validated methodology and were based on the ITT principle.

Importantly, the UNITI trial programme is thought to adequately reflect routine clinical practice in the UK with respect to population, treatment administration and outcomes assessed. Although formally placebo-controlled in design, patients were permitted to receive concomitant corticosteroid and immunosuppressant treatments, and thus, placebo groups represent conventional therapy as it is utilised in clinical practice.

Quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is presented in Table 14. The risk of bias in both induction trials (UNITI-1 and UNITI-2) and the maintenance trial (IM-UNITI) is considered to be low.

Table 14: Quality assessment results for UNITI-1, UNITI-2 and IM-UNITI

Study question	**How is the question addressed in the study?**			**Risk of bias**
	UNITI-1	**UNITI-2**	**IM-UNITI**	
Was randomisation carried out appropriately?	Yes	Yes	Yes	Low
	Patients were randomised using permuted block randomisation with stratification for key prognostic factors.			

Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Low
	Randomisation implemented via a centralised IVRS/IWRS.			
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Low
	Patient demographics were well balanced, with no key differences between treatment groups.			
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Low
	Patients and investigators remained blinded to the study allocation throughout.			
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	Low
	Few patients withdrew from the study and the numbers and reasons were well balanced across treatment arms.			
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Low
	Efficacy analyses were performed according to the ITT principle, with standard censoring methods used to account for missing data.			
Key: ITT, intention-to-treat; IVRS, interactive voice response system; IWRS, interactive web response system. **Source:** UNITI-1 CSR[135]; UNITI-2 CSR[136]; IM-UNITI CSR.[134]				

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Data for the two 8-week induction trials (UNITI-1 and UNITI-2) and the 44-week maintenance trial (IM-UNITI) have recently been published[133], but were predominantly taken from CSRs[134-136] and conference presentations[4, 5, 137-139] during submission development.

Primary and key secondary endpoints for UNITI-1 and UNITI-2 are summarised in Table 15 and Figure 12. Primary and key secondary endpoints for IM-UNITI are summarised in Table 16 and Figure 13.

4.7.1 Primary efficacy endpoint in UNITI-1 and UNITI-2

UNITI-1

Clinical response was defined as a reduction from baseline in the CDAI score of ≥100 points. The proportion of patients in clinical response (CDAI-100) at Week 6

was significantly greater in both the ~6 mg/kg (33.7%) and 130 mg (34.3%) ustekinumab groups compared with the placebo group (21.5%; p=0.003 and p=0.002, respectively).

UNITI-2

The proportions of patients in clinical response (CDAI-100) at Week 6 was significantly greater in both the ~6 mg/kg (55.5%) and 130 mg (51.7%) ustekinumab groups than in the placebo group (28.7%, p<0.001 for both comparisons).

4.7.2 Major secondary efficacy endpoints in UNITI-1 and UNITI-2

UNITI-1

Clinical remission was defined as a CDAI score of <150 points. The proportion of patients in clinical remission at Week 8 was significantly greater in both the ~6 mg/kg (20.9%) and 130 mg (15.9%) ustekinumab groups than in the placebo group (7.3%; p<0.001 and p=0.003, respectively). The proportion of patients in clinical remission at Week 8 was numerically greater for the ~6 mg/kg group compared with that in the 130 mg group.

The proportion of patients in clinical response (CDAI-100) at Week 8 was significantly greater in both the ~6 mg/kg (37.8%) and 130 mg (33.5%) ustekinumab groups compared with the placebo group (20.2%; p<0.001 and p=0.001, respectively). Of note, this was the response criterion adopted at re-randomisation for the IM-UNITI maintenance trial.

The proportion of patients in CDAI ≥70-point response at Week 6 was significantly greater in both the ~6 mg/kg (43.8%) and 130 mg (46.1%) groups compared with the placebo group (30.4%; p=0.002 and p<0.001, respectively). The proportion of patients in CDAI ≥70-point response at Week 3 was also significantly greater in both the ~6 mg/kg (40.6%) and 130 mg (38.4%) groups compared with the placebo group (27.1%; p=0.001 and p=0.009, respectively).

UNITI-2

The proportions of patients in clinical remission at Week 8 was significantly greater in both the ~6 mg/kg (40.2%) and 130 mg (30.6%) ustekinumab groups than in the placebo group (19.6%, p<0.001 and p=0.009, respectively). The proportion of

patients in clinical remission at Week 8 was numerically greater for the ~6 mg/kg group compared with that in the 130 mg group.

The proportion of patients in clinical response (CDAI-100) at Week 8 was significantly greater in both the ~6 mg/kg (57.9%) and 130 mg (47.4%) ustekinumab groups than in the placebo group (32.1%, p<0.001 for both comparisons).

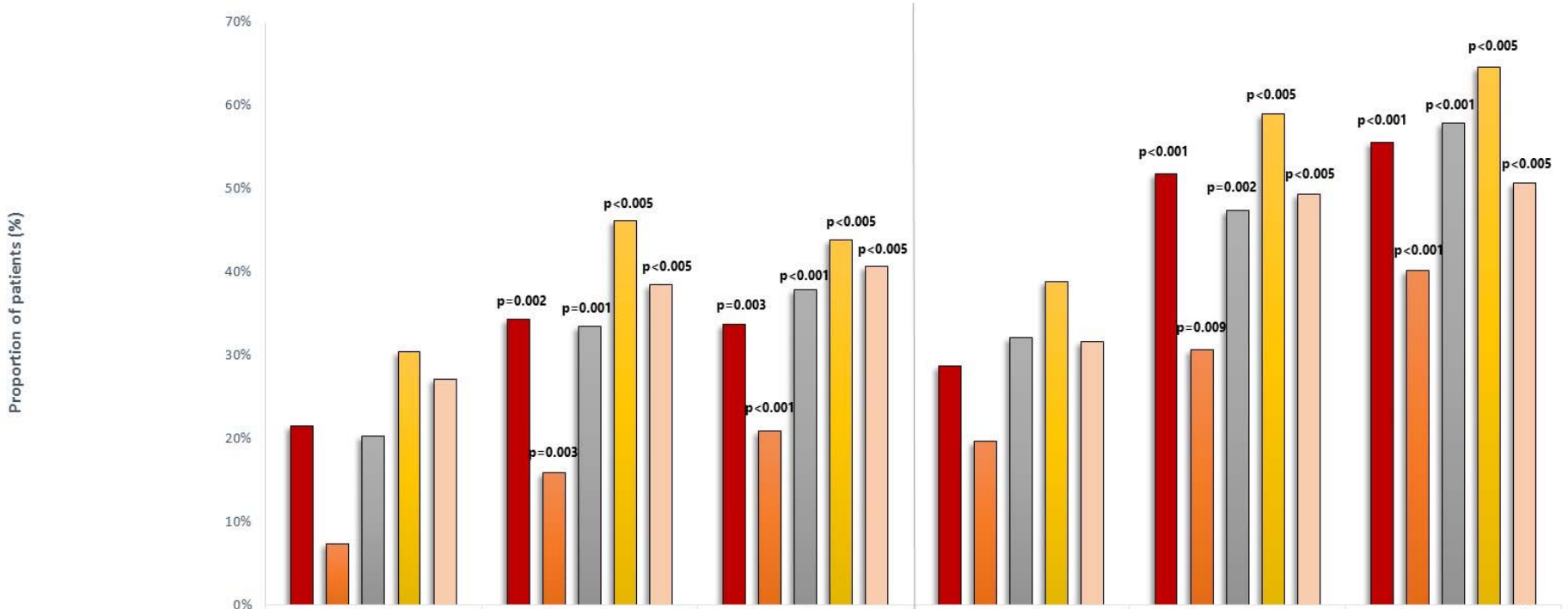
The proportion of patients in CDAI ≥70-point response at Week 6 was significantly greater in both the ~6 mg/kg (64.6%) and 130 mg (58.9%) groups than in the placebo group (38.8%, p<0.001 for both). The proportion of patients in CDAI ≥70-point response at Week 3 was also significantly greater in both the ~6 mg/kg (50.7%) and 130 mg (49.3%) groups than in the placebo group (31.6%; p<0.001 for both).

Table 15: Key efficacy endpoints for UNITI-1 and UNITI-2 (ITT population)

		UNITI-1 (failed anti-TNF therapy)			UNITI-2 (failed conventional therapy)		
		PBO	**UST 130 mg**	**UST ~6 mg/kg**	**PBO**	**UST 130 mg**	**UST ~6 mg/kg**
Randomised patients		247	245	249	209	209	209
Primary endpoint	CDAI-100 response at Week 6, n (%)	53 (21.5)	84 (34.3)[a]	84 (33.7)[a]	60 (28.7)	108 (51.7)[b]	116 (55.5)[b]
Major secondary endpoints	Clinical remission at Week 8, n (%)	18 (7.3)	39 (15.9)[a]	52 (20.9)[b]	41 (19.6)	64 (30.6)[a]	84 (40.2)[b]
	CDAI-100 response at Week 8, n (%)	50 (20.2)	82 (33.5)[a]	94 (37.8)[b]	67 (32.1)	99 (47.4)[b]	121 (57.9)[b]
	CDAI-70 response at Week 6, n (%)	75 (30.4)	113 (46.1)[b]	109 (43.8)[a]	81 (38.8)	123 (58.9)[b]	135 (64.6)[b]
	CDAI-70 response at Week 3, n (%)	67 (27.1)	94 (38.4)[a]	101 (40.6)[a]	66 (31.6)	103 (49.3)[b]	106 (50.7)[b]

Key: CDAI, Crohn's disease activity index; ITT, intention-to-treat; PBO, placebo; TNF, tumour necrosis factor; UST, ustekinumab.
Notes: [a], p <0.01 compared with placebo; [b], p <0.001 compared with placebo.
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]

Figure 12: Key efficacy endpoints for UNITI-1 and UNITI-2 (ITT population)



	Placebo	Ustekinumab 130 mg	Ustekinumab ~6 mg/kg	Placebo	Ustekinumab 130 mg	Ustekinumab ~6 mg/kg
	UNITI I (failed anti-TNF therapy)			UNITI II (failed conventional therapy)		
100-point response at week 6	22%	34%	34%	29%	52%	56%
Clinical remission at week 8	7%	16%	21%	20%	31%	40%
100-point response at week 8	20%	34%	38%	32%	47%	58%
70-point response at week 6	30%	46%	44%	39%	59%	65%
70-point response at week 3	27%	38%	41%	32%	49%	51%

Key: ITT, intent to treat; TNF, tumour necrosis factor.
Source: Adapted from UNITI-1 CSR[135]; UNITI-2 CSR[136]

4.7.3 Primary efficacy endpoint in IM-UNITI

The proportion of patients in clinical remission at Week 44 (1-year post treatment initiation) was significantly greater in both the 90mg q12w (48.8%) and q8w (53.1%) ustekinumab groups than in the placebo group (35.9%; p=0.040, p=0.005, respectively). The proportion of patients in clinical remission at Week 44 was slightly greater for the 8qw group compared with that in the q12w group (numerically; ustekinumab groups not statistically compared).

4.7.4 Major secondary endpoints in IM-UNITI

The proportion of patients in clinical response (CDAI-100) at Week 44 was significantly greater in both the 90mg q12w (58.1%) and q8w (59.4%) ustekinumab groups than in the placebo group (44.3%; p=0.033 and p=0.018, respectively). The proportion of patients maintaining clinical response (CDAI-100) at Week 44 was similar between the q12w and q8w ustekinumab groups.

Among the approximately 60% of patients (n=156) who were in clinical remission at baseline (Week 8 post ustekinumab IV induction), a significantly greater proportion of patients in the ustekinumab 90mg q8w group maintained clinical remission at Week 44 (66.7%) compared with the placebo group (45.6%; p=0.007). Maintenance of clinical remission was also numerically higher in the ustekinumab 90mg q12w group (56.4%) compared with the placebo group; however, this result did not achieve statistical significance (p=0.189).

Corticosteroid-free remission at Week 44 was achieved by a greater proportion of patients in the ustekinumab 90mg q12w and q8w groups (42.6% and 46.9%, respectively) compared with the placebo group (29.8%). Among patients who were receiving corticosteroids at baseline (n=181), a significantly greater proportion in the combined ustekinumab group (30.2%) were able to achieve clinical remission and not be receiving corticosteroids at Week 44 compared with the placebo group (15.5%; p=0.030). In addition, a higher proportion of patients in the ustekinumab 90mg q12w (42.1%) and 8qw (35.6%) groups were able to eliminate corticosteroid use by Week 44 compared with the placebo group (27.6%).

Among patients who were refractory or intolerant to TNFα inhibitor therapy (n=113), clinical remission rates at Week 44 were numerically greater in the 90mg q12w

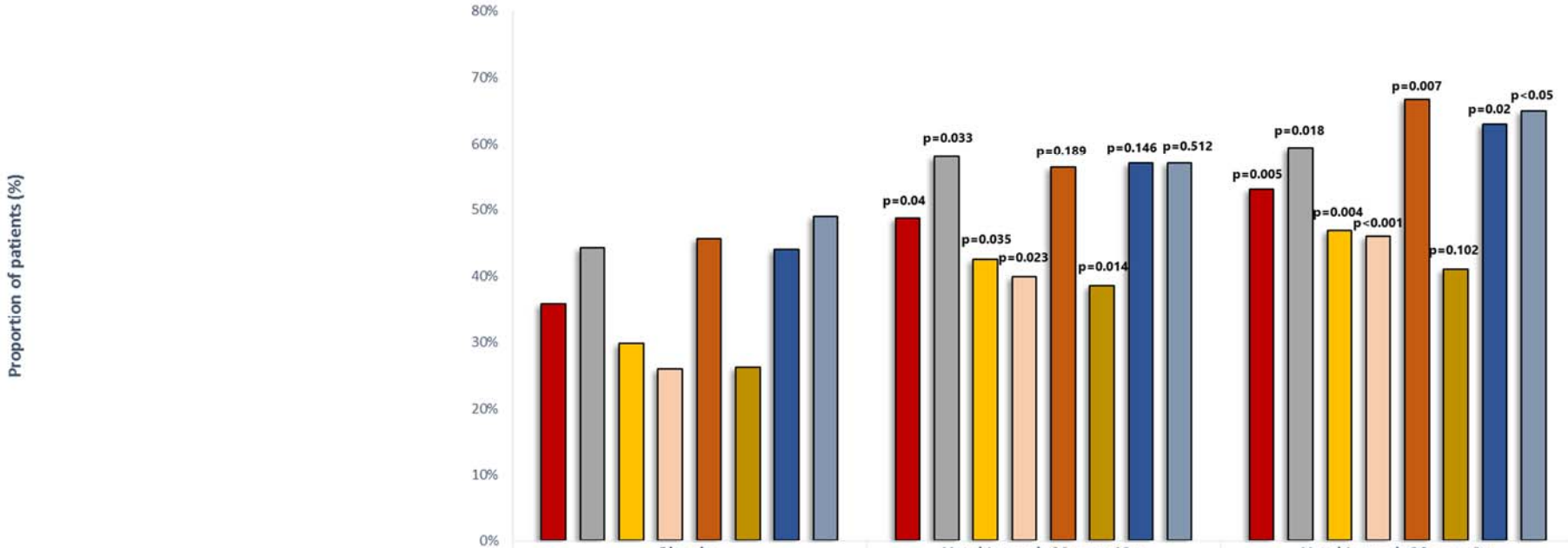
(38.6%) and q8w (41.1%) ustekinumab groups compared with the placebo group (26.2%). Although the relative treatment effects were similar to those in the overall population, there was not sufficient power to detect a significant difference from placebo as only 44.8% of the patients in the primary study population were included in this analysis.

Table 16: Key efficacy endpoints for IM-UNITI (ITT population)

		IM-UNITI		
		Placebo	**Ustekinumab 90mg q12w**	**Ustekinumab 90mg q8w**
Randomised patients		131	129	128
Primary endpoint	Clinical remission at Week 44, n (%)	47 (35.9%)	63 (48.8%)[b]	68 (53.1%)[a]
Major secondary endpoints	CDAI-100 response at Week 44, n (%)	58 (44.3%)	75 (58.1%)[b]	76 (59.4%)[b]
	CS-free clinical remission at Week 44	39 (29.8%)	55 (42.6%)[c]	60 (46.9%)[a]
	Clinical remission at Week 44 in patients:			
	in clinical remission at baseline, n/N (%)	36/79 (45.6%)	44/78 (56.4%)	52/78 (66.7%)[a]
	refractory or intolerant to TNFα inhibitor therapy, n/N (%)	16/61 (26.2%)	22/57 (38.6%)	23/56 (41.1%)

Key: CDAI, Crohn's disease activity index; CS, corticosteroid; ITT, intent-to-treat; q8w, every 8 weeks; q12w, every 12 weeks; TNF, tumour necrosis factor.
Notes: Sustained clinical remission=clinical remission at Weeks 36, 40, and 44.
[a], p<0.01; [b], p<0.05; [c], nominally significant (p<0.05).
Source: IM-UNITI CSR[134]

Figure 13: Key efficacy endpoints for IM-UNITI (ITT population)



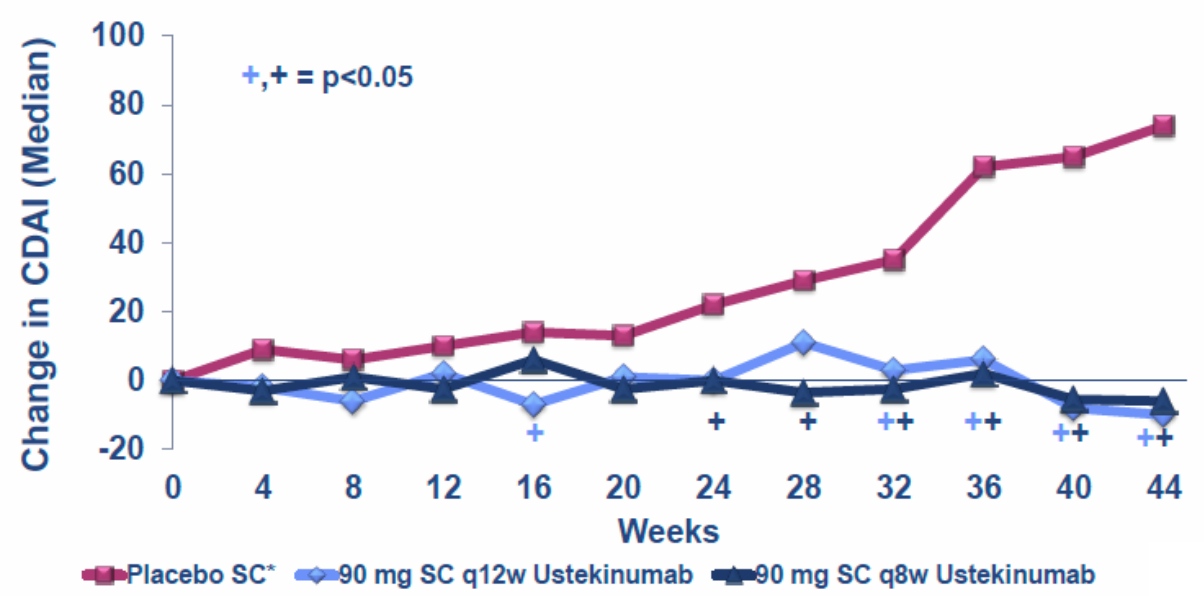
	Placebo	Ustekinumab 90 mg q12w	Ustekinumab 90 mg q8w
Clinical remission at week 44	36%	49%	53%
CDAI 100 clinical response at week 44	44%	58%	59%
CS-free clinical remission at week 44	30%	43%	47%
Sustained clinical remission	26%	40%	46%
Remission in patients in remission at Week 0 of maintenance	46%	56%	67%
Remission in patients who are TNF antagonist refractory	26%	39%	41%
Remission in patients who failed conventional therapy	44%	57%	63%
Remission in patients who are TNF-antagonist-naïve	49%	57%	65%

Key: CDAI, Crohn's disease activity index; CS, corticosteroid; ITT, intent-to-treat; q8w, every 8 weeks; q12w, every 12 weeks; TNF, tumour necrosis factor.
Source: Adapted from IM-UNITI CSR[134]

4.7.5 Loss of response and dose escalation

The change in CDAI over time is presented in Figure 14 and shows that patients who do not continue with ustekinumab maintenance therapy despite an initial response to ustekinumab induction (as represented by the placebo arm of IM-UNITI) lose response over time.

Figure 14: Change in CDAI through Week 44 in IM-UNITI (ITT population)



Key: CDAI, Crohn's Disease Activity Index; ITT, intention-to-treat; SC, subcutaneous; q8w, every 8 weeks; q12w, every 12 weeks.
Source: Sandborn *et al*. 2016.[4, 5]

Such loss of clinical response was the most common reason for patients meeting treatment failure criteria in IM-UNITI. The total proportion of patients who met treatment failure criteria prior to Week 44 was 45.0% in the placebo group compared with 36.4% and 28.9% in with the ustekinumab 90mg q12w and q8w groups, respectively; and the proportion of patients who met treatment failure criteria due to loss of clinical response was 38.9%, 22.5%, and 21.9% in the placebo, ustekinumab 90mg q12w and q8w groups, respectively.

As per trial protocol, there were 29 patients in the ustekinumab 90mg q12w group who had a dose adjustment to ustekinumab 90mg q8w after meeting loss of response criteria. When assessed 16 weeks after dose adjustment, 41.4% of these patients were in clinical remission, and 55.2% of patients had regained clinical

response (CDAI-100), supporting the use of dose adjustment in clinical practice (as per licensed dosing).

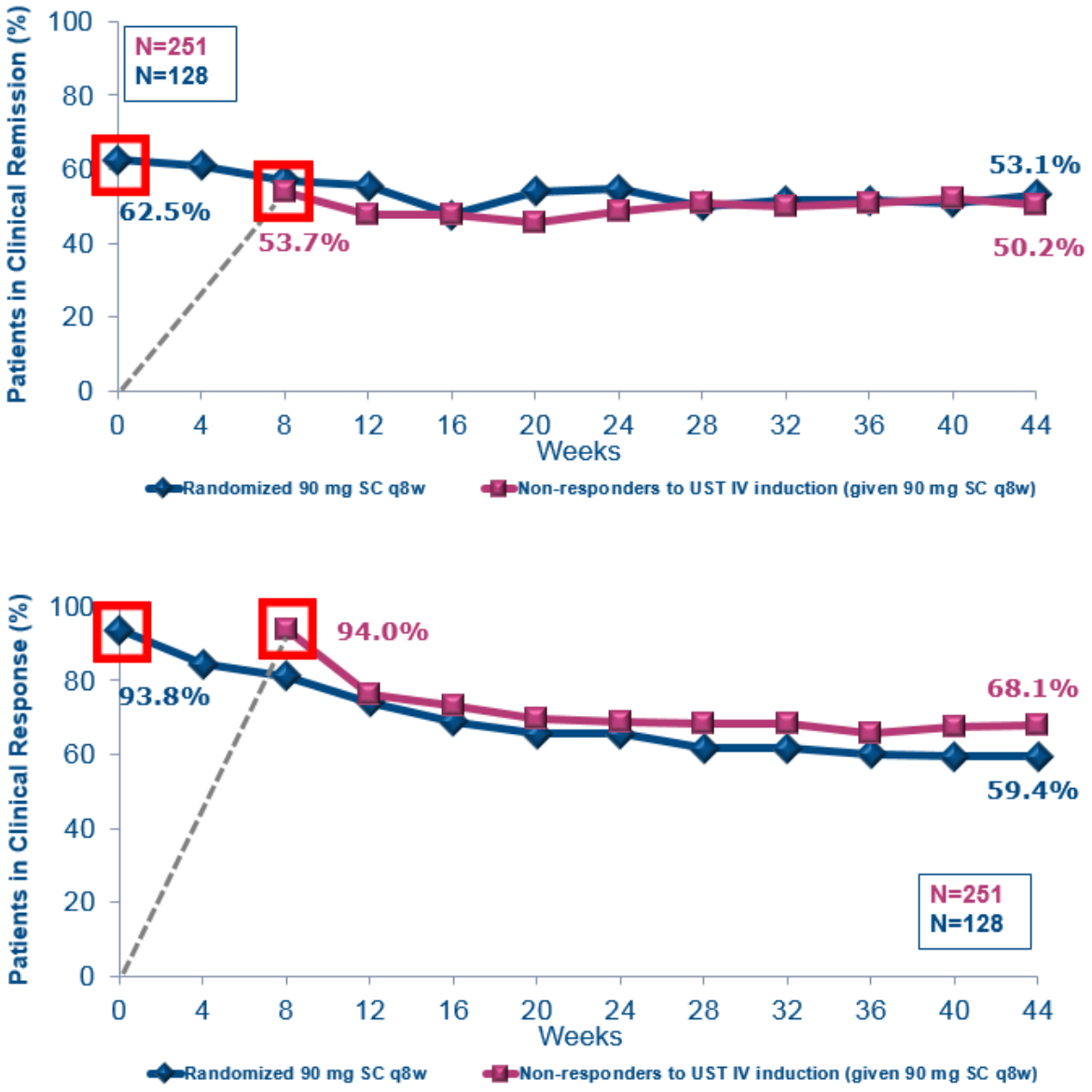
There were also 51 patients randomised to placebo who had a dose adjustment to ustekinumab 90mg q8w in IM-UNITI after meeting loss of response criteria. When assessed 16 weeks after dose adjustment, 39.2% of these patients were in clinical remission, and 70.6% of these patients had regained clinical response (CDAI-100). The majority of these patients (32/51) received dose adjustment within the first 16 weeks of the maintenance study.

4.7.6 Efficacy endpoints from the non-randomised component of IM-UNITI

Patients who failed to achieve the clinical response (CDAI-100) with ustekinumab IV induction infusion were treated with ustekinumab 90mg SC at Week 0 of the maintenance trial (8 weeks after IV ustekinumab). Although these patients were not considered in the primary study population for IM-UNITI, this group provides data in line with the licensed dosing for ustekinumab (see Section 2.3), and is therefore of interest to this appraisal.

Across UNITI-1 and UNITI-2, a total of 476 patients did not reach clinical response (CDAI-100) with ustekinumab IV induction infusion. After a dose of ustekinumab 90mg SC at Week 0 of the maintenance study (8 weeks post treatment initiation), 50.5% of these patients achieved clinical response (CDAI-100), and 28.9% achieved clinical remission at Week 8 (16 weeks post treatment initiation). Maintenance ustekinumab 90mg SC q8w was continued in 251 patients from Week 8 of the IM-UNITI trial (16 weeks post treatment initiation). Of these patients, 68.1% were in clinical response (CDAI-100) at Week 44 (1-year post treatment initiation), and 50.2% were in clinical remission. As depicted in Figure 15, patients who do not achieve clinical response (CDAI-100) but receive a further ustekinumab 90mg SC dose at Week 8 therefore achieve similar outcomes to patients who achieve clinical response (CDAI-100) to ustekinumab after the single IV induction dose.

Figure 15: Clinical remission and clinical response for patients receiving ustekinumab 90mg SC at Week 8 regardless of response to IV induction



Key: IV, intravenous; SC, subcutaneous; q8w, every 8 weeks; UST, ustekinumab.
Source: Sands *et al*. 2016.[137]

A total of 120 patients in the placebo groups of UNITI-1 and UNITI-2 who achieved clinical response (CDAI-100) continued to receive placebo in the maintenance trial. At Week 8 of the maintenance trial, 74.2% of these patients achieved clinical response (CDAI-100) and 53.3% achieved clinical remission. At Week 44 (1-year after treatment initiation), of the 118 patients who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 55.9%

achieved clinical response (CDAI-100) and 47.5% achieved clinical remission. Although this patient group represents a pure placebo group, it positively selects patients who respond well to conventional therapy, as reflected in the high levels of clinical response and clinical remission observed. We would not expect similarly high levels to be observed in a true placebo group.

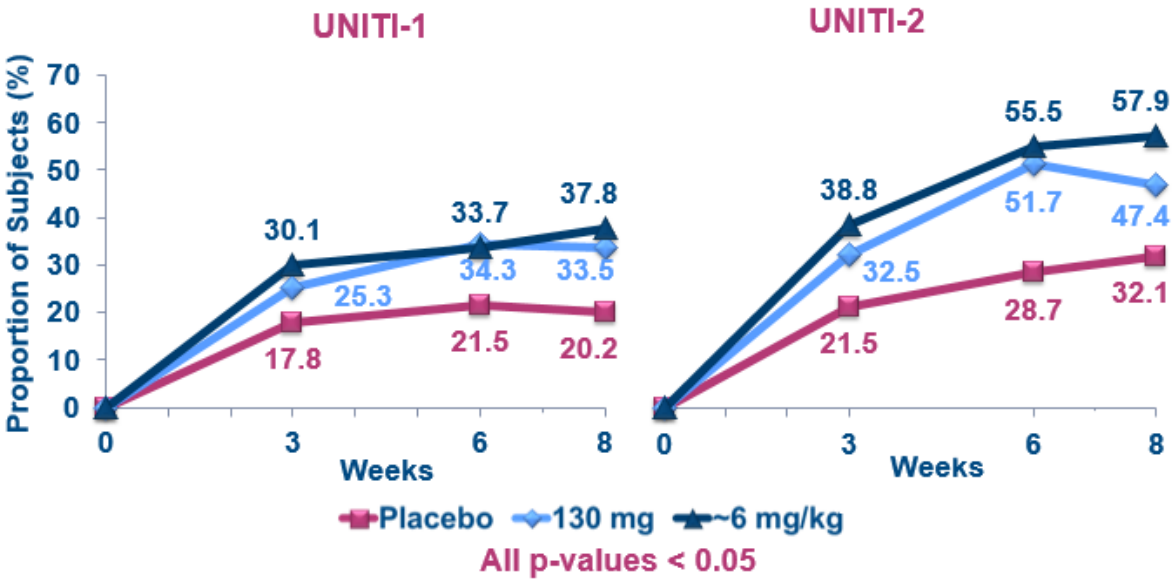
4.7.7 Other endpoints in UNITI-1 and UNITI-2

Clinical response/remission over time

Significantly greater proportions of patients were in clinical response (CDAI-100) in both ustekinumab dose groups compared with the placebo group at the first post-baseline visit at Week 3.

This was maintained through Week 8, as depicted in Figure 16.

Figure 16: Clinical response through Week 8 in UNITI-1 and UNITI-2 (ITT population)

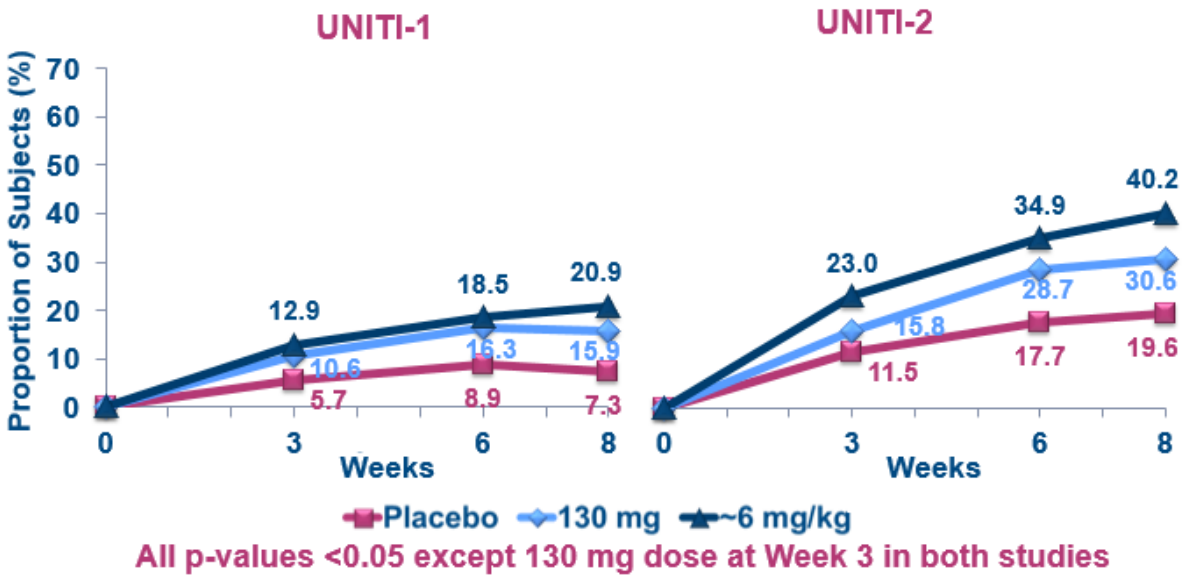


Key: ITT, intent to treat.
Source: Rutgeerts *et al*. 2016.[139]

The trend over time for clinical remission in the ustekinumab groups was similar to that observed for clinical response. Significantly greater proportions of patients were in clinical remission in both ustekinumab dose groups compared with the placebo group at the first post-baseline visit at Week 3.

This was maintained through Week 8, as depicted in Figure 17.

Figure 17: Clinical remission through Week 8 in UNITI-1 and UNITI-2 (ITT population)



Key: ITT, intent to treat.
Source: Rutgeerts *et al*. 2016.[139]

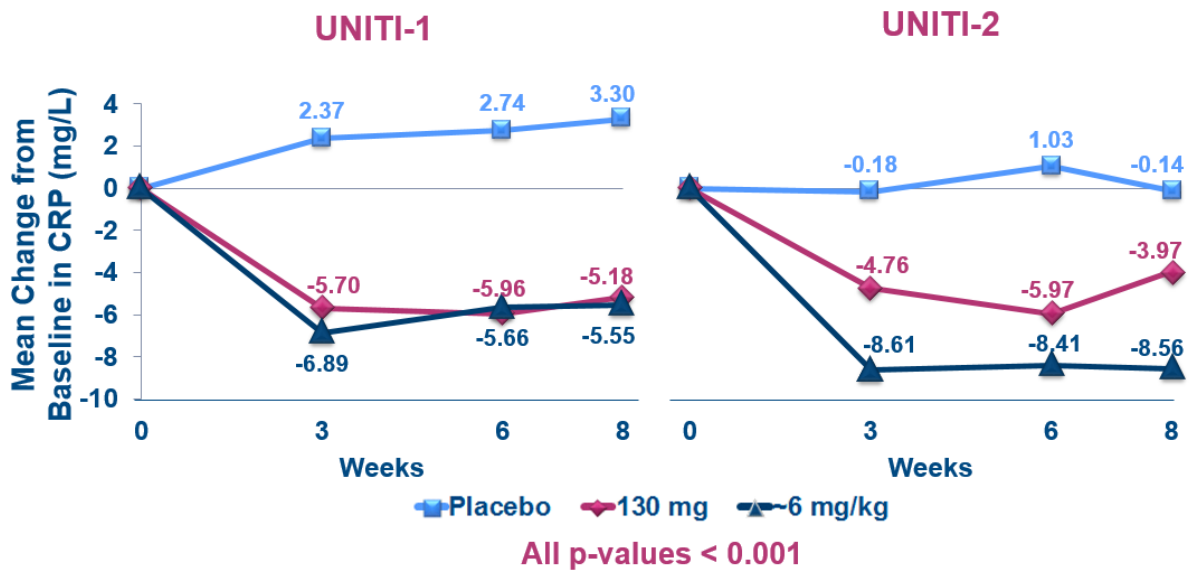
Inflammatory biomarkers

Ustekinumab was efficacious in reducing both serum- (CRP) and faecal- (calprotectin and lactoferrin) based biomarkers of inflammation. The reduction in or normalisation of CD inflammatory biomarkers support the efficacy findings for the clinical outcome endpoints.

C-reactive protein (CRP)

Significantly greater median reductions from baseline in CRP concentration were observed at Weeks 3, 6, and 8 in both ustekinumab dose groups compared with placebo in both induction studies, as summarised in Figure 18.

Figure 18: Change in median CRP from baseline through Week 8 in UNITI-1 and UNITI-2 (ITT population)



Key: CRP, C-reactive protein; ITT, intent to treat.
Source: Rutgeerts *et al*. 2016.[139]

Among patients with abnormal CRP at baseline (CRP >3mg/L), a significantly greater proportion of patients in the ustekinumab groups of both UNITI-1 and UNITI-2 had normalised CRP through Week 8 compared with the placebo groups.

Faecal calprotectin (fCal)

At Week 6 of UNITI-1, there was a significantly greater median reduction in fCal concentration in the ~6 mg/kg (−41.25) and 130mg (-38.57) ustekinumab groups compared with the placebo group (0.00; p<0.001 for both groups). At Week 6 of UNITI-2, the median reduction in fCal was also significantly greater in the ~6mg/kg (-106.32) and 130mg (-55.03) ustekinumab groups compared with the placebo group (0.00; p<0.001 for both groups).

Among patients with a baseline fCal >250 mg/kg, a significantly greater proportion of patients in the ustekinumab groups of both UNITI-1 and UNITI-2 had fCal values ≤100 mg/kg at Week 6 compared with the placebo groups.

Faecal lactoferrin

At Week 6 of UNITI-1, there was a significantly greater median reduction in faecal lactoferrin concentration in the ~6 mg/kg (−6.43) and 130mg (-3.70) ustekinumab

groups compared with the placebo group (0.00; p<0.001 and p=0.004, respectively). At Week 6 of UNITI-2, the median reduction in faecal lactoferrin was also significantly greater in the ~6mg/kg (-25.93) and 130mg (-10.35) ustekinumab groups compared with the placebo group (0.00; p<0.001 for both groups).

Among patients with a baseline faecal lactoferrin > 7.24µg/g, a significantly greater proportion of patients in the ustekinumab groups of both UNITI-1 and UNITI-2 had normalised lactoferrin (≤ 7.24µg/g) at Week 6 compared with the placebo groups.

Health-related quality of life

Improvements in clinical efficacy outcomes for CD were generally paralleled by improvements in IBD-specific and general HRQL outcomes, as determined by changes in the IBDQ score and SF-36 scores, respectively. These results are summarised in Table 17, and show that patients treated with ustekinumab can experience a reduction in common disease-related symptoms such as multiple bowel movements per day and abdominal inflammation/pain, sleep interruption and fatigue, compared with patients treated with conventional care which can be a reflection of the quick onset of action of ustekinumab on inflammatory markers. Patients treated with ustekinumab also reported improved energy levels and increased social interaction/activity, as well as reduced anxiety related to their illness.

A significantly greater proportion of patients in both ustekinumab groups demonstrated a clinically meaningful improvement in IBD-specific HRQL compared with placebo, as measured by the IBDQ at Week 8 (defined as ≥16 points[140]). The proportions of patients with a ≥16-point improvement from baseline was notably greater in the ~6 mg/kg group (54.8% and 68.1% in UNITI-1 and UNITI-2, respectively) compared with the 130 mg group (46.9% and 58.7% in UNITI-1 and UNITI-2, respectively).

A greater proportion of patients in both ustekinumab groups also demonstrated a clinically meaningful improvement in general HRQL compared with placebo, as measured by the SF-36 at Week 8 (defined as ≥5 points[141, 142]). Differences between treatment groups were statistically significant for the proportion of patients with a ≥5-point improvement from baseline in PCS and MCS for the ~6 mg/kg ustekinumab group of UNITI-2, and for the proportion of patients with a ≥5-point improvement from baseline in MCS for the ~6 mg/kg ustekinumab group of UNITI-1.

Table 17: Summary of patient-reported outcomes at Week 8 in UNITI-1 and UNITI-2 (ITT population)

	UNITI-1			UNITI-2		
	Ustekinumab		Placebo	Ustekinumab		Placebo
	130mg	~6mg/kg		130mg	~6mg/kg	
Patients randomised	245	249	247	209	209	209
IBDQ						
Baseline score, mean (SD)	119.5 (29.5)	118.2 (26.6)	120.0 (29.3)	118.2 (31.0)	122.8 (31.6)	122.7 (31.3)
Mean change from baseline (SD)	18.1 (28.0)[a]	22.1 (28.6)[a]	11.9 (26.5)	29.1 (33.8)[a]	35.3 (36.1)[a]	14.7 (27.0)
Proportion of patients with ≥16-point change, n (%)	114 (46.9)[b]	136 (54.8)[a]	89 (36.5)	122 (58.7)[a]	141 (68.1)a[a]	85 (41.1)
SF-36						
Baseline PCS score, mean (SD)	37.8 (7.1)	37.2 (7.1)	37.6 (7.1)	38.9 (7.6)	38.9 (7.0)	39.7 (7.2)
Mean change from baseline in PCS (SD)	3.21 (6.4)	3.57 (6.6)	2.62 (6.5)	5.1 (7.2)[c]	6.0 (7.7)[a]	2.6 (5.9)
Proportion of patients with ≥5-point improvement in PCS, n (%)	77 (33.3)	81 (34.9)	67 (30.0)	84 (44.0)[b]	96 (49.2)[b]	59 (31.2)
Baseline MCS score, mean (SD)	37.3 (10.0)	36.4 (9.9)	37.8 (10.6)	37.2 (10.8)	37.9 (11.2)	37.1 (10.7)
Mean change from baseline in MCS (SD)	3.34 (9.4)	4.86 (9.3)[c]	2.19 (8.5)	5.9 (10.5)[c]	6.8 (11.3)[a]	3.3 (9.5)
Proportion of patients with ≥5-point improvement in MCS, n (%)	84 (36.4)	98 (42.2)[c]	67 (30.0)	95 (49.2)[b]	100 (51.3)[b]	73 (38.6)

Key: IBDQ, inflammatory bowel disease questionnaire; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-36, 36-item short form health questionnaire.
Notes: [a], p<0.001; [b], p<0.05; [c], p<0.01 (all p-values are versus placebo).
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]

4.7.8 Other endpoints in IM-UNITI

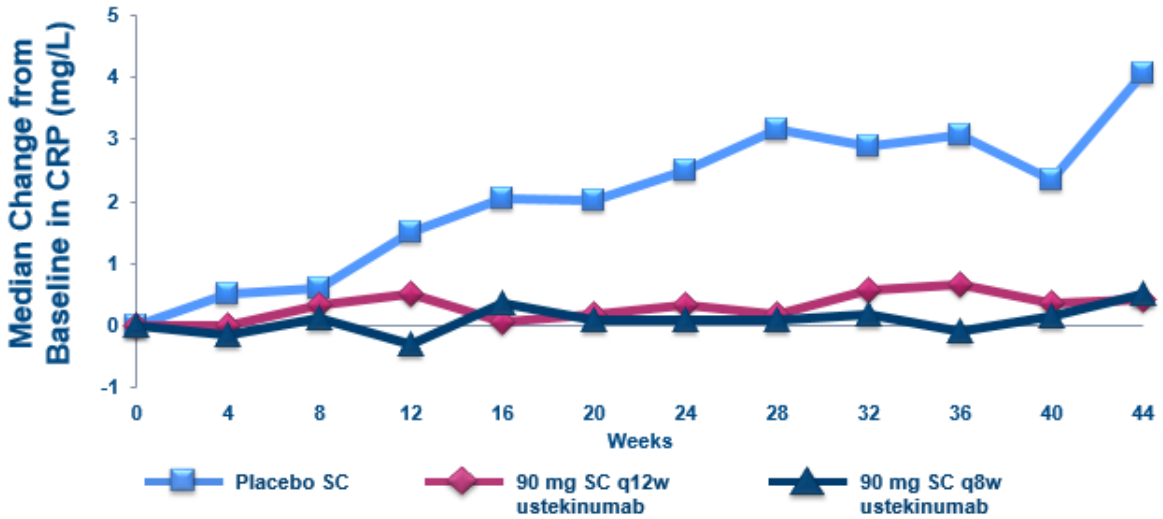
Inflammatory biomarkers

Along with maintenance of clinical efficacy, reductions in both serum- (CRP) and faecal- (calprotectin and lactoferrin) biomarkers were also significantly maintained at Week 44 (1-year post treatment initiation) in both ustekinumab dose groups compared with the placebo group.

C-reactive protein (CRP)

Patients in the ustekinumab dose groups had significantly smaller increases in CRP by the end of the maintenance phase, compared with the placebo group, with a median change from baseline at Week 44 of 0.42 mg/L and 0.51 mg/L in the ustekinumab 90 mg q12w and q8w groups, respectively, compared with 4.07 mg/L in the placebo group ($p=0.002$ and $p<0.001$, respectively). The median CRP in the placebo group increased over time, with clear separation from the q8w group beginning at Week 4 and from the q12w group beginning at Week 12, as can be observed in Figure 19. The q8w group maintained the reductions in CRP obtained in the induction study, while the q12w group showed more variability over time.

Figure 19: Median CRP through Week 44 in IM-UNITI (ITT population)



Key: CRP, C-reactive protein; ITT, intent to treat; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous.
Source: Sandborn *et al*. 2016.[4, 5]

After Week 12 through Week 44, both ustekinumab groups had larger proportions of patients with normalised CRP compared with the placebo group. At Week 44, the proportions of patients with normalised CRP were significantly greater in the ustekinumab q12w group (22.8%) and numerically greater in the ustekinumab q8w group (19.6%) compared with the placebo group (10.5%; p=0.019 and p=0.076, respectively).

Faecal calprotectin (fCal)

At 24 and 44 weeks, the median change from baseline in fCal was smaller in each ustekinumab group compared with the placebo group. At Week 44, the median change from baseline was 0.00 µg/g for each ustekinumab group, compared with 153.85 µg/g for the placebo group (p=0.002 and p<0.001 for the q12w and q8w groups, respectively).

Among patients with a baseline fCal >250 µg/g, the proportions of patients with fCal values ≤100 mg/kg at Week 44 were significantly greater in the 90mg q12w (15.4%) and q8w (19.3%) ustekinumab groups compared with the placebo group (5.4%; p=0.028 and p=0.008, respectively).

Faecal lactoferrin

At 24 and 44 weeks, the median change from baseline in faecal lactoferrin was smaller in each ustekinumab group compared with the placebo group. At Week 44, the median change from baseline was -2.99 µg/g for the ustekinumab 90mg 12qw group and 0.00 µg/g for the ustekinumab 90 mg q8w group, compared with 26.75 µg/g in the placebo group (p=0.007 and p=0.001, respectively).

The proportions of patients with normalised faecal lactoferrin remained stable or increased slightly over time in each ustekinumab group and were numerically greater at both Week 24 and Week 44 and was significantly greater in the ustekinumab 90 mg q12w group at Week 44 compared with placebo, where the proportion of normalised patients decreased over time.

Health-related quality of life

At baseline in the maintenance study (Week 0), patient-reported outcomes scores for IBDQ and SF-36 were close to the cut-off for disease remission (IBDQ≥170[140]) and population norms (SF-36 PCS and MCS = 50 ± 10[143, 144]), respectively. This

indicates significantly improved HRQL among clinical responders after ustekinumab induction treatment. Throughout IM-UNITI, these positive changes in HRQL remained, as summarised in Table 18. Consistent with the inflammatory marker results, these data show that ustekinumab treatment can maintain improvements in common disease-related symptoms (such as multiple bowel movements and abdominal inflammation/pain, sleep interruption and fatigue), and maintain improvements in energy and social interaction/activity levels, and anxiety related to their illness.

At Week 44, changes from baseline in the IBDQ score, as well as all four dimensions of the IBDQ, were significantly smaller in the ustekinumab groups compared with the placebo group of IM-UNITI. The proportions of patients with a clinically meaningful improvement in the IBDQ score at Week 44 were significantly greater for the ustekinumab 90 mg SC q8w group, and numerically greater for the q12w group, compared with the placebo group. Mean changes from baseline across the SF-36 dimension scores were generally smaller in the ustekinumab 90 mg q8w group compared with the placebo group ($p<0.05$ except for general health [$p=0.055$] and role emotional [$p=0.058$]). A significantly greater proportion of patients in the ustekinumab q8w group achieved a clinically meaningful improvement in PCS from baseline compared with placebo, and significantly greater proportions of patients in both ustekinumab groups achieved a clinically meaningful improvement in MCS from baseline compared with placebo.

These outcomes indicate that patients in the ustekinumab groups were better able to maintain the HRQL improvements observed during the induction studies across the maintenance period, when compared to placebo patients.

Table 18: Summary of patient-reported outcomes at Week 44 in IM-UNITI (ITT population)

	Ustekinumab		**Placebo**
	q12w	**q8w**	
IBDQ			
Patients randomised and evaluable*	129	128	131
IBDQ score at Week 0, mean (SD)	165.8 (32.8)	170.5 (29.3)	163.6 (31.8)
Mean change from baseline (SD)	-8.9 (43.1)[a]	-9.9 (34.8)[a]	-21.5 (39.3)

Proportion of patients with ≥16-point change, n (%)	73 (61.3)	76 (67.9)[b]	60 (50.4)
SF-36			
Patients randomised and evaluable*	121	121	122
PCS score at Week 0, mean (SD)	47.1 (8.1)	47.4 (7.5)	46.3 (8.2)
Mean change from baseline in PCS (SD)	-2.3 (9.3)	-0.93 (7.1)[a]	-3.56 (9.3)
Proportion of patients with ≥5-point improvement in PCS, n (%)	50 (41.7)	63 (52.1)[a]	42 (34.7)
MCS score at Week 0, mean (SD)	46.4 (10.7)	47.3 (9.9)	45.7 (10.9)
Mean change from baseline in MCS (SD)	-1.9 (12.7)[b]	-1.7 (9.8)[a]	-4.4 (11.1)
Proportion of patients with ≥5-point improvement in MCS, n (%)	56 (46.7)[a]	58 (47.9)[a]	35 (28.9)

Key: IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; q8w, every 8 weeks; q12w, every 12 weeks; SF-36, Short Form Health Survey.
Notes: *, Patients who were in clinical response to ustekinumab induction dosing at start of maintenance therapy; excludes patients randomised before study restart.
[a], p<0.01 vs placebo; [b], p<0.05 vs placebo.
Source: IM-UNITI CSR.[134]

Healthcare utilisation

The proportions of patients with a CD-related hospitalisation or surgery through Week 44 were low across all treatment groups, and no significant differences in the time to the first CD-related hospitalisation or surgery were observed across the placebo and ustekinumab groups.[134]

4.7.9 IM-UNITI study extension

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.7.10 Endoscopic substudy

An endoscopic substudy was performed in a subset of eligible patients (for whom data were available) across all three of the Phase III RCTs in order to examine the effects of ustekinumab on mucosal healing. Ustekinumab was effective in inducing endoscopic mucosal healing in patients with moderately to severely active CD, as substantiated by several lines of evidence based on the collective results from endoscopic and histologic evaluations.

A summary of the results from the induction studies (pooled analysis) is shown in Table 19.

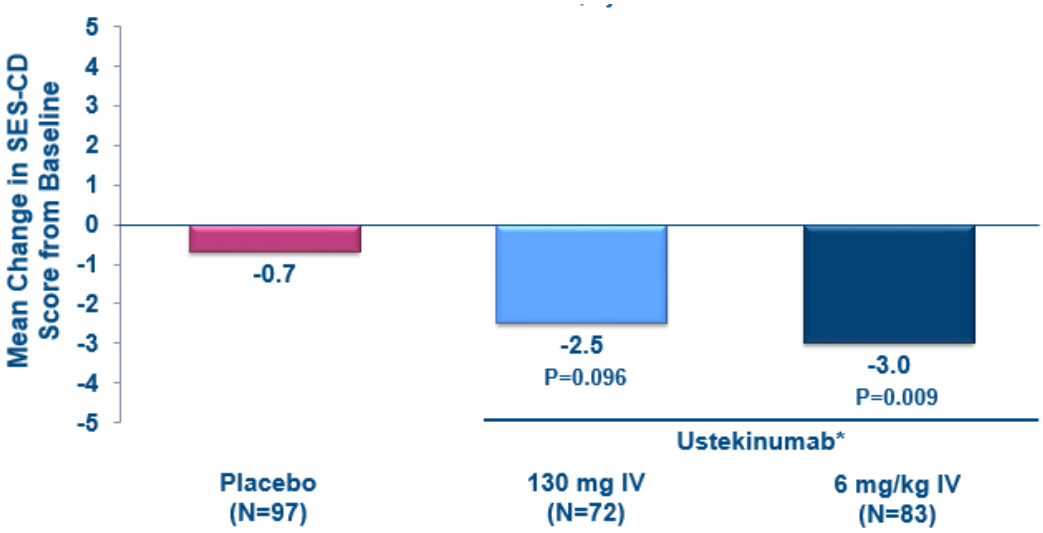
Table 19: Summary of results for endoscopic endpoints at Week 8 in UNITI-1 and UNITI-2 (Endoscopic substudy population)

	Ustekinumab[a]	**Placebo**	**p-value**
Patients with eligible SES-CD score at baseline, combined UNITI-1 and UNITI-2 studies	155	97	-
Change from baseline in SES-CD, mean (SD)	-2.8 (5.68)	-0.7 (4.97)	0.012
Patients with ≥3 point reduction from baseline in SES-CD score, n (%)	74 (47.7)	29 (29.9)	0.005
Patients in endoscopic response, %	21	13	NS
Patients in endoscopic remission, %	8	4	NS
Patients with mucosal healing, %	9	4	NS

Key: NS, not significant; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease.
Notes: Endoscopic response = reduction ≥50% from baseline in SES-CD score; endoscopic remission = total SES-CD score ≤2; mucosal healing = complete absence of any mucosal ulcerations among patients with ulceration in at least 1 ileocolonic segment at induction baseline [a], Ustekinumab 130 mg and tiered ustekinumab doses ~6 mg/kg combined.
Source: Rutgeerts *et al*. 2016.[138]

A total of 252 patients in UNITI-1 and UNITI-2 had eligible Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) scores (≥3) at baseline. In primary endpoint analysis of this substudy, change from baseline in SES-CD score at Week 8 was significantly greater in the ustekinumab groups than in the placebo group, as depicted in Figure 21.

Figure 21: Mean change in SES-CD from baseline at Week 8 in UNITI-1 and UNITI-2 (Endoscopic substudy population)



Key: IV, intravenous; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease.
Source: Rutgeerts *et al*. 2016.[138]

Results of sensitivity analyses (which examined different approaches to handling missing data), and results across subgroup analyses by induction study and by induction dose, were consistent with the main analysis.

The primary analysis was further supported by data showing that ustekinumab-treated patients were significantly more likely to achieve clinically meaningful endoscopic improvement at Week 8 of induction compared with placebo. Clinically meaningful improvement was considered to be a reduction of ≥3 points as this was anticipated to lead to the achievement of endoscopic disease improvement by 1 category in many patients, and would therefore likely meet the threshold for a clinically meaningful improvement.

The significant reductions in endoscopic disease activity from ustekinumab induction were corroborated by reductions in underlying histologic inflammation. At Week 8, a significant decrease from baseline in the Global Histology Activity Score (GHAS) was observed among patients who received ustekinumab (but not placebo) induction. Subgroup analyses by induction study and by induction dose showed consistent results.

Based on pre-planned and *post-hoc* analyses of maintenance endoscopic endpoints, the combined results from endoscopic and histologic evaluations showed a trend suggestive of a role for continued ustekinumab maintenance treatment in achieving long-term control of mucosal inflammation. However, due to the small number of patients in the maintenance portion of this substudy (n=70), the efficacy of ustekinumab maintenance for endoscopic endpoints could not be definitively established.

4.8 Subgroup analysis

In general, results across predefined subgroups in all RCTs were consistent with those of the overall study populations, as summarised in Appendix 4.

Subgroups listed in the decision problem include:

- People who have not previously received a TNFα inhibitor
- People for whom at least one TNFα inhibitor has failed
- People for whom TNFα inhibitors are not suitable because of intolerance or contraindication
- Location of CD (ileal, colonic and perianal)

People who have not previously received a TNFα inhibitor:

In subgroup analysis of UNITI-2, patients who had not previously received a TNFα inhibitor demonstrated similar efficacy (clinical response and clinical remission rates at Week 6) to those patients who had previously been exposed to a TNFα inhibitor (but who did not meet the failure criteria specified for UNITI-1). This subgroup will be covered within the cost-effectiveness analyses for the conventional care failure population (see Section 5).

People for whom at least one TNFα inhibitor has failed and people for whom TNFα inhibitors are not suitable because of intolerance or contraindication:

In subgroup analysis of UNITI-1, patients for whom at least one TNFα inhibitor had failed demonstrated similar efficacy (clinical response at Week 6 and clinical remission rates at Week 8) to those patients for whom TNFα inhibitors are not suitable because of intolerance or contraindication. In subgroup analysis of IM-UNITI, similar treatment effects were observed regardless of prior treatment history;

that is, in patients who have not previously failed a TNFα inhibitor and in patients for whom at least one TNFα inhibitor has failed or for whom TNFα inhibitors are not suitable because of intolerance or contraindication. These subgroups will be covered within the cost-effectiveness analyses for the TNF failure population (see Section 5).

Location of CD (ileal, colonic and perianal):

In subgroup analysis across the UNITI trial programme, ustekinumab was shown to be effective irrespective of location of CD. Although in the UNITI-1 trial, patients with CD limited to the ileum failed to demonstrate a clinical response benefit when treated with ustekinumab compared with placebo, this subgroup represents a small proportion of the total UNITI-1 study population such that no meaningful conclusions can be drawn from this analysis. Furthermore, this is not consistent with the subgroup data from the UNITI-2 and IM-UNITI studies.

4.9 Meta-analysis

Meta-analysis has not been performed because the RCTs that provide evidence for ustekinumab in CD were performed in patients with different treatment histories. It is important to understand the efficacy of ustekinumab in both patients who had failed conventional therapy, and those who have failed or are intolerant to TNFα inhibitor therapy as separate populations.

4.10 Indirect and mixed treatment comparisons

4.10.1 Search strategy

The SLR methods used to identify trials for potential inclusion in a NMA are described in Section 4.1.

The 31 RCTs identified through this review were qualitatively assessed with the NICE checklist based on the Centre for Reviews and Dissemination at the University of York.[146] The results of this assessment are provided in Appendix 5.

4.10.2 Study selection

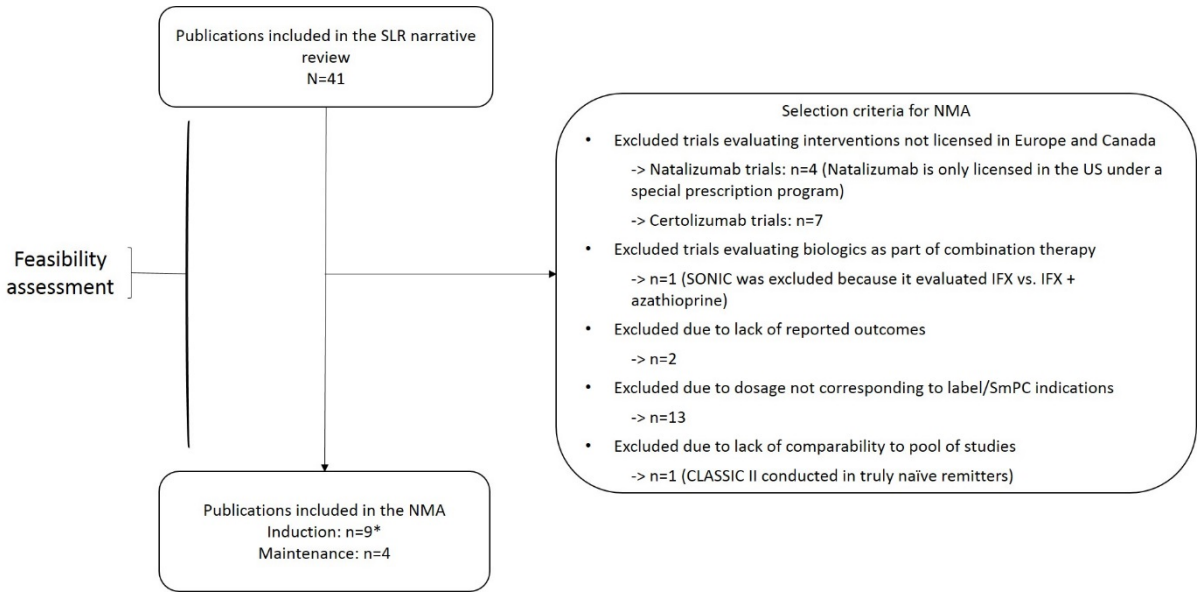
The objective of conducting a NMA was to assess the relative effect of ustekinumab compared with alternative biologics, based on studies identified in the SLR (see Section 4.1). NMA were separately performed for induction treatment, and for

induction and maintenance treatment (in treatment sequence analysis), and for patients who had failed conventional therapy (referred to as the conventional care failure subpopulation for NMA purposes) and for those who had failed or were contraindicated to TNFα inhibitor therapy (referred to as the TNF failure subpopulation for NMA purposes).

Studies evaluating interventions not licensed in Europe and Canada (as the NMA was conducted with a wider geographical focus than the UK), evaluating biologics as part of a combination therapy, using a dosage that did not correspond to label indications, or lacking reported outcomes of interest were excluded from the NMA. Figure 22 details the study selection process conducted as part of the feasibility assessment of the NMA. Of the 31 trials identified in the original SLR (see Section 4.1), a total of 9 induction RCTs and 4 maintenance RCTs met the eligibility criteria for inclusion in NMA.

The inclusion/exclusion assessment used to compile the final list of studies linking the treatments of interest is reported in Appendix 5.

Figure 22: Selection process for data analysis of trials included in the narrative review



Key: IFX, infliximab; n, number; NMA, network meta-analysis; SLR, systematic literature review; SmPC, summary of product characteristics.
Notes: *, induction study count includes CERTIFI[132] as it was included in a sensitivity analysis and in treatment sequence analysis.

The update to SLR identified three further studies that could be considered for inclusion in an NMA update. However, one of these studies was the IM-UNITI trial that was included in the original NMA, and the remaining studies were ongoing and thus only available as conference abstracts.[147, 148]

Induction phase

Induction phase trials in CD were deemed similar enough, in terms of study design and patient characteristics, for their findings to be pooled together. Potential treatment effect modifiers in the induction phase were determined based on the literature.[149] The following characteristics were assessed and deemed comparable across trials: duration of disease, CDAI score at baseline, CRP concentration and fistula at baseline, and administration of concomitant/allowed therapies (see Appendix 5 for details on these baseline characteristics).

Only trials assessing at least one intervention of interest were included in the analysis. Table 20 lists all included studies in the NMA for the induction phase. Data from each study used in the NMA are included in Appendix 5.

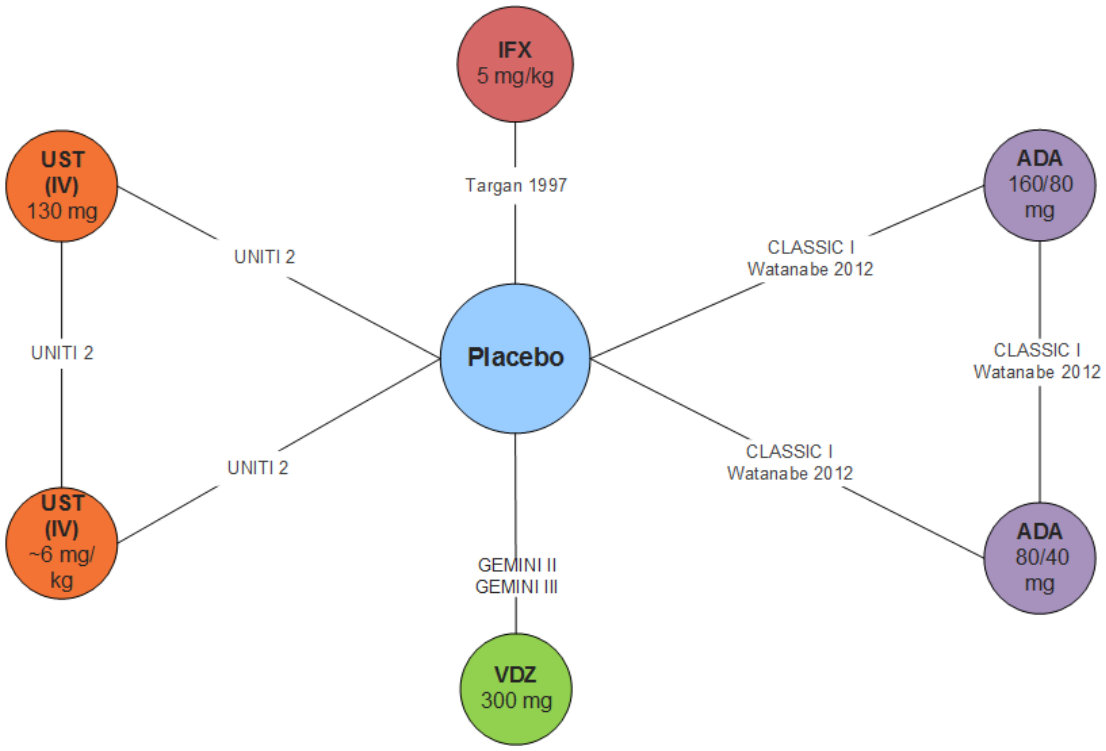
Table 20: List of included studies in induction phase NMA

Trial	Subpopulation	Intervention	Trial length	BCA time point selected (weeks)	Included in BCA
Targan 1997[25]	Conventional care failure	Infliximab	Week 4	4	Yes
CLASSIC I[150]	Conventional care failure	Adalimumab	Week 4	4	Yes
Watanabe 2012[151]	Conventional care failure and TNF failure	Adalimumab	Week 4	4	Yes
GAIN[152]	TNF failure	Adalimumab	Week 4	4	Yes
GEMINI II[17]	Conventional care failure and TNF failure	Vedolizumab	Week 6	6	Yes
GEMINI III[131]	Conventional care failure and TNF failure	Vedolizumab	Week 10	6	Yes
UNITI-1[153]	TNF failure	Ustekinumab	Week 8	6	Yes
UNITI-2[136]	Conventional care failure	Ustekinumab	Week 8	6	Yes

CERTIFI[132]*	TNF failure	Ustekinumab	Week 8	6	No
Key: BCA, base case analysis; TNF, tumour necrosis factor. **Notes:** *, CERTIFI was excluded from the BCA.					

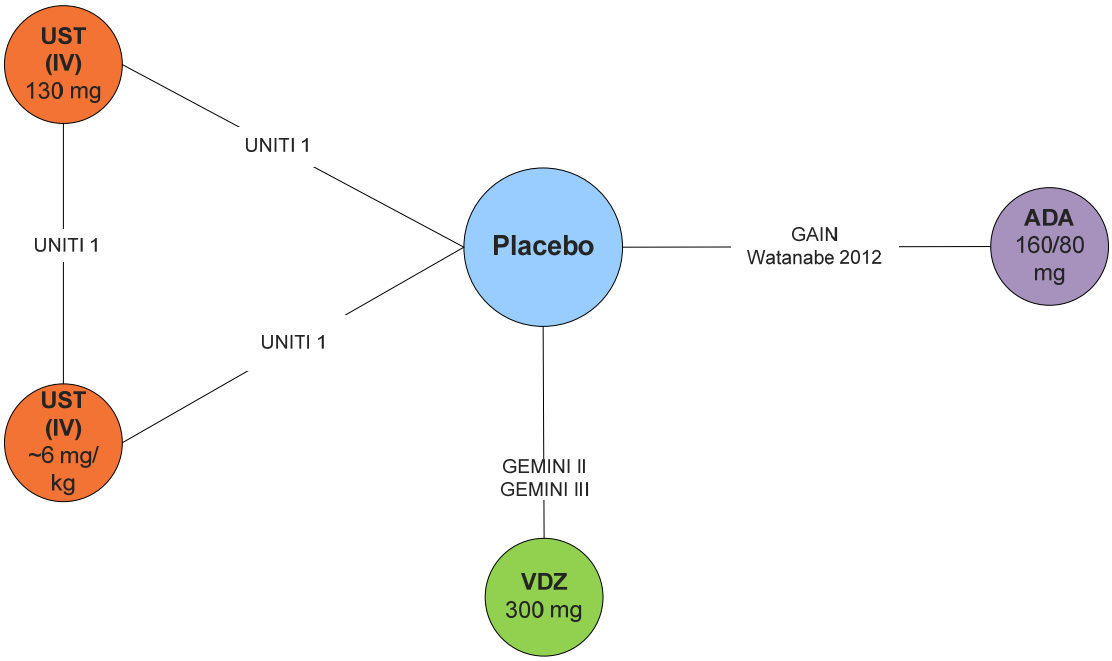
The studies identified through the SLR process and included in the statistical analyses are shown in Figure 23 for the conventional care failure population and in Figure 24 for the TNF failure population.

Figure 23: Network for the induction NMA – conventional care failure



Key: ADA, adalimumab; IFX, infliximab; IV, intravenous; UST, ustekinumab; VDZ, vedolizumab.

Figure 24: Network for the induction NMA – TNF failure



Key: ADA, adalimumab; IV, intravenous; UST, ustekinumab; VDZ, vedolizumab.

Maintenance phase

Maintenance phase trials in CD were not deemed similar enough for their findings to be pooled together in a conventional NMA. However, analyses of response/ remission maintenance are critical to understanding the clinical benefit of biologic treatment, and therefore, a treatment sequencing method was adopted to account for these differences while estimating comparative efficacy (see Sections 4.10.4 and 4.10.5).

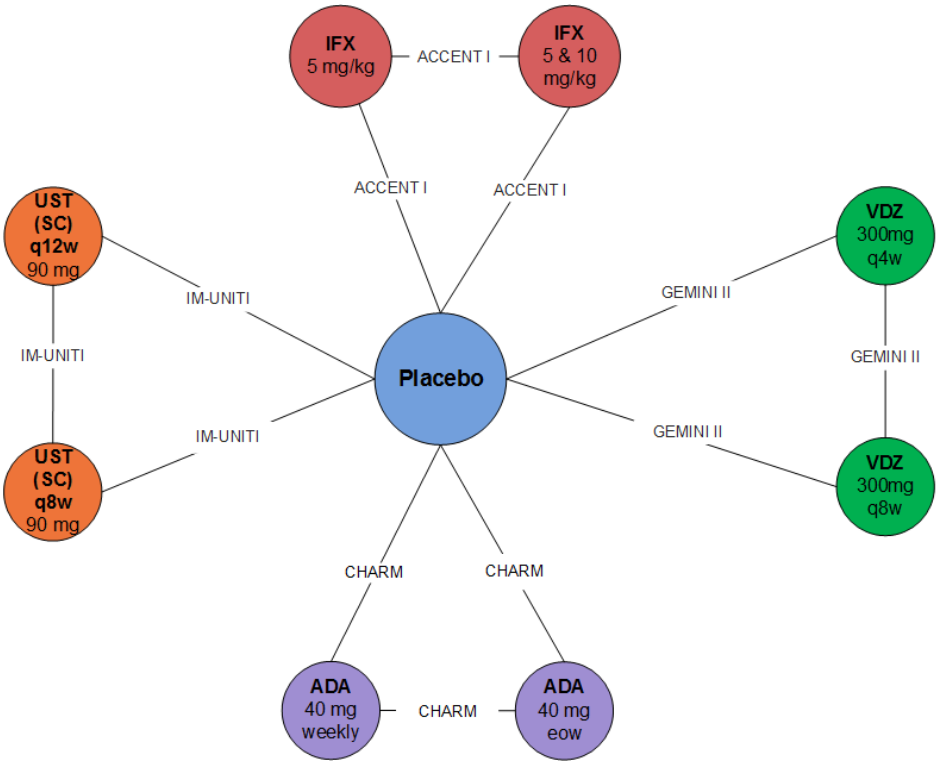
Only trials assessing at least one intervention of interest were included in the analysis. Table 21 lists all included studies in the NMA for the maintenance phase. Data from each study used in the NMA are included in Appendix 5.

Table 21: Study design – included maintenance trials

Study	Treatment	Patient selection	Study design
IM-UNITI[134]	Ustekinumab	Ustekinumab responders (CDAI-100) at Week 8	Double blind for induction and maintenance
CHARM[154]	Adalimumab	Adalimumab responders (CDAI-70) at Week 4	Induction phase not blinded and not comparative Induction dose received: 80/40mg
ACCENT I[155]	Infliximab	Infliximab responders (CDAI-70) at Week 2	Induction phase not blinded
GEMINI II[17]	Vedolizumab	Vedolizumab responders (CDAI-70) at Week 6	Most patients from unblinded induction phase (96/461)
Key: CDAI, Crohn's Disease Activity Index.			

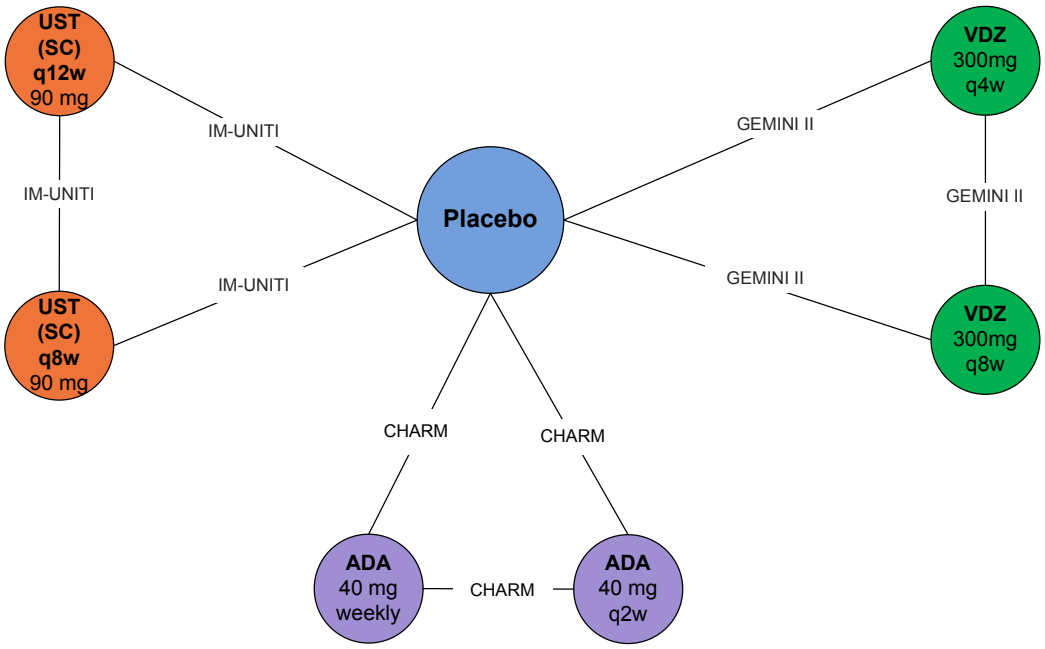
The studies identified through the SLR process and included in the statistical analyses are shown in Figure 25 for the conventional care failure population and in Figure 26 for the TNF failure population.

Figure 25: Network for the maintenance NMA – conventional care failure



Key: ADA, adalimumab; IFX, infliximab; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Figure 26: Network for the maintenance NMA – TNF failure



Key: ADA, adalimumab; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

Safety

A NMA of safety endpoints was deemed not feasible due to the lack of comparability between trials' definitions of adverse events. For example, AEs can include GI events that are CD-related. As such, many placebo arms in individual trial results are associated with higher proportions of AEs than in the active treatment arms. It could be argued that active treatments reduce signs of CD and thus reduce the occurrence of these signs when they are counted in the definition of adverse events. The lack of evidence on this particular topic increases the uncertainty around true treatment effects and complicates the comparison of safety of biologics in the treatment for CD. Another example of challenges faced in the analysis of safety was that splitting the analysis by subpopulation resulted in small proportions for some adverse events and consequently in a substantial loss of power and lack of model convergence. Therefore, an analysis of most safety endpoints was not feasible from a statistical standpoint. However, conducting the NMA for safety endpoints on a mixed population (i.e. pooling conventional care failure and TNF failure subpopulations) was not acceptable from a clinical standpoint as pooling results for both subpopulations would lead to confounding. Therefore, although reported in individual trials, safety endpoints were not analysed as part of the NMA.

4.10.3 Methods and outcomes of included studies

Overall, trials evaluating biologics in CD have certain important features in common. Most studies start with a short-term placebo controlled induction phase with times of assessments varying from 4 to 12 weeks. Patients are then re-randomised into a longer-term maintenance phase. Despite this similarity in core trial design, trials differentiate in the transition from induction to maintenance. For instance, the definition of efficacy endpoints assessed and their corresponding time of assessment vary across trials. The most commonly reported primary efficacy endpoint was remission (defined as a CDAI score<150) but time of assessment varied from Week 4 to Week 6 in induction trials and from Week 26 to Week 56 in maintenance trials. Therefore, attention should be paid to individual trial differences in study design, and caution should be applied when interpreting individual trial results.

The eligibility criteria based on previous treatments received and on concomitant therapies allowed throughout the trial were also considered to be sources of heterogeneity across studies.

Sample size varied across trials: from less than 10 patients per arm to more than 700 patients in induction trials, and from less than 20 patients per arm to more than 250 patients per arm in maintenance trials.

Induction phase

At the trial outset, the main differences observed across studies were disease duration at inclusion, patients' CDAI score at baseline, CRP concentration at baseline, smoking status, fistula history and IBDQ score at baseline.

Endpoints for the NMA of the induction phase were selected based on published data availability across trials.

- Clinical response, defined as a reduction in CDAI score of 70 points
- Clinical response, defined as a reduction in CDAI score of 100 points
- Clinical remission, defined as a CDAI score of or inferior to 150 points

CDAI is commonly used as primary efficacy endpoint in clinical trials assessing treatments of CD, with response defined as a reduction of a minimum of 70 to 100 points.[156] In the context of economic evaluations, CDAI scores have been mapped to EQ-5D and SF-6D utilities, which makes this measure convenient and acceptable to use.[157]

Time point selection for the NMA of induction was based on comparability to the time of assessment of the primary endpoint in ustekinumab trials: 6 weeks. For infliximab and adalimumab, data at 4 weeks was used. For vedolizumab, data at 6 weeks were used.

In the failed conventional population, placebo rates are generally comparable across trials, except for two small studies. The lowest placebo response rates were observed in a small Japanese study (15% CDAI-100 placebo response rates)[151], and a small Phase II study (17% CDAI-70 placebo response rates).[25] The latter study also happened to be impacted by a proportion of missing data in the placebo arm (3/25 patients in the placebo arm [12%] had missing data), which were classed as non-responders[158]; in addition, a smaller magnitude of effect in the higher doses of

infliximab were reported, than in the lower doses. This suggests that the results of Targan *et al*. 1997 should be interpreted with caution.

In patients who had failed anti-TNF therapy, similar placebo rates were observed across trials, even though adalimumab trials were conducted in a more restricted patient population. For instance, patients in the GAIN trial[152] had intolerance or secondary non-response to infliximab.

Individual trial results for each endpoint are reported by subpopulations in Appendix 5.

Maintenance phase

"Placebo" rates in maintenance trials are not true placebo rates, as they are conditional on the rates of patients having responded to induction with different biologics and having been re-randomised to a placebo arm in maintenance. Moreover, ustekinumab has an extended half-life, which contributes to a suspected 'carryover effect'; that is, patients may still be benefiting from ustekinumab treatment within the first few months of receiving placebo in IM-UNITI. In patients who failed conventional therapy, the lowest placebo response rates were observed in CHARM[154] (19%), and highest rates were observed in IM-UNITI[134] (50%). Similarly, placebo remission rates in that subpopulation ranged from 13% (CHARM) to 44% (IM-UNITI). In patients who had failed anti-TNF therapy, placebo response rates ranged from 14% in CHARM to 38% in IM-UNITI, and placebo remission rates ranged from 10% in CHARM to 26% in IM-UNITI. Moreover, when comparing active treatment arms across trials, while visual cross-study comparison of infliximab and adalimumab maintenance studies suggests similar maintenance of effect of both anti-TNFs, maintenance of effect during maintenance is not independent of the induction drug used, as demonstrated by the SWITCH trial.[159] As such, analysing maintenance independently from induction is prone to misinterpretation.

Individual trial inputs for the maintenance phase are reported in Appendix 5.

Safety

Safety outcomes in included studies are presented in Appendix 5.

4.10.4 Risk of bias

Induction phase

One of the main challenges in a NMA is to assess the comparability between trials. If trials differ in terms of study design or if the populations are different in terms of prognostic factors, it could lead to heterogeneity between studies. If these characteristics are modifiers of the treatment effect, then the results of the network meta-analysis will be biased and unreliable.[160]

Time of assessment was found to vary across induction trials. As such, when multiple time points were reported, similar times of assessment were selected for each intervention for conducting this indirect comparison. Endpoints reported at 4 weeks were used as inputs for infliximab and adalimumab, and endpoints reported at 6 weeks were used as inputs for vedolizumab and ustekinumab. This selection of times of assessment was in line with the primary endpoints of each trial included in the analysis.

Prior TNFα inhibitor therapy failure was also found to impact relative treatment effects. To further minimise heterogeneity, separate analyses were performed for trials conducted in patients who had failed conventional therapy (conventional care failure) and patients who had failed, or are contraindicated to, TNFα inhibitor therapy (TNF failure). Moreover, trials evaluating the same therapy but in different subpopulations revealed important differences in treatment effects across prior treatment exposure types (conventional care failure vs TNF failure). For instance, adalimumab trials were conducted in more restricted patient populations (intolerance or secondary non-response to infliximab) in the TNF failure subpopulation.

Comparisons to infliximab in patients who had failed conventional therapy were also undermined by numerous factors. First, the only infliximab data on which the indirect comparison of ustekinumab relied came from a small and relatively old phase II study.[25] Moreover, this study also reported a proportion of missing data in the placebo arm (3/25 patients in the placebo arm [12%] had missing data and were considered non-responders).[158] Targan *et al*. (1997) also reported a smaller magnitude of effect in the higher doses of infliximab than in the lower doses.[25] This suggests that the only data available for infliximab in induction should be interpreted with caution. Lastly, the results observed in Targan *et al*. were not repeated in the open-label induction part of the ACCENT-I maintenance trial evaluating infliximab.[155]

Maintenance phase

Indirect comparisons rely on the assumption that patients are comparable across trials and that a common comparator is available to link interventions that have not previously been evaluated in a head-to-head fashion. At baseline of the maintenance phase, patients are not truly comparable across trials.

Heterogeneity can result from the fact that maintenance trials are 'withdrawal' trials: patients who enter the maintenance phase were initially selected for their ability to respond to the intervention being evaluated. Furthermore, different re-randomisation criteria (CDAI-100 in IM-UNITI[134], CDAI<150 in CLASSIC II[161], and CDAI-70 in all other trials) and times of assessments are applied to different trials at the end of the induction phase. Response to placebo in maintenance could thus result from a 'carry-over' effect from active induction treatment and variations in drugs used and induction time could drive maintenance placebo response rates to fluctuate across trials. This has been associated with the overestimation of maintenance phase treatment effects.[149] Due to the withdrawal study design used in Crohn's trials, 'placebo' arms in maintenance studies are not comparable and cannot readily be used as a common comparator in the network of evidence.

In addition, the number of prior failures to TNFα inhibitor therapy is suspected to impact the comparison of ustekinumab to other biologics. For instance, imbalances between trial populations such as when more patients failed on infliximab therapy only rather than having experienced multiple failure or failure of TNFα inhibitor therapy other than infliximab can impact the response and remission rates obtained. Such differences are likely to impact the comparison between ustekinumab and adalimumab because patients in adalimumab trials have failed only infliximab, while patients in IM-UNITI may have failed up to three different TNFα inhibitor agents.

A third element of heterogeneity in the maintenance phase lies in the difference between primary and secondary failure of TNFα inhibitor therapy. For instance, adalimumab trials only included secondary failure patients with contraindications for infliximab. As adalimumab and infliximab have the same mechanism of action, this resulted in excluding patients that may not respond to adalimumab. However, trials evaluating ustekinumab and vedolizumab included both primary and secondary failures to TNFα inhibitor therapy. As such, patients in trials evaluating ustekinumab and vedolizumab are more inclusive and are comprised of more severe patients that may not respond to treatment with ustekinumab/vedolizumab, while adalimumab

trials were more selective in terms of types of failure. This key difference may underestimate the relative treatment effect of ustekinumab (and vedolizumab) when indirectly compared to adalimumab.

Thus, several challenges arise in the comparison of maintenance trials in CD. Multiple sources of heterogeneity in study design complicate the assessment of relative treatment efficacy and safety in the maintenance phase due to a lack of comparability between 'placebo' arms across trials. However, given the current therapeutic landscape and lack of head-to-head clinical evidence to support the comparisons of biologics against each other, an indirect treatment comparison can still bring added value to the evidence synthesis in CD.

The important differences in the placebo rates in the maintenance studies suggest that the transitivity assumption may also be violated and that placebo arms across trials are not true common comparators. As there are no existing head-to-head comparisons of biologics, pooling the included studies' findings together in an analysis to estimate the long-term relative efficacy and safety of biologics for the treatment of CD was seriously questioned.

When clinical heterogeneity is observed in the inputs from individual clinical trials but cannot be explained from a clinical standpoint, statistical heterogeneity can also be tested. To explore the placebo arm heterogeneity, a chi-square test was conducted in which the observed placebo response and remission rates were compared to those that would be expected if placebo arms truly were common comparators (Table 22). A statistically significant chi-square p-value was interpreted as a high probability that there is a difference between the observed trial data and what would be expected if placebo rates were comparable across trials evaluating different biologics.

Table 22: Results from the chi-square test for statistical heterogeneity among maintenance trials

	Response	Remission
Conventional care failure	<0.001	<0.001
TNF failure	0.003	0.021

Key: TNF, tumour necrosis factor.
Notes: Chi-square p-values are reported for each endpoint by subpopulation. Placebo remission and response rates were found to be significantly different across trials evaluating different biologics.

A significant level of heterogeneity was detected by this statistical test, suggesting that placebo arms are not appropriate common comparators and challenging the feasibility of a traditional NMA in the maintenance phase. In the presence of heterogeneity, key opinion leaders (biostatisticians and clinicians) have argued that results of network meta-analyses comparing therapies in Crohn's disease need to be interpreted with caution.[162]

To adjust for the heterogeneity observed across placebo rates from different trials, a baseline meta-regression was first conducted in accordance with methodological guidance published by NICE.[163] This statistical method consists in plotting the relative treatment effects as a function of placebo rates. As a rule of thumb, the number of studies included in the analysis must be larger than the number of treatments in the network in order for this analysis to generate valid and generalisable results. That is, reaching Markov chain convergence is necessary in order to ensure that the results simulated are plausible. For this reason, convergence was not reached in the analysis of either clinical response or remission, despite raising the number of burn-ins and iterations and increasing prior distribution precision.

As such, the use of exploratory methods such as the proposed treatment sequence analysis, were considered to reduce bias inherently associated with the analysis of long-term relative treatment effect estimates for ustekinumab. The objective of conducting this analysis was twofold: first, to increase comparability of placebo arms in across maintenance phase trials, and second, to evaluate treatment effects over the entire treatment sequence (e.g. induction followed by maintenance as opposed to maintenance only), taking into account different induction regimens. The rationale

behind the treatment sequence analysis is supported by the literature base[164, 165], and development of the method was conducted in line with clinical and methodological expert advice. Outcomes of this treatment sequence analysis were recently reported at the 19th Annual European Conference of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). [166]

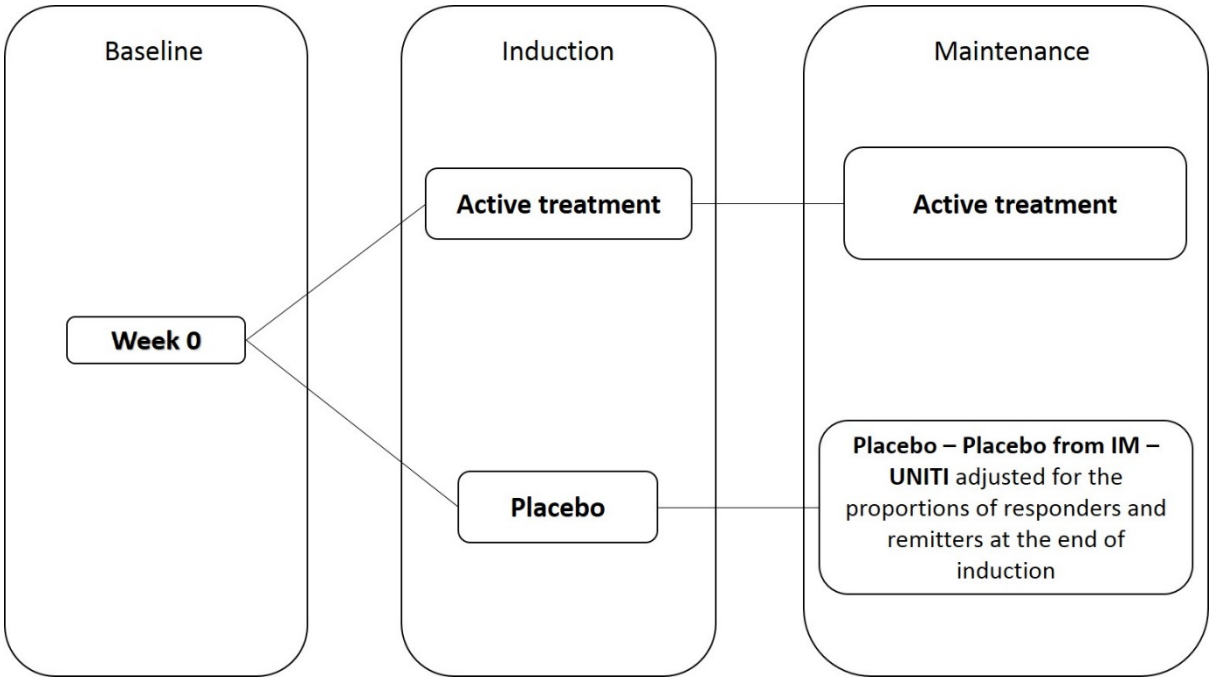
4.10.5 Methods of analysis

Separate analyses were conducted in the conventional care failure and TNF failure subpopulations. Standard analyses were conducted for the analysis of induction. For the maintenance phase, a treatment sequence analysis was considered more appropriate to assess the relative efficacy of ustekinumab at 1 year, that assessed treatment effects over induction and maintenance phases of treatment.

NMA analyses were conducted within a Bayesian framework, preserving the randomisation of each trial. A standard NMA approach was taken for all analyses, as recommended by NICE.[167, 168] The relative goodness of fit of the models was assessed using the Deviance Information Criterion (DIC). All analyses was performed in WinBUGS V1.4[169] using the MCMC (Markov Chain Monte Carlo) simulation method. Additional details of the methods of analysis are provided in Appendix 5.

Conducting NMAs require important assumptions around similarity and transitivity. Feasibility assessment of the induction phase NMA concluded that although heterogeneity across trials is observed (see Section 4.10.4), a standard approach to NMA was appropriate, with a series of sensitivity analyses supporting base case analysis to investigate potential sources of bias. Sensitivity analyses conducted are detailed in Appendix 5. Feasibility assessment of the maintenance phase NMA concluded that several important conceptual differences between trials necessitated a more complex approach to NMA. As the maintenance of treatment effect is conditional on treatment effect observed in the preceding induction phase, a proper assessment of the maintenance phase needs to take into account the full treatment pathway. Therefore, a treatment sequence approach was adopted, as depicted in Figure 27.

Figure 27: Treatment sequence analysis strategy



As part of treatment sequence analysis, maintenance data for placebo arms of comparator trials were imputed using IM-UNITI individual patient level data, adjusted for the proportion of responders and remitters at the end of induction phase. This was considered necessary in order to reduce bias associated with the violation of the transitivity assumption given that the 'placebo' arms in maintenance studies are not comparable (see Section 4.10.4). Data inputs for the treatment sequence analysis were as follows and are reported in Appendix 5:

- Induction: CDAI-70 rates at Week 6 (for ustekinumab and vedolizumab) or Week 4 (for adalimumab and infliximab). CDAI-70 was selected for all trials. The rationale for selecting this definition of clinical response for ustekinumab when it was not its re-randomisation criterion for entry into maintenance was to optimise the comparability of ustekinumab to other biologics
- Maintenance data for active treatments: CDAI-100 or CDAI<150 data at the end of maintenance
- Maintenance data for placebo arms: estimated based on the placebo-to-placebo arm of IM-UNITI and adjusted for the proportions of "responders non-remitters" and remitters at the end of induction using a weighted average of

placebo rates in these two subpopulations (see Figure 28 and Figure 29 for details on imputations methods)

To estimate the probability of achieving and maintaining response by the end of maintenance, the relative probability of achieving response based on the re-randomisation criterion was multiplied by the conditional probability of maintaining response (obtained from maintenance trials for active treatment arms and estimated via a weighted average for placebo arms).

Details on how the inputs for the treatment sequence analysis were estimated are reported in Figure 30 and Figure 31.

A Bayesian network meta-analysis was conducted as the base case analysis to generate relative treatment effects for ustekinumab. To obtain odds ratios (OR), the number of patients estimated with the treatment sequence analysis was rounded up. A sensitivity analysis was conducted to generate the same relative treatment effects through an adjusted indirect comparison using the Bucher method.[170] The following sensitivity analyses were also conducted to test the robustness of the treatment sequence analysis:

- The base case analysis was also conducted under a frequentist framework based on the approach by Bucher *et al*.[170]
- Individual patient data were used to generate inputs for patients from the UNITI program who were "truly naïve" to biologics.[1] These inputs replaced those used in the conventional care failure subpopulation analysis
- Maintenance doses were pooled in order to assess if an increase in statistical power of direct comparisons to placebo affected the uncertainty around the indirect treatment effect estimates obtained through the treatment sequence analysis when different maintenance doses of the same biologic were compared to each other

Details on the results for these sensitivity analyses are reported in Appendix 5.

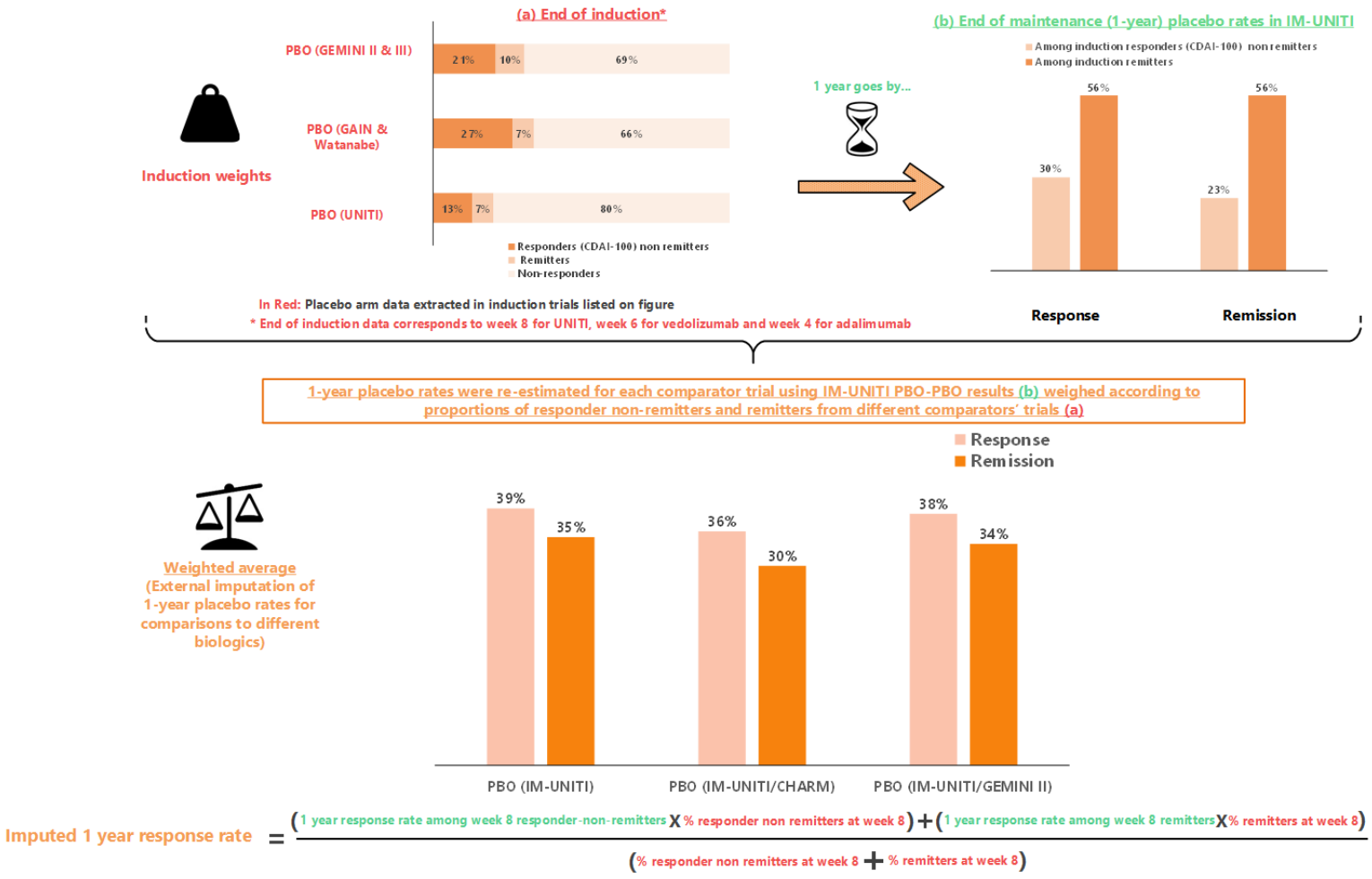
[1] "Truly naïve" patients are defined as a subpopulation of failed patients having failed conventional care and having never received any anti-TNFs.

In addition to these sensitivity analyses, it was identified upon consulting with a key opinion leader of biostatistics that while sampling uncertainty has been taken into account in the base case analysis, prediction uncertainty around the imputed placebo-to-placebo arms generated based on weights obtained via the IM-UNITI population was not accounted for in this analysis. This comment was raised at the time of incorporation of treatment sequence analysis results in the cost-effectiveness model. Therefore, an additional scenario analysis was conducted to account for the uncertainty associated with the imputed placebo-to-placebo rates used in the treatment sequence analysis. Full details of the methods and results of this analysis are provided in Appendix 5.

Figure 28: Conventional care failure population – placebo–placebo maintenance arm imputation

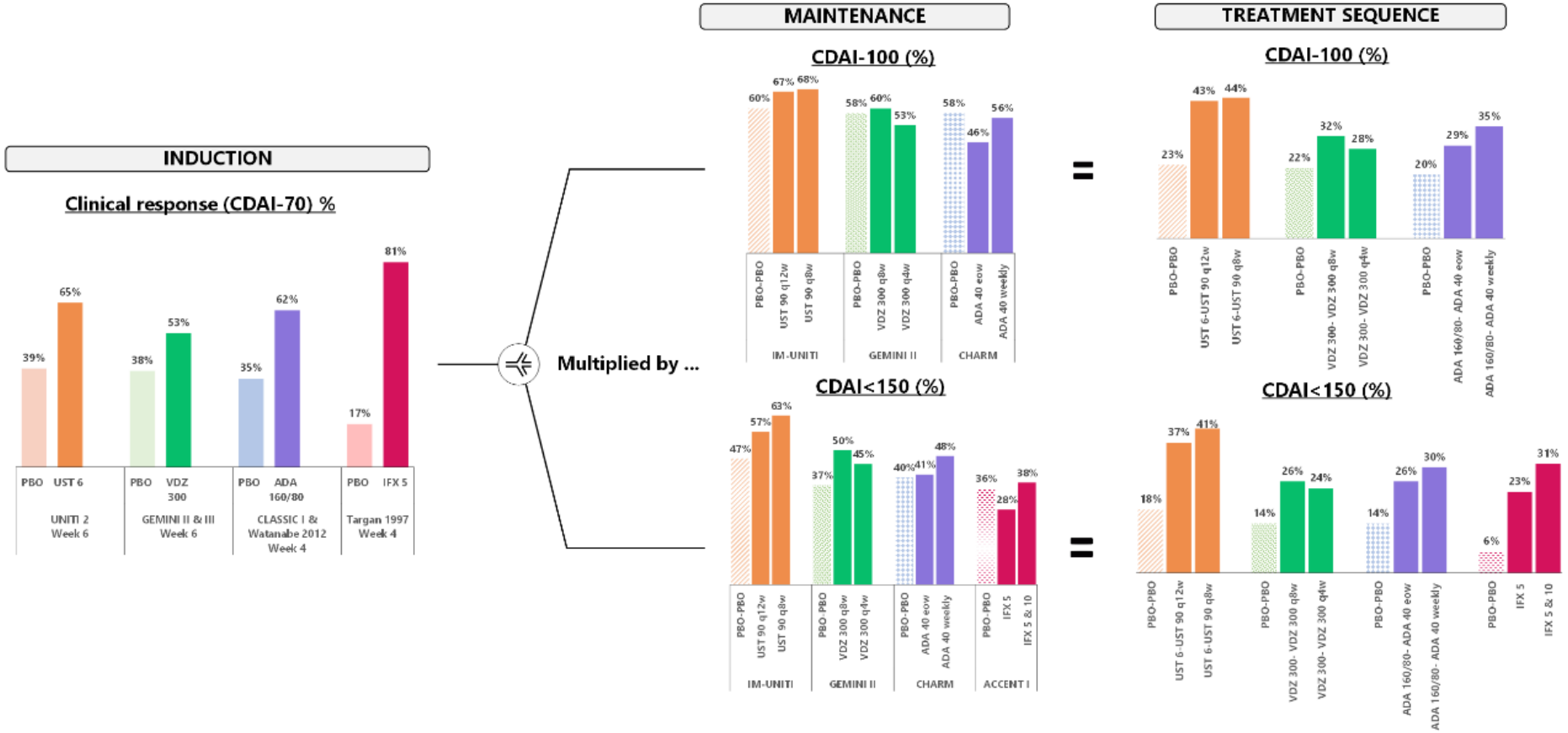
Key: CDAI, Crohn's Disease Activity Index; PBO, placebo.

Figure 29: TNF failure population – placebo–placebo maintenance arm imputation



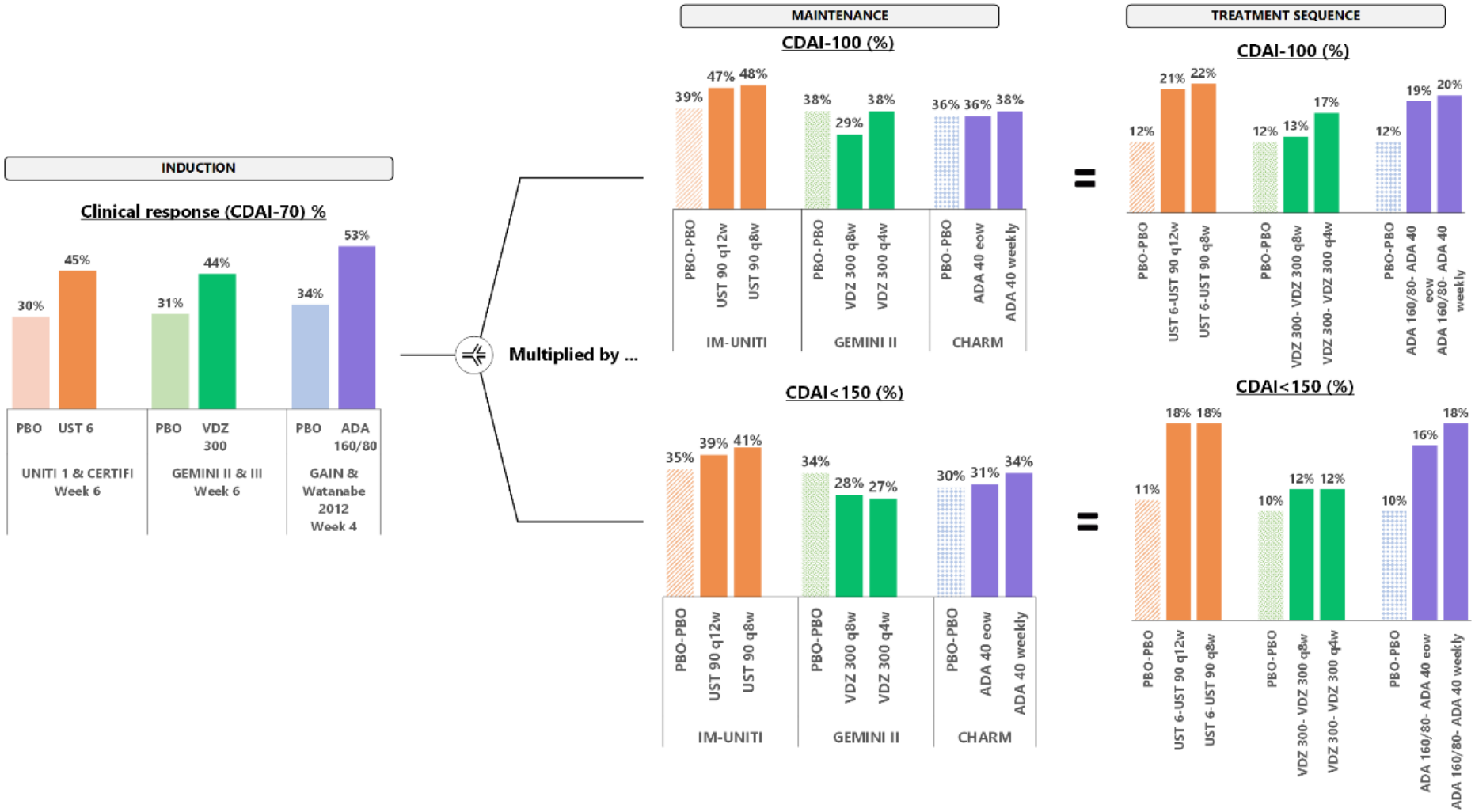
Key: CDAI, Crohn's Disease Activity Index; PBO, placebo.

Figure 30: Treatment sequence analysis – generation of inputs for the conventional care failure subpopulation



Key: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; IFX, infliximab; PBO, placebo; UST, ustekinumab; VDZ, vedolizumab.

Figure 31: Treatment sequence analysis – generation of inputs for the TNF failure subpopulation



Key: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; PBO, placebo; UST, ustekinumab; VDZ, vedolizumab.

4.10.6 Presentation of results

Full details on ORs and their credible intervals (CrI) for base case and all sensitivity analyses can be found in Appendix 5. In all cases for the induction phase, findings obtained with the sensitivity analyses did not change the interpretation of the results, suggesting that the base case analysis is robust.

Induction phase

A summary of results from induction phase NMA of most relevance to current UK practice are provided in Table 23. As noted previously, results for infliximab should be interpreted with caution, due to concerns with the reliability of data feeding into these estimates.

Table 23: Summary of induction NMA results of relevance to UK practice

OR (95% CI) ustekinumab vs	Response (CDAI-70)	Response (CDAI-100)	Remission
Conventional care failure population			
Adalimumab 80/40mg	0.98 (0.46; 2.05)	1.39 (0.64, 2.97)	1.14 (0.44, 2.82)
Adalimumab 160/80mg	0.92 (0.43; 1.91)	1.03 (0.47, 2.20)	0.64 (0.25, 1.53)
Placebo	2.89 (1.95; 4.32)	3.12 (2.08, 4.68)	2.5 (1.60, 3.98)
Infliximab 5mg/kg*	0.11 (0.02; 0.48)	N/A	0.08 (0.01, 0.59)
TNF failure population			
Vedolizumab 300mg	0.96 (0.57, 1.62)	1.05 (0.59, 1.85)	1.53 (0.69, 3.39)
Placebo	1.79 (1.24, 2.60)	1.87 (1.26, 2.80)	2.34 (1.37, 4.08)
Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; OR, odds ratio. **Notes:** *infliximab included as scenario analysis only. Results shown for week 4 (infliximab and adalimumab) and week 6 (ustekinumab and vedolizumab).			

Conventional care failure: CDAI-70

The forest plot for the analysis of CDAI-70 at the end of induction for the conventional care failure subpopulation is presented in Appendix 5.

Ustekinumab was comparable to adalimumab with probabilities of being better than the latter ranging between 41 and 48% (OR was 0.92 when compared to both adalimumab doses, and CrIs included 1).

The point estimates were in favour of ustekinumab when compared to vedolizumab. The probability for ustekinumab to be better than vedolizumab in terms of CDAI-70 clinical response was 93% (OR: 1.58, CrI: 0.85, 2.94).

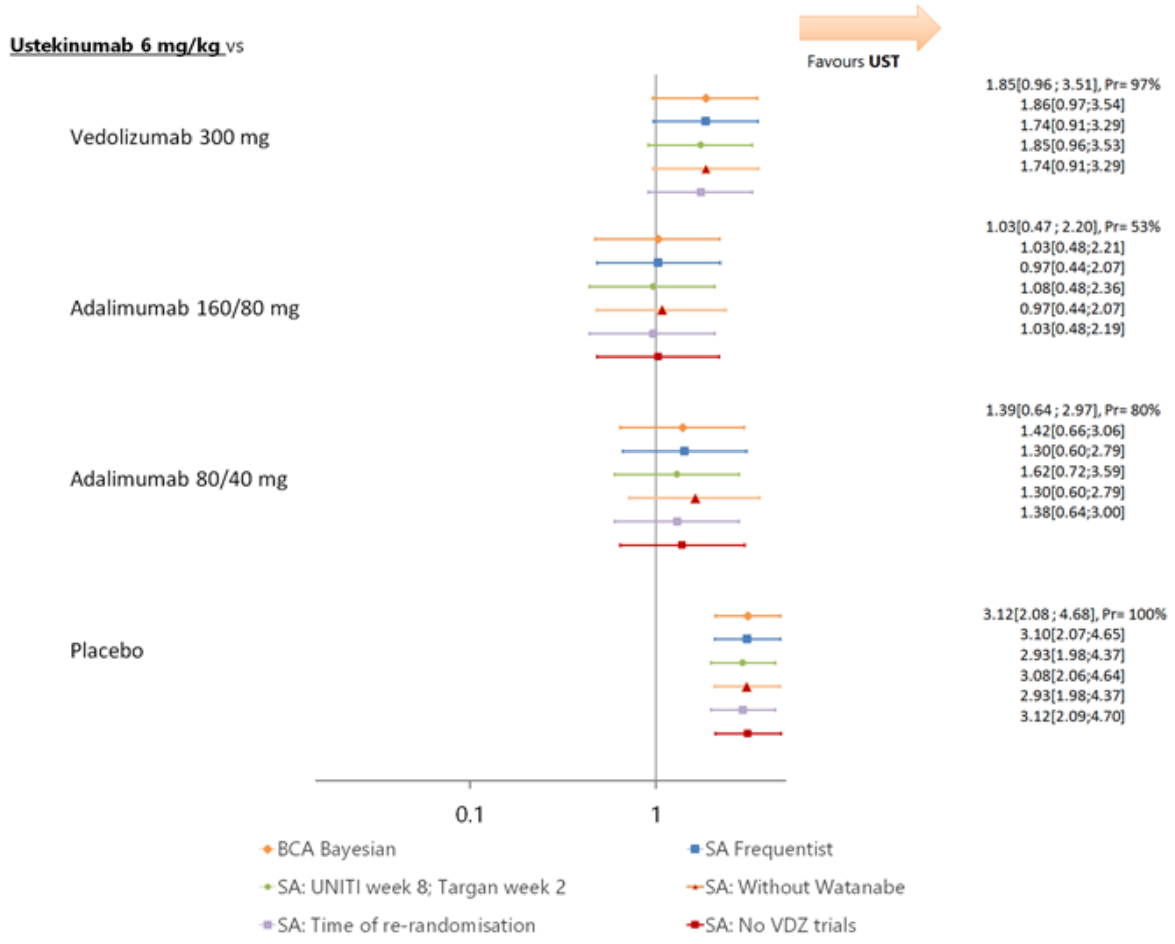
Ustekinumab seemed less effective than infliximab 5 mg/kg, based on data inputs available for infliximab in the literature (OR: 0.11, CrI: 0.02, 0.48). This finding was reflected in the Bayesian probabilities obtained (0%). However, the relative treatment effects obtained for ustekinumab compared to infliximab are based on one small and older study with a high proportion of missing data in the placebo arm.

Conventional care failure: CDAI-100

The forest plot for the analysis of CDAI-100 at the end of induction for the conventional care failure subpopulation is presented in Figure 32.

Ustekinumab was comparable to adalimumab, and the point estimates were in favour of ustekinumab when compared to vedolizumab.

Figure 32: Forest plot for the analysis of CDAI-100 at the end of induction – conventional care failure (median OR and 95% CrI)



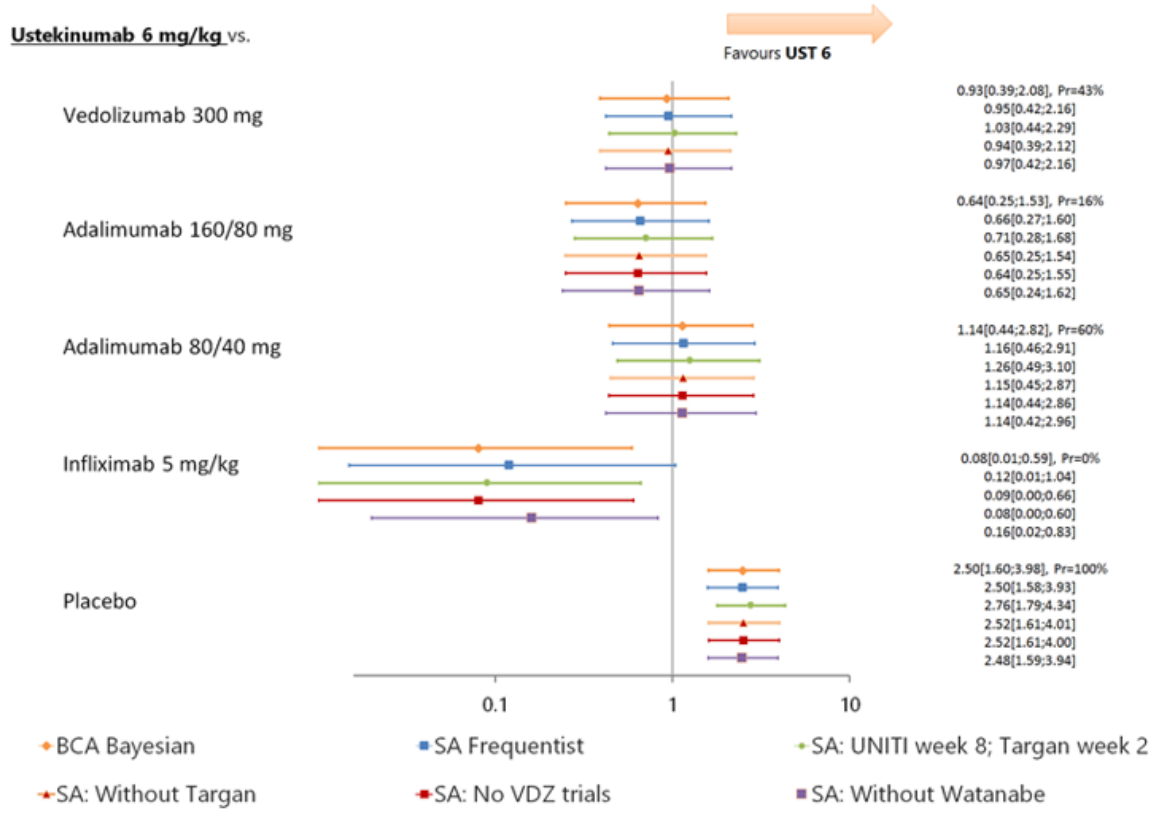
Key: BCA, base case analysis; Pr, probability; SA, sensitivity analysis; UST, ustekinumab; VDZ, vedolizumab.

Conventional care failure: CDAI <150

The forest plot for the analysis of CDAI <150 at the end of induction for the conventional care failure subpopulation is presented in Figure 33.

Ustekinumab was comparable to adalimumab 80/40 mg and vedolizumab 300 mg. The point estimates were not in favour of ustekinumab when compared to adalimumab 160/80 mg, and ustekinumab seemed less effective than infliximab 5 mg/kg, based on limited data inputs available for infliximab in the literature.[25]

Figure 33: Forest plot for the analysis of CDAI<150 at the end of induction – conventional care failure (median OR and 95% CrI)



Key: BCA, base case analysis; Pr, probability; SA, sensitivity analysis; UST, ustekinumab; VDZ, vedolizumab.

TNF failure: CDAI-70

The forest plot for the analysis of CDAI-70 at the end of induction for the TNF failure subpopulation is presented in Appendix 5.

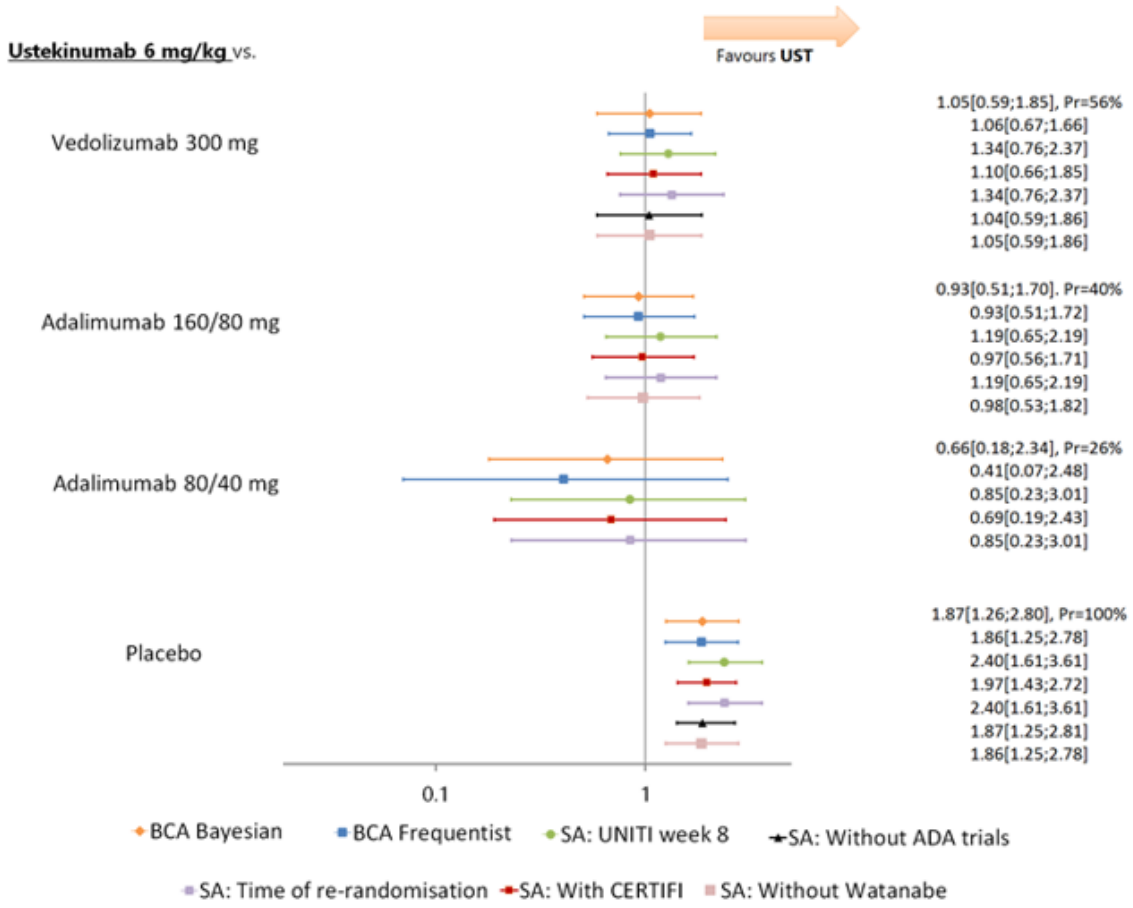
Ustekinumab was comparable to adalimumab 160/80 mg (OR [CrI]: 0.83 [0.47, 1.46], Pr: 26%) and vedolizumab 300 mg (OR [CrI]: 0.96 [0.57, 1.62], Pr: 45%). The point estimates were in favour of ustekinumab when compared to adalimumab 80/40 mg (OR (CrI): 1.29 (0.38, 4.40), Pr: 66).

TNF failure: CDAI-100

The forest plot for the analysis of CDAI-100 at the end of induction for the TNF failure subpopulation is presented in Figure 34.

Ustekinumab is comparable to adalimumab 160/80 mg and vedolizumab 300 mg. The point estimates were not in favour of ustekinumab when compared to adalimumab 80/40 mg.

Figure 34: Forest plot for the analysis of CDAI-100 at the end of induction – TNF failure (median OR and 95% CrI)



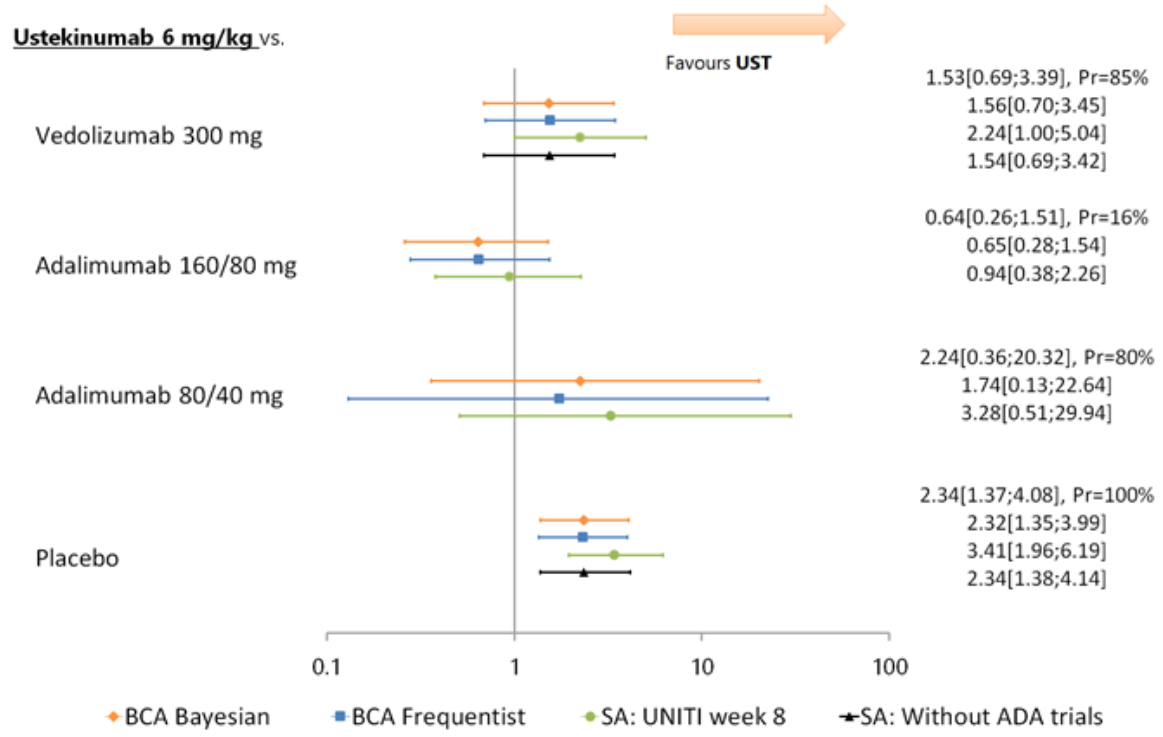
Key: BCA, base case analysis; Pr, probability; SA, sensitivity analysis; UST, ustekinumab.

TNF failure: CDAI <150

The forest plot for the analysis of CDAI <150 at the end of induction for the TNF failure subpopulation is presented in Figure 35.

Point estimates were in favour of ustekinumab when compared to adalimumab 80/40 mg and vedolizumab 300 mg. The point estimates were not in favour of ustekinumab when compared to adalimumab 160/80 mg.

Figure 35: Forest plot for the analysis of CDAI<150 at the end of induction – TNF failure (median OR and 95% CrI)



Key: BCA, base case analysis; Pr, probability; SA, sensitivity analysis; UST, ustekinumab.

Maintenance phase

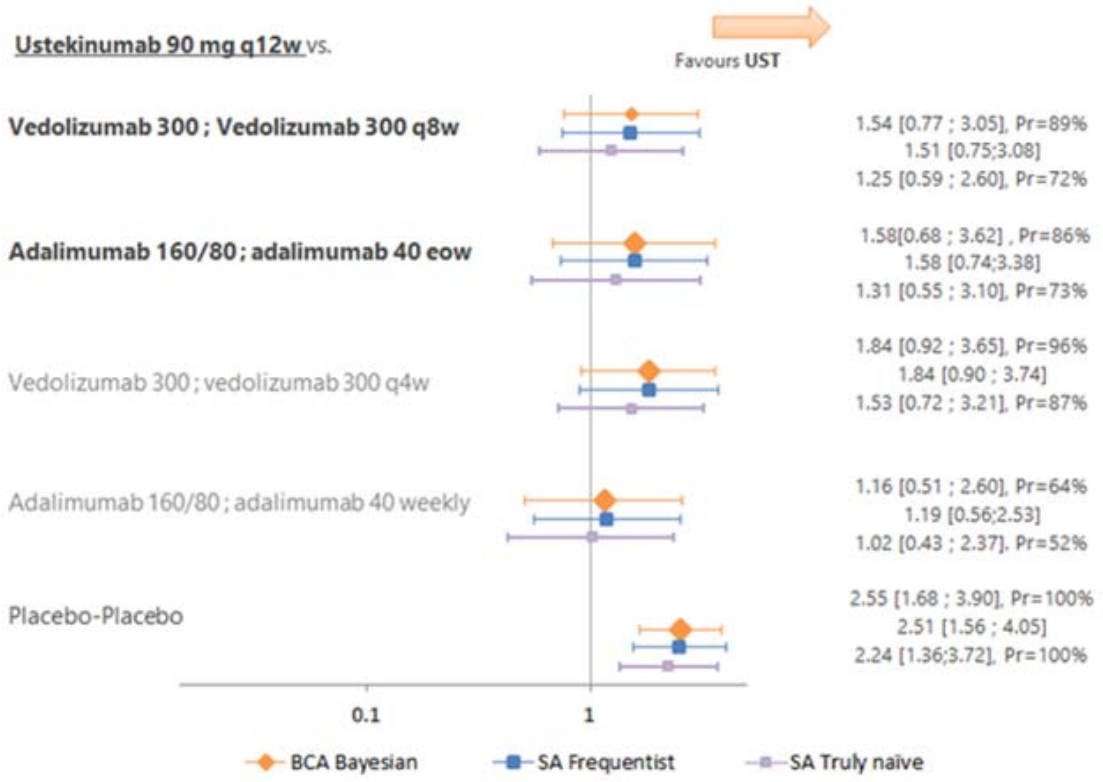
Conventional care failure: CDAI-100

The forest plot for the analysis of CDAI-100 at 1-year post induction for the conventional care failure subpopulation is presented for ustekinumab q12w in Figure 36. The forest plot for the same analysis for ustekinumab q8w is provided in Appendix 5.

When compared to standard licensed doses for each comparator, ustekinumab q12w had high probabilities of performing better than vedolizumab q8w and adalimumab eow in terms of clinical response after 1 year. Ustekinumab q8w also had high probabilities of performing better than vedolizumab q8w (91%, OR [CrI]: 1.60 [0.81, 3.15]) and adalimumab eow (88%, OR [CrI]: 1.64 [0.71, 3.73]).

When comparing ustekinumab to infliximab in patients who failed conventional therapy, there was a 16% to 34% probability for infliximab of reaching and maintaining remission. However, there was a large level of uncertainty around these estimates as the infliximab induction data could only be based on an old trial with low placebo remission rate and small sample size (Targan *et al*.[25]). In addition, several other challenges (discussed in Section 4.10.4) are associated with the inclusion of the study by Targan *et al*.[25], making the comparison of ustekinumab to infliximab difficult to interpret.

Figure 36: Maintenance of response (CDAI-100) after 1 year in treatment sequence analysis – conventional care failure, ustekinumab q12w (median OR and 95% CrI)



Key: BCA, base case analysis; eow, every other week; Pr, probability; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SA, sensitivity analysis.

Conventional care failure: CDAI <150

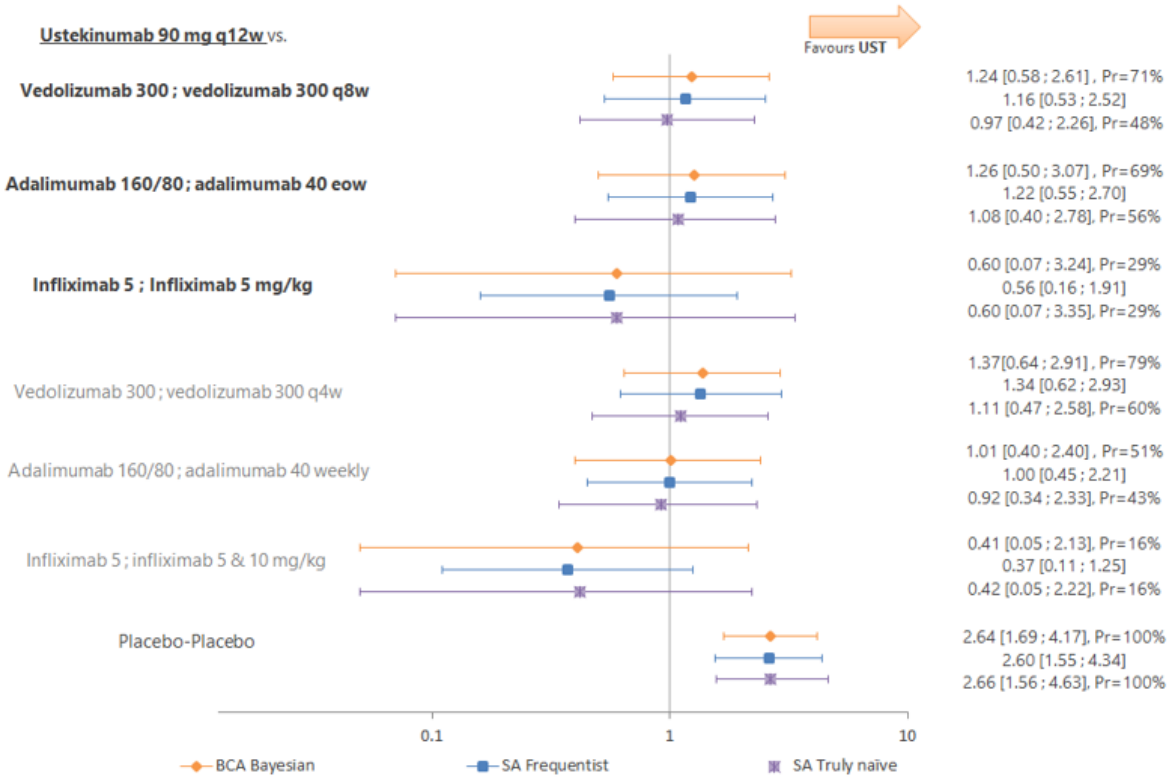
The forest plot for the analysis of CDAI <150 at 1-year post induction for the conventional care failure subpopulation is presented for ustekinumab q12w in

Figure 37. The forest plot for the same analysis for ustekinumab q8w is provided in Appendix 5.

When compared to standard licensed doses for each comparator, ustekinumab q12w had high probabilities of performing better than vedolizumab q8w and adalimumab eow in terms of clinical remission after 1 year. Ustekinumab q8w also had high probabilities of performing better than vedolizumab q8w (82%, OR [CrI]: 1.43 [0.66, 2.99]) and adalimumab eow (79%, OR [CrI]: 1.45 [0.58, 3.53]).

Compared to infliximab, the point estimates were not in favour of ustekinumab, and probabilities for ustekinumab to be better than either doses of infliximab were low (16–34%).

Figure 37: Maintenance of remission after 1 year in treatment sequence analysis – conventional care failure, ustekinumab q12w (median OR and 95% CrI)



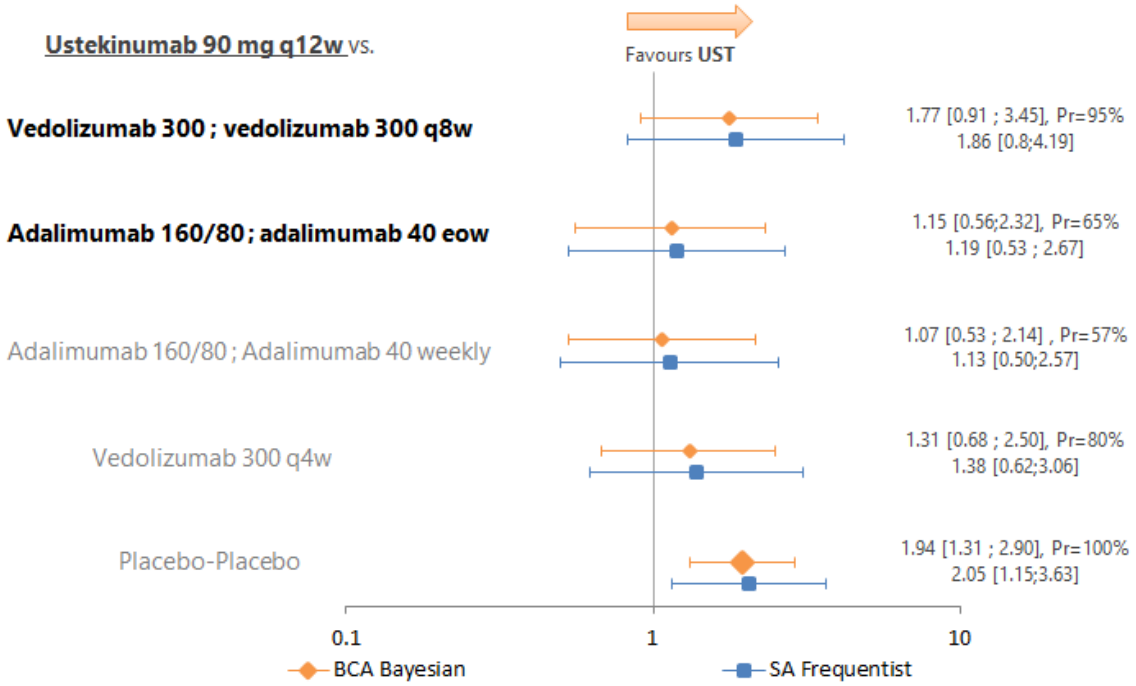
Key: BCA, base case analysis; eow, every other week; Pr, probability; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SA, sensitivity analysis.

TNF failure: CDAI-100

The forest plot for the analysis of CDAI-100 at 1-year post induction for the TNF failure subpopulation is presented for ustekinumab q12w in Figure 38. The forest plot for the same analysis for ustekinumab q8w is provided in Appendix 5.

When compared to standard licensed doses for each comparator, ustekinumab q12w had high probabilities of performing better than vedolizumab q8w and adalimumab eow in terms of clinical response after 1 year. Ustekinumab q8w also had high probabilities of performing better than vedolizumab q8w (97%, OR [CrI]: 1.89 [0.97, 3.67]) and adalimumab eow (71%, OR [CrI]: 1.22 [0.60, 2.46]).

Figure 38: Maintenance of response (CDAI-100) after 1 year in treatment sequence analysis – TNF failure, ustekinumab q12w (median OR and 95% CrI)



Key: BCA, base case analysis; eow, every other week; Pr, probability; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SA, sensitivity analysis.

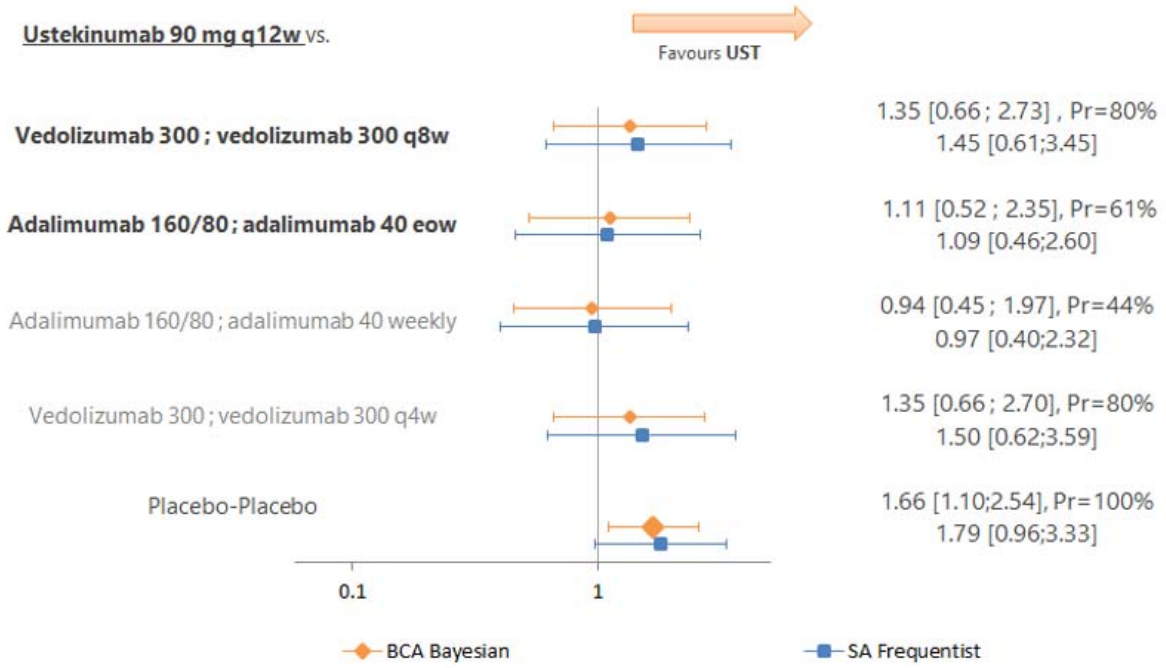
TNF failure: CDAI <150

The forest plot for the analysis of CDAI <150 at 1-year post induction for the TNF failure subpopulation is presented for ustekinumab q12w in Figure 39. The forest plot for the same analysis for ustekinumab q8w is provided in Appendix 5.

When compared to standard licensed doses for each comparator, ustekinumab q12w had high probabilities of performing better than vedolizumab q8w and adalimumab eow in terms of clinical remission after 1 year. Ustekinumab q8w also

had high probabilities of performing better than vedolizumab q8w (84%, OR [CrI]: 1.43 [0.70, 2.88]) and adalimumab eow (66%, OR [CrI]: 1.17 [0.56, 2.49]).

Figure 39: Maintenance of remission after 1 year in treatment sequence analysis– TNF failure, ustekinumab q12w (median OR and 95% CrI)



Key: BCA, base case analysis; eow, every other week; Pr, probability; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SA, sensitivity analysis.

4.10.7 Limitations

While an NMA for assessing the relative efficacy of ustekinumab in the induction phase was possible, a traditional NMA for maintenance data was deemed not feasible due to the lack of comparability of placebo arms of the maintenance studies. This is due to maintenance trials being inherently different by design: patients are selected for entry into maintenance using different response criteria (CDAI-70, CDAI-100, or CDAI<150) at different times of assessments and most importantly after induction with different biologics. It has been highlighted in the literature that these important differences (when study duration is increased and when robust objective endpoints are chosen) can result in high variations in placebo response across time.[171, 172] Hence, the very different induction treatment experiences of patients from different trials receiving placebo in maintenance contribute to the observed heterogeneity. Moreover, while visual cross-study comparison of infliximab and

adalimumab maintenance trials suggests similar maintenance of effect of both anti-TNFs, the SWITCH trial[159] indicates that relative treatment effects observed in the maintenance phase are conditional on the induction drug used. For this reason, variations in placebo effect sizes from induction trials were considered to be too important, and placebo was not deemed to be a reliable common comparator due to numerous and not easily quantifiable differences in placebo arm results.[173]

Others have faced similar challenges in attempts to synthesise the available evidence on biologics in moderate-to-severe CD. For instance, Hazlewood *et al*.[174] conducted a network meta-analysis in 2015 in the mixed population, where a sensitivity analysis was conducted for the induction phase excluding patients with prior exposure to anti-TNF therapy. Maintenance sensitivity analyses were also conducted: one including only trials with maintenance of remission at 1 year or longer as the primary endpoint, and another including only trials randomising patients after successful induction period. A baseline risk meta-regression was also attempted in order to take into account placebo response rates. However, none of these methods led to conclusive results. A commentary on this NMA, published by Bonovas *et al*.[162], pointed out various non-negligible issues. For instance, there was important conceptual heterogeneity due to different doses of the same treatment being pooled together, or due to pooling patients regardless of prior TNF-exposure. In addition, Bonovas *et al*.[162] suggested that results for this NMA should be interpreted with caution as different drug classes were included in the comparison (not just biologics), times of assessments were different for the induction phases across trials, definitions of remissions varied (CDAI vs HBI or other definitions), there were differences in baseline disease severity across trials, and different concomitant interventions were allowed.

Another NMA conducted by Stidham *et al*. in 2014[175] raised similar concerns. For instance, the CDAI score was deemed not sufficiently accurate or reproducible as a measure of disease activity, and induction regimens were considered to not be uniform (different maintenance selection criteria and length of induction phases). However, an important limitation of their work was that all analyses were conducted in the mixed population, pooling results for patients who had failed conventional and anti-TNF therapy. Therefore, Stidham *et al*. acknowledged that the standardisation or

stratification of prior anti-TNF exposure status may have made the indirect comparisons more accurate.

Singh *et al*.[176] also conducted a meta-analysis in 2014 but only in patients who had failed conventional therapy. They also only analysed clinical remission as an endpoint and did not generate relative efficacy estimates for clinical response. Issues such as variations in rates of concomitant use of immunomodulatory therapy, placebo-response rates, and times of assessments across studies were once again raised in the discussion section. Moreover, Singh *et al*. identified that early studies did not use standard induction doses and pointed out important study design differences between studies, such as CLASSIC II[161] selecting induction remitters into maintenance as opposed to induction responders.

Finally, NICE also commissioned a report by an Evidence Review Group (ERG) in 2008 in order to assess the use of adalimumab and infliximab for CD.[23] The lack of a common comparator arm for the maintenance phase was pointed out due to variations in placebo effect sizes. The report concluded that an indirect comparison with these two biologics was not possible because of the low placebo rate for Targan *et al*.[25] and the non-comparability of the "placebo" arms in maintenance. However, in a more recent HTA report published by NICE for the manufacturer's submission for reimbursement of vedolizumab[177], variations in placebo response rates between studies were said to be expected and dealt with in the statistical analysis by estimating treatment effects within studies. Consequently, the ERG did not challenge the feasibility of the NMA conducted by the manufacturer, nor did they comment on the lack of common comparators in the maintenance phase.

This lack of consensus on the feasibility of an NMA of the maintenance phase data alone led us to consider alternative methods that would more accurately capture the relative efficacy of biologics in CD. The rationale behind the treatment sequence analysis is supported by publications.[164, 165] It allows us to assess the probability of reaching and maintaining response and remission until the end of maintenance despite the aforementioned limitations. As such, the analysis incorporates induction and maintenance data for each intervention, allowing us to account for the full treatment pathway of CD patients. This analysis preserves the randomisation of each trial up to the end of induction. Randomisation is not maintained after re-randomisation because placebo arms of the trials were replaced by the placebo–

placebo arm of IM-UNITI, adjusted for the proportions of responders and remitters at the end of induction. The inclusion criteria and placebo rates of induction trials were similar, suggesting a similarity between patient populations included in the different induction trials. Thus, after the induction, placebo response and remission rates were imputed across trials using patients induced by placebo and (conditional upon response) continued on placebo in the IM-UNITI trial[134] (i.e. the only available data from a placebo-to-placebo arm). Despite the methodological limitations associated with this approach, it is considered here as an alternative method to synthesise the maintenance data providing that patients' characteristics are comparable across trials.

In addition to expert recommendation, additional sensitivity analysis was conducted *a posteriori* to account for uncertainty around the imputed placebo-to-placebo arms generated based on weights obtained via the IM-UNITI population, alongside sampling uncertainty. The impact of this sensitivity analysis on the ORs generated was minor; on average, there was a difference of ~0.01 between ORs generated through the base case analysis (see Section 4.10.6), and the ORs obtained with the log-odds model used in sensitivity analysis. Credibility intervals were generally wider (as we might expect when accounting for uncertainty), although not for the relative treatment effects of ustekinumab compared to other biologics. Importantly, none of the conclusions on how to interpret the results of the base case analysis were modified in this sensitivity analysis. Full details of the methods and results of this analysis are provided in Appendix 5.

Further to limitations of the NMA due to 'placebo' concerns, there were additional sources of heterogeneity that should be discussed. As the re-randomisation criteria were not homogeneous across trials, these were not always used for the induction response rates used in the treatment sequence analysis. Comparators use CDAI-70 at Weeks 4 or 6, while ustekinumab uses CDAI-100 at Week 8. CDAI-70 at Week 6 was thus used across all trials to optimise comparability of active treatments to ustekinumab. However, the impact of this induction response criterion selection did not significantly impact the analysis as results for IM-UNITI[134] in CDAI-70 responders at Week 3 or Week 6 are similar to those with the original re-randomisation criterion. Post-hoc analysis exploring the influence of varying response re-randomisation criterion in IM-UNITI supports this conclusion, demonstrating that the overall Week

52 remission rates were comparable across patients with an induction response of CDAI-70 at Week 3 (56%) or Week 6 (52%), and patients with an induction response of CDAI-100 at Week 8 (53%).[178] Overall Week 52 CDAI response rates were also comparable across patients with an induction response of CDAI-70 at Week 3 or Week 6 and patients with an induction response of CDAI-100 at Week 8, at 61%, 58% and 59%, respectively. These data (based on ustekinumab 90mg 8qw maintenance dosing) suggest different qualifiers for response to ustekinumab induction did not result in different response or remission rates after 1 year of treatment.

Patients' characteristics are globally comparable across trials in patients who failed conventional therapies. In the failed anti-TNF population, the heterogeneity in the prior treatment failure between patients from the adalimumab trials and the vedolizumab and ustekinumab trials has been identified as a major limitation in the analysis. More precisely, patients in adalimumab trials who are reported to have previously failed anti-TNF therapy can only have failed infliximab and were excluded if they had primary non-response to infliximab compared to patients in vedolizumab trials who can have failed infliximab and adalimumab, or patients in ustekinumab trials who can have failed up to three different biologics. As such, patients who have failed more than one biologic can be construed as being more refractory, which could lead to the underestimation of the relative treatment effects obtained for ustekinumab.[171]

Moreover, most comparators' trials used for the maintenance data had an open-label induction phase (except for Watanabe 2012[151]), whereas the ustekinumab trials were double-blinded in both induction and maintenance phases. This is expected to bias results against ustekinumab as a qualitatively better maintenance of effect was observed in the patients from the open-label induction cohort 2 than in the double-blinded cohort 1 of the GEMINI II[17] study evaluating vedolizumab.

Finally, another limitation to the NMA and treatment sequence analysis is inherent to how endpoints are defined in CD trials. Clinical response and remission are categorical criteria defined based on changes in CDAI score from baseline. Despite the fact that CDAI is the most commonly used and regulatory accepted endpoint for the assessment of treatment efficacy in CD, a number of issues are known to be associated with it[179], including: reported inter-observer variability[180]; a significant

component of the total CDAI score being derived from highly subjective items, such as “general well-being” and “intensity of abdominal pain”, which are heavily impacted by a patient’s perception of the disease[181]; CDAI refers to the 7 days before the actual day of assessment, precluding its use in everyday practice; some items such as “liquid” stools could be difficult to define precisely; and CDAI is not so accurate in patients with fistulising and stenosing CD behaviour.[179] Additionally, clinical scoring systems such as CDAI are known to be poorly correlated with objective markers of inflammation (i.e. endoscopic assessment, or CRP to assess disease activity and response to treatment).[171, 182, 183] The limitations associated with CDAI have been recognised by some regulatory agencies such as the US Food and Drug Administration (FDA), which is moving away from CDAI and focusing on Patient Reported Outcomes (PROs) and objective measures of disease, such as findings from endoscopy.[184] A recent large international consensus statement clearly set the goal of therapy in CD as modification of natural history of the disease by taking a “treat-to-target” approach.[182] Regardless, the authors acknowledge that the use of clinical scoring systems is important in practice to allow for proper monitoring and management of symptoms. The overall consensus among experts regarding the use of clinical scoring systems (such as CDAI) is that “*Resolution of symptoms alone is not a sufficient target. Objective evidence of inflammation of the bowel is necessary when making clinical decisions*”.[182] As such, subjectivity and variability around individual CDAI scores need to be taken into account when interpreting the results obtained for clinical response and remission endpoints.

The conclusions of the treatment sequence analysis are limited, and results should be interpreted with caution. Comparisons with infliximab should be interpreted with caution given that several factors associated with the induction study for infliximab[25] limit the interpretation. Similarly, comparisons to adalimumab in patients who had failed anti-TNF therapy should also be interpreted with caution due to important differences in exclusion/inclusion criteria. However, given the lack of head-to-head evidence and the need for the evaluation of the relative efficacy of ustekinumab, the treatment sequence analysis may be the best possible approach given the lack of comparable maintenance data across comparators.

4.10.8 Conclusion

The objective of this NMA was to evaluate the relative efficacy of ustekinumab in the treatment of moderately to severely active CD. The comparators of interest were infliximab, adalimumab, and vedolizumab. Only RCTs were included. Separate analyses were conducted for clinical response (CDAI score reduction of 70 or 100 points) and clinical remission (CDAI score under 150 reached). Separate analyses were also conducted in patients who had failed conventional therapy (conventional care failure) and in patients who had failed, or are contraindicated to, TNFα inhibitor therapy (TNF failure). All analyses were performed in a Bayesian framework. The analysis of safety endpoints at the end of induction or maintenance was deemed not feasible, and results were not presented.

Induction phase trials in CD were deemed similar enough, in terms of study design and patient characteristics, for their findings to be pooled together in a standard network meta-analysis. In the conventional care failure subpopulation, ustekinumab was associated with a high probability of reaching either CDAI-70 (93%, OR [CrI]: 1.58 [0.85, 2.94]) or CDAI-100 (97%, OR [CrI]: 1.85 [0.96, 3.51]) response compared to vedolizumab, and was comparable to adalimumab (probabilities ranging from 41% (OR [CrI]: 0.92 [0.43, 1.91]) to 80% (OR [CrI]: 1.39 [0.64, 2.97])). Ustekinumab was comparable to adalimumab and vedolizumab in terms of probabilities of reaching remission at the end of induction (probabilities of performing better of 16% versus adalimumab 160/80 mg (OR [CrI]: 0.64 [0.25, 1.53]) and 60% versus adalimumab 80/40 mg (OR [CrI]: 1.14 [0.44, 2.82]). In the TNF failure subpopulation, ustekinumab had odds of reaching clinical response comparable to those of adalimumab and vedolizumab (probabilities ranging between 26% (OR [CrI] vs adalimumab 160/80 mg 0.83 [0.47, 1.46]) and 66% (OR [CrI] vs adalimumab 80/40 mg 1.29 [0.38, 4.40]). The odds of reaching remission with ustekinumab were also comparable to these biologics (probabilities ranging between 16% (OR [CrI] vs adalimumab 160/80 mg 0.64 [0.26, 1.51]) and 85% (OR [CrI] vs vedolizumab 300 mg 1.53 [0.69, 3.39]). Comparisons with infliximab suggested that ustekinumab performs poorly (null probabilities of being better), but this comparison should be interpreted with caution due to the number of factors associated with the induction study used as a data source for infliximab.

The analysis of maintenance data alone was deemed not feasible due to the non-comparability of the 'placebo' arms and proven statistical heterogeneity. A treatment sequence analysis was considered more appropriate to assess the relative efficacy of ustekinumab at 1 year. When looking at the entire treatment sequence (conditional on response after induction), there is a higher likelihood of reaching response or remission at 1 year with ustekinumab compared to vedolizumab 300 mg q8w (OR [CrI]: 1.89 [0.97, 3.67]) or adalimumab 40 eow (OR [CrI]: 1.64 [0.71, 3.73]) in both conventional care and TNF failure subpopulations. Comparisons with infliximab suggested that ustekinumab has a lower probability of reaching response or remission at 1 year; however, results compared to infliximab need to be interpreted with caution.

4.11 Non-randomised and non-controlled evidence

Non-RCT evidence was not formally considered as part of comparative efficacy or cost-effectiveness assessments as RCT data were available for the intervention and for named comparators of interest to the decision problem.

4.12 Adverse reactions

The safety profile of ustekinumab for the management of CD was generally in line with that observed in other indications; except for a few events of acne, asthenia, vomiting, and vulvovaginal mycotic infections, no new types or patterns of AEs were identified.

4.12.1 Summary of safety data from UNITI-1 and UNITI-2

A summary of safety events from the Phase III induction trials is provided in Table 24. IV ustekinumab at doses of 130mg and ~6mg/kg was generally well tolerated. The proportions of patients with AEs and serious adverse events (SAEs) were comparable across treatment groups, with no evidence of an ustekinumab dose effect. Similarly, the proportions of patients who discontinued due to AEs were comparable (ustekinumab no higher than placebo) across treatment groups with no evidence of an ustekinumab dose effect.

Common AEs emerging with ustekinumab treatment across trials (≥5% of patients in either ustekinumab group) were arthralgia, headache, nausea, pyrexia,

nasopharyngitis, abdominal pain and CD, as summarised in Table 25. SAEs that occurred in patients treated with ustekinumab were predominantly events of GI disorders, or other CD related symptoms and complications, as summarised in Table 26.

Table 24: Summary of key safety events during induction (Week 0 to Week 8) in UNITI-1 and UNITI-2 (safety population)

	UNITI-1			UNITI-2		
	Ustekinumab 130mg	**Ustekinumab ~6mg/kg**	**Placebo**	**Ustekinumab 130mg**	**Ustekinumab ~6mg/kg**	**Placebo**
Patients treated	246	249	245	212	207	208
Average duration of follow-up (weeks)	7.89	7.79	7.85	7.89	7.8	7.88
Average exposure (number of administrations)	1.0	1.0	1.0	1.0	1.0	1.0
Patients who died	0	0	0	0	0	0
Patients who discontinued because of 1 or more AEs, n (%)	3 (1.2)	7 (2.8)	14 (5.7)	4 (1.9)	1 (0.5)	5 (2.4)
Total number of patients with the following, n (%):						
Adverse events	159 (64.6)	164 (65.9)	159 (64.9)	106 (50.0)	115 (55.6)	113 (54.3)
Serious adverse events	12 (4.9)	18 (7.2)	15 (6.1)	10 (4.7)	6 (2.9)	12 (5.8)
Infections[a]	57 (23.2)	64 (25.7)	58 (23.7)	31 (14.6)	45 (21.7)	48 (23.1)
Serious infections[a]	3 (1.2)	7 (2.8)	3 (1.2)	3 (1.4)	1 (0.5)	3 (1.4)
AEs temporally related to infusion	11 (4.5)	9 (3.6)	5 (2.0)	5 (2.4)	3 (1.4)	6 (2.9)

Key: AE, adverse events.
Notes: [a], infection as assessed by the investigator.
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]

Table 25: Treatment-emergent adverse events with frequency ≥5% during induction in any treatment group (Week 0 to Week 8) in UNITI-1 and UNITI-2 (safety population)

	UNITI-1			UNITI-2		
	Ustekinumab 130mg	**Ustekinumab ~6mg/kg**	**Placebo**	**Ustekinumab 130mg**	**Ustekinumab ~6mg/kg**	**Placebo**
Patients treated	246	249	245	212	207	208
Average duration of follow-up (weeks)	7.89	7.79	7.85	7.89	7.8	7.88
Average exposure (number of administrations)	1.0	1.0	1.0	1.0	1.0	1.0
Total number of patients with the following, n (%):						
Any adverse event	159 (64.6)	164 (65.9)	159 (64.9)	106 (50.0)	115 (55.6)	113 (54.3)
Arthralgia	26 (10.6)	15 (6.0)	18 (7.3)	-	-	-
Headache	20 (8.1)	20 (8.0)	22 (9.0)	20 (9.4)	10 (4.8)	14 (6.7)
Nausea	20 (8.1)	13 (5.2)	18 (7.3)	7 (3.3)	11 (5.3)	5 (2.4)
Pyrexia	14 (5.7)	15 (6.0)	15 (6.1)	6 (2.8)	11 (5.3)	10 (4.8)
Nasopharyngitis	12 (4.9)	11 (4.4)	13 (5.3)	10 (4.7)	14 (6.8)	10 (4.8)
Abdominal pain	9 (3.7)	13 (5.2)	13 (5.3)	-	-	-
Crohn's disease	13 (5.3)	6 (2.4)	24 (9.8)	-	-	-
Fatigue	6 (2.4)	9 (3.6)	13 (5.3)	-	-	-

Key: AE, adverse events.
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]

Table 26: Treatment-emergent serious adverse events during induction (Week 0 to Week 8) in UNITI-1 and UNITI-2 (safety population)

	UNITI-1			UNITI-2		
	Ustekinumab 130mg	**Ustekinumab ~6mg/kg**	**Placebo**	**Ustekinumab 130mg**	**Ustekinumab ~6mg/kg**	**Placebo**
Patients treated	246	249	245	212	207	208
Average duration of follow-up (weeks)	7.89	7.79	7.85	7.89	7.8	7.88
Average exposure (number of administrations)	1.0	1.0	1.0	1.0	1.0	1.0
Total number of patients with the following, n (%):						
Any serious adverse event	12 (4.9)	18 (7.2)	15 (6.1)	10 (4.7)	6 (2.9)	12 (5.8)
Gastrointestinal disorders	7 (2.8)	8 (3.2)	10 (4.1)	5 (2.4)	5 (2.4)	7 (3.4)
• Crohn's disease	7 (2.8)	5 (2.0)	7 (2.9)	5 (2.4)	2 (1.0)	5 (2.4)
Infections and infestations	3 (1.2)	6 (2.4)	3 (1.2)	2 (0.9)	1 (0.5)	2 (1.0)
Blood and lymphatic system disorders	NA	NA	NA	1 (0.5)	0 (0)	2 (1.0)
Metabolism and nutrition disorders	2 (0.8)	0 (0)	2 (0.8)	-	-	-
Vascular disorders	1 (0.4)	1 (0.4)	0 (0)	-	-	-
Cardiac disorders	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.5)
Hepatobiliary disorders	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.5)
Immune system disorders	0 (0)	1 (0.4)	0 (0)			
Injury, poisoning and procedural complications	0 (0)	1 (0.4)	0 (0)	1 (0.5)	0 (0)	0 (0)

	UNITI-1			UNITI-2		
	Ustekinumab 130mg	**Ustekinumab ~6mg/kg**	**Placebo**	**Ustekinumab 130mg**	**Ustekinumab ~6mg/kg**	**Placebo**
Respiratory, thoracic and mediastinal disorders	NA	NA	NA	1 (0.5)	0 (0)	0 (0)
Investigations	1 (0.8)	0 (0)	0 (0)	-	-	-
Renal and urinary disorders	1 (0.8)	0 (0)	0 (0)	-	-	-
Reproductive system and breast disorders	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.5)
General disorders and administration site conditions	0 (0)	0 (0)	1 (0.4)	2 (0.9)	0 (0)	0 (0)

Key: AE, adverse events; NA, not applicable.
Source: UNITI-1 CSR[135]; UNITI-2 CSR[136]

4.12.2 Summary of safety data from IM-UNITI

A summary of safety events from the Phase III maintenance trial is provided in Table 27. SC ustekinumab at doses of 90mg q12w or q8w was generally well tolerated. As was observed in induction trials, the proportions of patients with AEs and SAEs were comparable across treatment groups, with no evidence of an ustekinumab dose effect. Similarly, the proportions of patients who discontinued due to AEs were comparable (ustekinumab no higher than placebo) across treatment groups, with no evidence of an ustekinumab dose effect.

Table 27: Summary of key safety findings through Week 44 or up to the time of dose adjustment in IM-UNITI (treated patients who were randomised)

	Ustekinumab 90mg SC q12w	Ustekinumab 90mg SC q8w	Combined ustekinumab	Placebo
Patients treated (who were randomised)	132	131	263	133
Average duration of follow-up (weeks)	36.6	35.2	35.9	32
Patients who died	0	0	0	0
Patients who discontinued because of 1 or more AEs	10 (7.6%)	4 (3.1%)	14 (5.3%)	8 (6.0%)
Total number of patients with the following, n (%):				
Adverse events	106 (80.3%)	107 (81.7%)	213 (81.0%)	111 (83.5%)
Serious adverse events	16 (12.1%)	13 (9.9%)	29 (11.0%)	20 (15.0%)
Infections[a]	61 (46.2%)	63 (48.1%)	124 (47.1%)	66 (49.6%)
Serious infections[a]	7 (5.3%)	3 (2.3%)	10 (3.8%)	3 (2.3%)

Key: AE, adverse events; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous.
Notes: [a], infection as assessed by the investigator.
Source: IM-UNITI CSR[134]

Common AEs emerging with ustekinumab treatment through Week 44 of IM-UNITI (≥5% of patients in ustekinumab combined group) were arthralgia, CD, headache, nasopharyngitis, abdominal pain, upper respiratory tract infection, pyrexia, diarrhoea, fatigue, and nausea as summarised in Table 28.

Table 28: Treatment-emergent adverse events with frequency ≥5% during induction in any treatment group through Week 44 in IM-UNITI (safety population)

	Ustekinumab 90mg SC[a]			Placebo[a, b]
	q12w	**q8w**	**Combined**	
Patients treated (who were randomised)	132	131	263	133
Average duration of follow-up (weeks)	36.6	35.2	35.9	32
Total number of patients with the following, n (%):				
≥1 TEAE	106 (80.3)	107 (81.7)	213 (81.0)	111 (83.5)
Arthralgia	22 (16.7)	18 (13.7)	40 (15.2)	19 (14.3)
Crohn's disease	16 (12.1)	16 (12.2)	32 (12.2)	19 (14.3)
Headache	15 (11.4)	16 (12.2)	31 (11.8)	15 (11.3)
Nasopharyngitis	17 (12.9)	14 (10.7)	31 (11.8)	10 (7.5)
Abdominal pain	13 (9.8)	11 (8.4)	24 (9.1)	16 (12.0)
Upper respiratory tract infection	9 (6.8)	13 (9.9)	22 (8.4)	21 (15.8)
Pyrexia	11 (8.3)	8 (6.1)	19 (7.2)	10 (7.5)
Diarrhoea	11 (8.3)	5 (3.8)	16 (6.1)	7 (5.3)
Fatigue	8 (6.1)	6 (4.6)	14 (5.3)	6 (4.5)
Nausea	10 (7.6)	4 (3.1)	14 (5.3)	9 (6.8)
Influenza	8 (6.1)	5 (3.8)	13 (4.9)	5 (3.8)
Urinary tract infection	8 (6.1)	4 (3.1)	12 (4.6)	3 (2.3)
Cough	4 (3.0)	7 (5.3)	11 (4.2)	3 (2.3)
Rash	4 (3.0)	7 (5.3)	11 (4.2)	5 (3.8)
Vomiting	5 (3.8)	4 (3.1)	9 (3.4)	9 (6.8)
Injection site erythema	1 (0.8)	7 (5.3)	8 (3.0)	0 (0)

Key: AE, adverse events; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.
Notes: [a], includes data up to the time of dose adjustment (i.e. time of meeting loss of response criteria); [b], subjects who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.
Source: IM-UNITI CSR[134]

As was the case during induction, maintenance ustekinumab was associated with very few SAEs, and those that did occur were predominantly events of GI disorders or other CD related symptoms and complications, as summarised in Table 29.

Table 29: Treatment-emergent serious adverse events through Week 44 in IM-UNITI (safety population)

	Ustekinumab 90mg SC[a]			Placebo[a, b]
	q12w	**q8w**	**Combined**	
Patients treated (who were randomised)	132	131	263	133
Average duration of follow-up (weeks)	36.6	35.2	35.9	32
Total number of patients with the following, n (%):				
Any serious adverse event	16 (12.1)	13 (9.9)	29 (11.0)	20 (15.0)
Gastrointestinal disorders	6 (4.5)	8 (6.1)	14 (5.3)	11 (8.3)
• Crohn's disease	5 (3.8)	4 (3.1)	9 (3.4)	7 (5.3)
Infections and infestations	7 (5.3)	3 (2.3)	10 (3.8)	3 (2.3)
Vascular disorders	2 (1.5)	0 (0)	2 (0.8)	0 (0)
Injury, poisoning and procedural complications	1 (0.8)	0 (0)	1 (0.4)	0 (0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0)	1 (0.8)	1 (0.4)	1 (0.8)
Nervous system disorders	0 (0)	1 (0.8)	1 (0.4)	1 (0.8)
Psychiatric disorders	1 (0.8)	0 (0)	1 (0.4)	0 (0)
Musculoskeletal and connective tissue disorders	0 (0)	0 (0)	0 (0)	3 (2.3)
Social circumstances	0 (0)	0 (0)	0 (0)	1 (0.8)

Key: AE, adverse events; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.
Notes: [a], includes data up to the time of dose adjustment (i.e. time of meeting loss of response criteria); [b], patients who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.
Source: IM-UNITI CSR[134]

4.12.3 Pooled safety analysis

The safety profile observed in CD trials was generally in line with that observed in other indications (PsO and PsA), for which 5 years of data registry provide conclusive evidence of the favourable long-term safety profile of ustekinumab.[126-130]

In a recent pooled analysis involving 6,280 patients treated with at least one dose of ustekinumab for CD or psoriatic disease (PsO or PsA); rates of AEs, SAEs, and

infection/serious infection were comparable across ustekinumab and placebo groups.[185] Further details on the pooled safety analysis are presented in Appendix 6.

4.13 Interpretation of clinical effectiveness and safety evidence

Ustekinumab is the first interleukin inhibitor to receive a marketing authorisation for the treatment of patients with moderately to severely active CD who have failed, or are intolerant to conventional therapy or TNFα inhibitor therapy. Ustekinumab also received CHMP recommendation for an extended marketing protection due to significant clinical benefit in comparison with existing therapies based on a major contribution to patient care.

The clinical benefits and potential harms associated with ustekinumab have been comprehensively demonstrated in a high-quality clinical trial programme that provides data up to 2 years.

Principal conclusions from this clinical trial programme are summarised below:

- Ustekinumab IV induction rapidly and effectively induces therapeutic response in patients with moderately to severely active CD
- Ustekinumab SC maintenance conveniently and effectively maintains therapeutic response in patients with moderately to severely active CD
- Ustekinumab can improve both disease-specific and general HRQL for patients with moderately to severely active CD
- Ustekinumab effectively reduces both serum- (CRP) and faecal- (calprotectin and lactoferrin) based biomarkers of inflammation
- Ustekinumab effectively induces endoscopic mucosal healing in patients with moderately to severely active CD
- Ustekinumab is generally well tolerated with an established safety profile consistent across indications
- Ustekinumab can further improve patient safety by reducing the use of concomitant corticosteroids that can be associated with significant toxicity

The UNITI-1 and UNITI-2 trials were designed to provide comparative efficacy and safety data for ustekinumab induction treatment versus placebo with permitted

concomitant medications representative of conventional therapy use in clinical practice, such that the placebo groups represent patients receiving conventional therapy alone. Across these trials, a significantly greater proportion of patients with moderately to severely active CD who have failed, or are contraindicated to, conventional therapy or TNFα inhibitor therapy achieved clinical response or clinical remission with ustekinumab induction treatment compared with conventional therapy; and a significantly greater proportion of patients demonstrated clinically meaningful improvements in disease-specific HRQL.

The IM-UNITI trial was designed to provide comparative efficacy and safety data for ustekinumab maintenance treatment versus placebo (again representative of conventional therapy) in patients who had achieved clinical response to ustekinumab induction treatment. In this trial, a significantly greater proportion of patients with moderately to severely active CD who have failed, or are contraindicated to, conventional therapy or TNFα inhibitor therapy achieved clinical response or clinical remission with ustekinumab maintenance treatment compared with conventional therapy; and at least a numerically greater proportion of patients demonstrated clinically meaningful improvements in disease-specific HRQL. Importantly, in consideration of the potential toxicity associated with corticosteroid treatment, a greater proportion of patients treated with ustekinumab achieved corticosteroid-free remission, and a significantly greater proportion of patients treated with ustekinumab were able to eliminate corticosteroid use.

An unavoidable limitation of this study is that in order to investigate the impact of not continuing ustekinumab into the maintenance phase of therapy, the placebo arm of IM-UNITI is not a true placebo arm; that is, the placebo arm actually represents patients who achieve clinical response to ustekinumab induction treatment but are subsequently treated with conventional therapy. Although this is common to all maintenance trials of biologic treatments, a high proportion (60%) of patients in the ‘placebo’ arm of IM-UNITI were in clinical remission at randomisation. Furthermore, ustekinumab provides an extended half-life such that patients randomised to placebo may still be benefiting from ustekinumab treatment within the first few months of IM-UNITI (a so-called ‘carryover effect’). This is reflected in the change in CDAI over time with patients who do not continue to receive ustekinumab maintenance therapy,

as represented by the placebo arm of IM-UNITI, losing response within a few months of ustekinumab induction treatment.

As an improvement to previous maintenance trials of biologic treatments, all patients enrolled in UNITI-1 and UNITI-2 were given the option to enrol in IM-UNITI. An additional patient group of interest to this technology appraisal are patients who failed to achieve clinical response (trial definition) to the IV induction infusion of ustekinumab but who went on to receive SC ustekinumab at Week 0 of IM-UNITI (8 weeks after treatment initiation), as this patient group provides data in line with the licensed dosing for ustekinumab in CD. In this cohort, rates of clinical response and clinical remission were at least as high as those observed in patients who achieved clinical response following the first ustekinumab dose (IV). In addition, the IM-UNITI trial provided data to support dose-escalation for patients without an adequate response to ustekinumab 16 weeks after treatment initiation, which is also reflected in the licensed dosing for ustekinumab in CD. Although there was also a patient cohort in IM-UNITI that represented a pure placebo group, this consisted of patients who had achieved clinical response during induction trials, and thus was a selective population of patients who responded well to conventional therapy. Data from this cohort are highly likely to overestimate clinical response and clinical remission rates that would be observed in a true placebo group that would represent all patients with moderately to severely active CD who receive conventional therapy alone during induction and maintenance phases of treatment. Unfortunately, no data are available for a cohort of patients representative of this group.

Due to well-accepted complexities with comparing biologic treatments in a head-to-head trial design, a key limitation of the evidence base informing CD management is the need for indirect estimates of comparative efficacy for biologics, despite the level of heterogeneity across trials. In recognition of advancements in CD therapeutics over recent years, and aligning with recent clinical guidelines that state response should be defined in this manner[104], the UNITI trial programme adopted a clinical response definition of a reduction in CDAI from baseline of ≥100 points. Historically, a more conventional clinical response definition of a reduction in CDAI from baseline of ≥70 points had been adopted. Primary efficacy data were thus based on the CDAI-70 point outcome for comparator induction trials, as was randomisation for comparator maintenance trials. Additional sources of heterogeneity arise from further

differences in trial design and patient populations, for example treatment history reflective of disease severity, and there are further complexities with synthesis of maintenance trial data due to contaminated nature of the placebo arm in the IM-UNITI trial. Although measures were taken to reduce the risk of bias where possible, these factors warrant caution when interpreting the results of the NMA; particularly analyses of ustekinumab versus infliximab and ustekinumab versus adalimumab in the TNF failure subpopulation.

In induction phase analysis, ustekinumab was associated with a high probability of reaching CDAI-100 response compared to vedolizumab (97%, OR [CrI]: 1.85 [0.96, 3.51]) and adalimumab (80%, OR [CrI]: 1.39 [0.64, 2.97]) in the conventional care failure subpopulation. In the TNF failure subpopulation, ustekinumab was associated with a similar probability of reaching CDAI-100 response compared to vedolizumab (56%, OR [CrI]: 1.05 [0.59, 1.85]); the relevant comparator for this patient group in UK practice. Ustekinumab was associated with a lower probability of reaching CDAI-100 response compared to adalimumab (26%, OR [95% CrI]: 0.66 [0.18, 2.34]; however, these results should be interpreted with caution due to the restricted patient population providing data for adalimumab that only included secondary failure patients (those who had responded to treatment but subsequently lost response) with contraindications for infliximab. Moreover, in both alternative outcomes, ustekinumab was associated with a higher probability of reaching CDAI-70 response (66%, OR [CrI]: 1.29 [0.38, 4.40]) and clinical remission (80%, OR [CrI]: 2.24 [0.36, 20.32]) compared with adalimumab in the TNF failure subpopulation. Infliximab was associated with the highest chance of being in clinical response/ remission in induction phase analysis (conventional care subpopulation); however, these results should be interpreted with caution due to low patient numbers (n=52), missing data in the placebo control group (that were classed as treatment failures), and inverse dose relationships observed in the infliximab group of the induction treatment trial providing data for this treatment.

In treatment sequence analysis that combined data from induction and maintenance phases of therapy, ustekinumab was associated with a high probability of reaching CDAI-100 response at 1 year compared to vedolizumab (89%, OR [CrI]: 1.54 [0.77, 3.05]) and adalimumab (86%, OR [CrI]: 1.58 [0.68, 3.62]) in the conventional care failure subpopulation. Ustekinumab was also associated with a high probability of

reaching clinical remission at 1 year compared to vedolizumab (71%, OR [CrI]: 1.24 [0.58, 2.61]) and adalimumab (69%, OR [CrI]: 1.26 [0.50, 3.07]) in the conventional care failure subpopulation. In the TNF failure subpopulation, ustekinumab was associated with a high probability of reaching CDAI-100 response at 1 year compared to vedolizumab (95%, OR [CrI]: 1.77 [0.91, 3.45]) and adalimumab (65%, OR [CrI]: 1.15 [0.56, 2.32]); similar results were observed in clinical remission analysis at 1 year (vedolizumab: 80%, OR [CrI]: 1.35 [0.66, 2.73]; adalimumab: 61%, OR [CrI]: 1.11 [0.52, 2.35]). Infliximab was associated with the highest chance of being in clinical remission at 1 year in the conventional care subpopulation (data not available for clinical response), but again results should be interpreted with caution due to the aforementioned concerns of bias.

Taking the totality of this evidence base into consideration, it can be concluded that ustekinumab addresses a current unmet medical need by providing an additional treatment option for patients with moderately to severely active CD with a novel mechanism of action (that may target the underlying condition of CD) that can induce and maintain clinical response/remission and thus improve patient HRQL, while providing a favourable benefit/risk profile and a minimally invasive dosing schedule.

4.14 Ongoing studies

Outside of the IM-UNITI trial, which is ongoing, no further studies will provide additional evidence for the indication being appraised within the next 12 months.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Methodology

5.1.1.1 Identification of studies

The strategies used to retrieve health economic evaluation studies from the published literature are described in Appendix 7. Justification of the methods used with reference to the decision problem and the NICE reference case are reported, and the rationale for the inclusion and exclusion criteria used is also described in appendix 7.[168]

Full methodology and results are given in Appendix 7.

5.1.2 Discussion

5.1.2.1 Summary of main findings

Twenty-one articles were identified in the SLR of health economic evaluation studies in moderate-to-severely active CD, corresponding to 20 CUAs and one BIA. The modelling approaches of the CUAs included Markov models, decision trees and regression models. All included studies evaluated at least one anti-TNF agent, which is consistent with current recommendations on the implementation of a “top-down” approach which includes biological agents and corticosteroids to achieve rapid control of moderate-to-severity CD.[186] Previous exposure to anti-TNFs ranged from none (biological-naïve patients) to third-line biological treatment (following failure to two previous biological treatment lines).

The most frequent duration of anti-TNF treatment was between one and two years, and duration of treatment has shown to be a driver of the cost-effectiveness results.[1] Only a minority of the studies included a lifetime horizon, as it was considered by most authors that shorter horizons would suffice to reflect the impact of the assessed interventions. Short time horizons were also cited as a justification for not including the effects of treatment-related adverse events. In terms of cycle length, there was a tendency for the duration to differ between the induction and maintenance phases in

order to better capture the relevant changes in disease progression and costs in these phases of treatment.

The health states included in the CUAs were largely based on those defined by Silverstein *et al.* (1999), which included remission, mild-disease, severe-disease (drug-responsive, drug-dependent or drug-refractory), surgery, post-surgery and death.[37] The Olmsted retrospective cohort study was the most frequent source informing transition probabilities between health states. In addition, large RCTs such as the ACCENT 1, ACCENT 2, CHARM, CLASSIC 1, CLASSIC 2 and GEMINI were also used to estimate transition probabilities. Utility estimates in multiple CUA studies were obtained from the Gregor *et al.* study, which derived utility values using the time trade-off, standard gamble, and visual analogue scale methods from 180 patients with CD.[140]

Drivers of cost-effectiveness results in economic evaluations in CD in the identified studies included duration of treatment and response rate with anti-TNFs, which are aligned with the key drivers of this model (Section 5.8.2). The use of a lifetime horizon was identified by Bodger *et al*. as the main driver of their results, given that shorter time horizons were associated with higher ICERs. Other studies have supported this finding, reporting that biological agents were not cost effective when assessed over a 1-year time horizon and were more cost effective over a 5-year time horizon.[187, 188] Response rate to biologic treatments was also cited as a driver of cost-effectiveness results.

5.2 De novo analysis

5.2.1 Patient population

The population included in the cost-effectiveness analysis is patients with moderate to severe Crohn's disease (defined as a CDAI score of 220–600) at baseline, in line with the expected marketing authorisation. It should be noted that the inclusion criteria for baseline CDAI score in UNITI-1 and UNITI-2 was 220-450, representing a subset of the modelled population.[135, 136]

Analyses are provided for two populations, TNF failure and conventional care failure, defined according to inclusion criteria for the UNITI-1 and UNITI-2 trials, respectively.[135, 136] Definitions for the populations are described below:

- Conventional care failure: patients who have either failed conventional care, have been exposed to TNFα antagonist and maintained response while on treatment but subsequently lost response, or are intolerant to 1 or more TNFα antagonist therapies
- TNF failure: patients who received TNFα antagonist treatment and did not respond initially (primary failure), initially responded but then lost response while on treatment (secondary failure), or are intolerant to TNFα antagonist

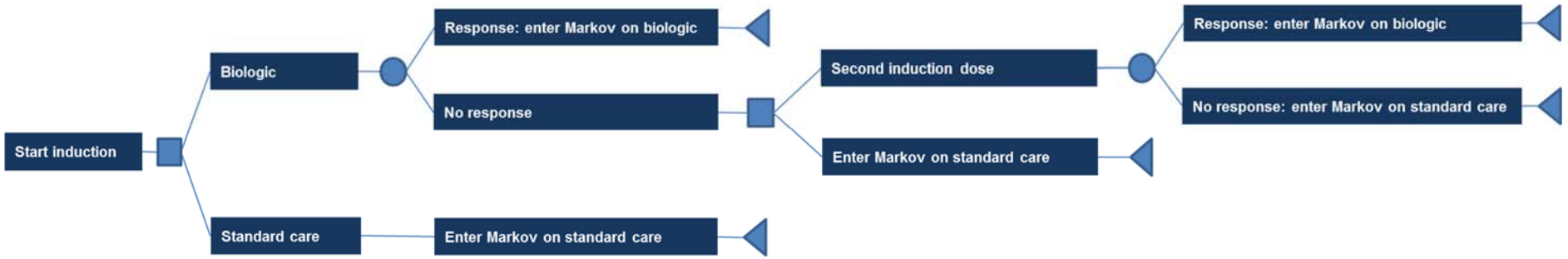
Patient demographics and baseline characteristics, efficacy inputs and relevant comparators are dependent on the population.

5.2.2 Model structure

The model is structured with health states that are designed to capture response to treatment based on CDAI score for consistency with the clinical trials. The CDAI was created by Best *et al.*, and it captures the symptoms of Crohn's disease using eight factors to calculate a total score between 0 and 600, with higher scores representing more severe disease.[189] A further description of the CDAI by Dretzke *et al.* is given in Appendix 10.

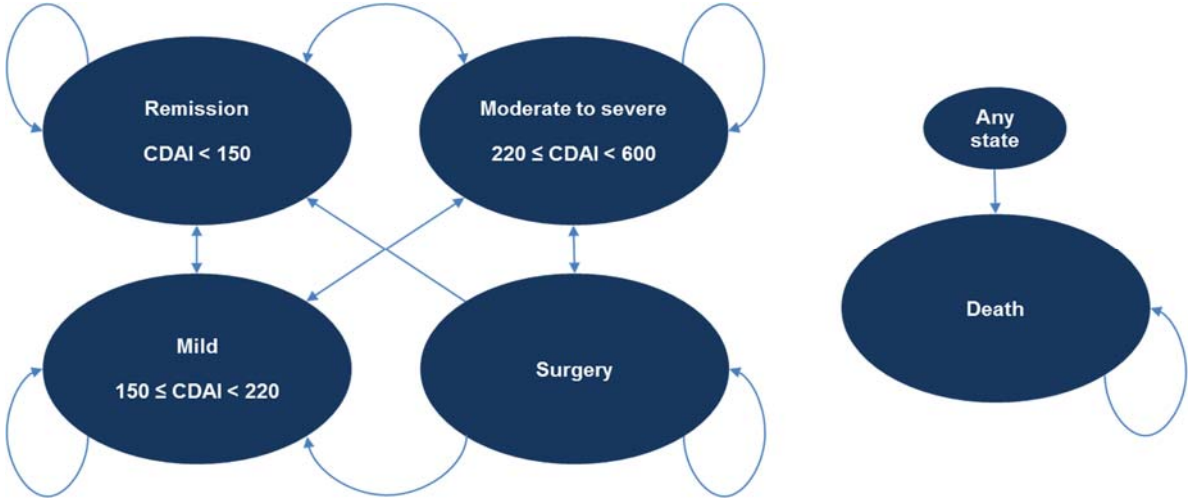
The model consists of two parts: a short-term induction phase, represented by a decision tree (Figure 40), and a long-term maintenance phase, represented by a Markov model (Figure 41). All patients in the model have moderate to severe Crohn's disease at baseline.

Figure 40: Induction phase (decision tree)



Note: 'No response' in the induction phase is defined as not achieving a reduction in Crohn's Disease Activity Index score of >100 points.

Figure 41: Maintenance phase (Markov model)



Key: CDAI, Crohn's Disease Activity Index.

Patients enter the model at the start of the induction period, the length of which varies by treatment based on the length of their respective induction trials (Section 5.2.4). At the end of the induction period, patients on biologic therapy will remain on treatment if they have responded. Response is defined as a decrease in CDAI score of greater than 100 points (CDAI-100) in the base case, consistent with Bodger *et al.* and the ustekinumab induction trials primary endpoints.[1] Other induction trials had a primary endpoint of a reduction of greater than 70 points (CDAI-70). This response definition is used in scenario analysis.

Patients receiving ustekinumab, vedolizumab or adalimumab who do not respond to the initial induction dose(s) are eligible to receive the first maintenance dose to assess delayed response to treatment, in line with the marketing authorisations.[91, 92] The impact of modelling as per the clinical trials, whereby patients were discontinued from biologic treatment if they did not respond to the initial induction dose(s), is tested in scenario analysis.

Non-responders in the induction phase move onto conventional care at the start of the maintenance phase or after the first maintenance dose where applicable. Non-responders who switch to conventional care are assumed to follow the same prognosis as those who enter the model on conventional care; this is consistent with the work by Bodger *et al.* and in TA352.[1, 190] Patients who enter the model on conventional care continue to receive conventional care in the maintenance phase.

Patients enter the maintenance phase in health states dependent on their level of response to treatment in the induction phase and then move between the health states according to the transition probabilities of the treatment they are currently on. The health states in the model are defined as follows:

- Moderate to severe: 220 ≤ CDAI < 600
- Mild: 150 ≤ CDAI < 220
- Remission: CDAI < 150
- Surgery
- Death

In the base case, all patients on biologic therapies are assumed to have a maximum treatment period of 1 year, after which all patients are assumed to switch to

conventional care; this is consistent with the work by Bodger *et al.* and the final appraisal determination in TA352, and is also in line with the findings of the economic evaluation SLR (see Section 5.1.2.1).[1, 3] The treatment length has been adjusted to 2 and 3 years in scenario analyses to examine the sensitivity of this assumption. Attendees at the advisory board for ustekinumab suggested that, in clinical practice some patients may stay on treatment for longer than 1 year.[191] This was confirmed by a leading clinical expert, and data from the Royal College of Physicians 2015 IBD audit; after 1 year of treatment, 93% and 88% of Crohn's disease patients continued treatment with infliximab and adalimumab, respectively.[192] After biologic treatment, patients are assumed to remain on conventional care until either the end of the modelled time horizon or death.

The model has a 2-week cycle length to enable the use of different induction periods. The model includes a half-cycle correction, which assumes that transitions occur in the middle of each cycle, rather than at the end. It is noted that this is expected to have little impact due to the short cycle length. As Crohn's disease is a chronic condition, the model time horizon is lifetime; this should capture the whole of the disease, in line with the NICE reference case.[168] Due to the low starting age of patients, the lifetime horizon is assumed to be 60 years in the deterministic analysis (see Section 5.3.2).

Beyond the first year of the model, costs and QALYs are discounted at a rate of 3.5% per annum. A NHS and personal social services (PSS) perspective was taken. Both of these assumptions are in line with the NICE reference case.[168]

Key features of the model are detailed in Table 30.

Table 30: Features of the *de novo* analysis

Factor	Chosen values	Justification	Reference
Cycle length	2 weeks	Allows for variable inductions and accurate capturing of differences between treatments	
Time horizon	60 years (lifetime)	Crohn's disease is a lifetime condition, and therefore, we should consider the duration of the whole disease for consistency with the NICE reference case; 60 years due to low patient starting age and the value used by Bodger *et al.*	Bodger *et al.*; NICE reference case; UNITI-1 CSR; UNITI-2 CSR.[1, 135, 136, 168]
Health effects measured	QALYs	NICE reference case	NICE 2013[168]
Discount rate for utilities and costs	3.5%	NICE reference case	NICE 2013[168]
Perspective	NHS/PSS	NICE reference case	NICE 2013[168]
Key: NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years.			

5.2.3 Justification of structure

The model structure and CDAI scores used to define health states are consistent with the work by Bodger *et al.*[1] Previous economic models in Crohn's disease were reviewed prior to model building. The structure used by Bodger *et al.* was considered the most appropriate as it best reflected the structure of the ustekinumab trials, and it was used in the NICE MTA of infliximab and adalimumab (TA187) in addition to the vedolizumab NICE submission (TA352).[2, 3]

A 2-week cycle length was chosen as a consequence of varying induction lengths; the shorter cycle length allows for more accurate capturing of differences between treatments than a longer cycle length, such as the 8-week cycle length used in TA352.[190] The induction phase lengths, which vary by treatment, were chosen to best reflect each treatment's label (Section 5.2.4); it was noted in the evidence review group (ERG) report for TA352 that assuming the same induction length for all treatments is not reflective of the labelling.[177]

5.2.4 Intervention technology and comparators

Ustekinumab may be used to treat patients who have failed conventional care but who have not failed treatment with TNFα antagonist (conventional care failure population) and those who have failed TNFα antagonist treatment (TNF failure population). Infliximab and adalimumab are both approved by NICE for the treatment of Crohn's disease in TA187.[2] Infliximab and adalimumab are TNFα antagonists that are primarily used in the conventional care failure population, and the clinical trial evidence in the TNFα antagonist failure population is scarce. Infliximab was the first TNFα antagonist to market, and its registration trials were in a truly biologic naïve population. Adalimumab was the second TNFα antagonist approved and was used in one trial in patients with secondary failure to infliximab.[152] This trial excludes patients with primary failure to infliximab (i.e. patients that initially did not respond; see Section 5.2.1), including only secondary non-responders to infliximab (i.e. patients who initially responded but subsequently lost response; see Section 5.2.1) and may therefore reflect a population of patients who are likely to respond to adalimumab, as both treatments have the same mode of action. Therefore, anti-TNFs are only considered as comparators in conventional care failure population, and it is assumed that for the purposes of economic modelling, if a patient fails an anti-TNF treatment, they would not receive another anti-TNF as they have the same mechanism of action. This a simplifying assumption as cycling of biologic treatments does exist in clinical practice; however, this assumption was also accepted within the vedolizumab submission to NICE given the paucity of data.[193]

As of August 2015, vedolizumab has been approved by NICE only in patients for whom TNF treatments are not suitable or who have previously failed TNF treatment (TA352); hence, vedolizumab is a comparator only in the TNF failure population.[193]

Additionally, as of July 2015, NICE approved two infliximab biosimilars, Remsima® and Inflectra®, for the treatment of Crohn's Disease.[194] In the absence of evidence for biosimilars in Crohn's disease, infliximab biosimilars are assumed to have equal efficacy to Remicade®, which may overestimate their efficacy. Recent evidence suggests that Crohn's patients who are switched from Remicade to an infliximab biosimilar experience a worsening of the disease compared to those that continue on Remicade.[195] Therefore, only the treatment costs of Inflectra and Remsima vary from the Remicade calculations. For all other inputs considered, biosimilars are assumed

to use the same inputs as Remicade. Infliximab comparators are only considered in sensitivity analyses due to lack of data for CDAI-100, the primary efficacy endpoint of the UNITI trial programme and the measure of response to treatment used in the base case economic analysis.

The comparators for each population are summarised in Table 31.

Table 31: Summary of comparators by population

Conventional care failure	TNF failure
Adalimumab	Vedolizumab
Conventional care	Conventional care
Infliximab (Remicade)*	
Infliximab (Remsima)*	
Infliximab (Inflectra)*	
Key: TNF, tumour necrosis factor **Notes:** *infliximab included as scenario analysis only	

The induction period uses a patient-weight-based dose of ustekinumab (approximately equivalent to 6mg/kg), delivered intravenously at baseline (Week 0).[135, 136] Details of induction dosing are shown in Table 32.

Table 32: Details of weight-based induction dosing for ustekinumab

Weight	Dose
<55kg	260mg
>55kg and ≤85kg	390mg
>85kg	520mg

The cost of ustekinumab induction therapy is calculated based on the distribution of patient weight across the three intervals specified in Table 32. The weight distribution for the TNF failure and conventional care populations are based on data from the UNITI-1 and UNITI-2 trials, respectively.[135, 136]

For the maintenance phase, ustekinumab is delivered as a 90mg subcutaneous injection every 8 or 12 weeks (q8w and q12w, respectively). The base case assumes a proportion of patients starting on each dosing regimen (see Section 5.5.2).

Dosing regimens for infliximab, adalimumab and vedolizumab are assumed to be in line with their marketing authorisations.[91-93] Details of the dosing regimens for all treatments are given in Table 33.

Table 33: Dosing regimens

Treatment	Induction duration (weeks)	Response assessed (weeks)	Induction dosing		Second induction dose?	Second induction details	Second induction end (weeks)	Maintenance dosing	Dose escalated maintenance dosing	Population
Ustekinumab	8	6 and 8	Weight based:	<55kg: 260mg at Week 0	Yes	Additional dose at Week 8; response assessed at Week 16	16	90mg 12 weeks	90 mg every 8 weeks	Conventional care failure, TNF failure
				>55kg and <85kg: 390mg at Week 0						
				>85kg: 520mg at Week 0						
			130mg at Week 0							
Adalimumab	4	4	160mg at Week 0, 80mg at Week 2 (dose used in UK practice, base case)		Yes	Continued 40mg dose through Week 12	12	40mg on alternate weeks	40mg every week	Conventional care failure
			80mg at Week 0, 40mg at Week 2 (licensed dose, scenario analysis)							
Vedolizumab	10	6 and 10	300mg at Weeks 0, 2 and 6		Yes	Additional dose at Week 10; Response assessed at Week 14	14	300mg every 8 weeks	300mg every 4 weeks	TNF failure
Conventional care	8	8	N/A							Conventional care failure, TNF failure

Treatment	Induction duration (weeks)	Response assessed (weeks)	Induction dosing	Second induction dose?	Second induction details	Second induction end (weeks)	Maintenance dosing	Dose escalated maintenance dosing	Population
Infliximab– Remicade®*	6	2	5mg/kg at Weeks 0 and 2. Dose at Week 6 for responders	No	N/A	N/A	5mg/kg every 8 weeks	10mg/kg every 8 weeks	Conventional care failure
Infliximab– Inflectra®*	6	2	5mg/kg at Weeks 0 and 2. Dose at Week 6 for responders	No	N/A	N/A	5mg/kg every 8 weeks	10mg/kg every 8 weeks	Conventional care failure
Infliximab– Remsima®*	6	2	5mg/kg at Weeks 0 and 2. Dose at Week 6 for responders	No	N/A	N/A	5mg/kg every 8 weeks	10mg/kg every 8 weeks	Conventional care failure

Key: N/A, not applicable; TNF, tumour necrosis factor.
Notes: *infliximab included as scenario analysis only.

Conventional care is defined as a mixture of treatments, based on the report from the Inflammatory Bowel Disease Audit Steering Group by the Royal College of Physicians.[196] This is in line with the assumptions used in TA352.[190] Details of treatments making up conventional care and their expected usage are given in Table 34.

Table 34: Details of conventional care

Treatment	Details	Patients receiving treatment in practice (%)
Balsalazide	1.5g twice daily, adjusted according to response (maximum: 6g daily)	5%
Mesalazine	1.2–2.4g daily in divided doses	5%
Olsalazine	500mg twice daily	5%
Sulfasalazine	500mg four times daily	5%
Budesonide	3mg three times daily for up to 8 weeks	6%
Prednisolone	1 metered application (20mg prednisolone) once or twice daily for 2 weeks	19%
Azathioprine	1–3mg/kg daily	57%
Mercaptopurine	Initially 2.5mg/kg, adjusted according to response	10%
Methotrexate	10–25mg once weekly	11%

5.3 Clinical parameters and variables

5.3.1 Patient characteristics

Patient baseline characteristics for mean age, gender and weight, and proportions of patients in each weight category (for ustekinumab induction dosing), are based on mean values from pooled data taken from the UNITI-1 and UNITI-2 clinical study reports (CSRs) for the TNF failure and conventional care failure populations, respectively.[135, 136] The baseline values for each trial are given in Table 35.

Table 35: Baseline patient characteristics

Characteristic	UNITI-2 (conventional care failure)	UNITI-1 (TNF failure)
Mean patient weight (kg)	73.41	69.8
Mean patient age (years)	39.2	37.3
Mean percent female	52.90%	57.20%
% patients in <55kg	22.86%	19.42%
% patients in >55kg and <85kg	58.78%	59.71%
% patients in >85kg	18.37%	20.87%
Key: TNF, tumour necrosis factor.		

Patient age and gender are used to estimate the background all-cause mortality rate in the model. The mean baseline patient weight is used to estimate infliximab dosage and vial wastage.

5.3.2 Efficacy: induction phase

Induction efficacy data for ustekinumab come from the ustekinumab induction trials (UNITI-1, TNF failure; UNITI-2, conventional care failure), and efficacy data for all comparators of interest come from the network meta-analysis (NMA) (Section 4.10).[135, 136] As detailed in Section 4.10.4, there are several limitations of the Targan *et al*. study, used for infliximab. Due to uncertainty stemming from this, and that the base case analysis uses CDAI-100 which is not reported for infliximab, infliximab is only considered in sensitivity analysis.

Induction transition probabilities are calculated from: the rate of remission (α), the rate of response (β) and the percentage of responders who remain in the moderate to severe state (γ). This is consistent with the manufacturer's submission for vedolizumab (TA352).[190] The rates of response and remission are dependent on treatment option and the population selected. Rates for ustekinumab are given in Table 36.

Table 36: Ustekinumab induction response and remission rates

	Conventional care failure	TNF failure
	~6mg/kg (N=209)	**~6mg/kg (N=249)**
Patient numbers (percentage)		
Response (CDAI-70)	135 (64.6%)	109 (43.8%)
Response (CDAI-100)	116 (55.5%)	84 (33.7%)
Remission	73 (34.9%)	46 (18.5%)
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor. **Definitions:** Remission, absolute CDAI score of <150; Response (CDAI-70), reduction in CDAI score of >70 points; Response (CDAI-100), reduction in CDAI score of >100 points.		

Induction probabilities of response and remission for comparator treatments are derived by applying odds ratios calculated in the induction NMA (Section 4.10.6) to ustekinumab induction results. Results for each treatment are shown in Table 37.

Table 37: Probabilities of response and remission for comparators

Comparators	Probabilities		
	Response (CDAI-70)	**Response (CDAI-100)**	**Remission**
Conventional care failure population			
Adalimumab 80/40mg	65.1%	47.3%	32.0%
Adalimumab 160/80mg	66.5%	54.8%	45.6%
Conventional care	38.7%	28.6%	17.7%
Infliximab 5mg/kg*	94.3%	N/A	87.0%
TNF failure population			
Vedolizumab 300 mg	44.8%	33.2%	12.90%
Conventional care	30.3%	21.8%	8.83%
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor. **Notes:** *infliximab included as scenario analysis only			

The percentages of moderate to severe responders are taken from the IM-UNITI study data. Moderate to severe responders are patients who respond but still are in the moderate to severe health state (220 < CDAI < 600). The proportion of moderate to severe responders is used to convert the response endpoint in the clinical trials into the mild and moderate to severe health states in the economic model. The rates are assumed to be the same for all treatments, but may be different according to population, and are given in Table 38.

Table 38: Percentage of moderate to severe responders (γ)

Treatment	Conventional care failure	TNF failure
All	[redacted]	[redacted]
Key: TNF, tumour necrosis factor.		

These values are applied using the formulas shown in Table 39 to calculate transition probabilities during the induction phase. The proportion of non-responders is one minus the proportion of responders (β). The proportion of moderate to severe responders (β * γ) is the proportion who respond to treatment (β) multiplied by the percentage of moderate to severe responders (γ). The proportion of patients who remain in the moderate to severe health state is the sum of the non-responders and moderate to severe responders. The proportion of patients who move to remission (α) is equal to the probability of remission, while the proportion of patients who move to the mild state is the proportion of responders (β) minus the proportion of patients in remission (α) and minus the proportion of moderate to severe responders (β * γ).

Table 39: Induction transition probability calculations

	Responders (β)			Non-responders
	Remission	Mild	Moderate-severe	
Probability	α	β - (α + (β * γ))	β * γ	1 - β

The efficacy inputs for delayed responders (i.e. patients who respond after the first maintenance dose) are taken from the best available sources for each treatment. For ustekinumab and vedolizumab, the data are sourced from the relevant CSRs and trial publications.[134, 197] For adalimumab, no such data were available; therefore, adalimumab data come from a conference abstract by Panaccione *et al.*[198] There is a lack of data for CDAI-70 response criteria; therefore, for all treatments, it is assumed that the proportion of patients achieving a CDAI-70 response is equal to the proportion of patients achieving a CDAI-100 response. This will likely underestimate the proportion of delayed responders; however, it is not possible to estimate the true proportion.

Table 40: Delayed responder's efficacy inputs

	N	Events	%	Source
Ustekinumab (conventional care failure)				
Response (CDAI-70)		N/A: Assumed equal to CDAI-100	64.5%	IM-UNITI data
Response (CDAI-100)	185	120	64.5%	
Remission	185	83	44.6%	
Ustekinumab (TNF failure)				
Response (CDAI-70)		N/A: Assumed equal to CDAI-100	41.4%	IM-UNITI data
Response (CDAI-100)	282	116	41.4%	
Remission	282	52	18.6%	
Vedolizumab (failure)				
Response (CDAI-70)	86	N/A: Assumed equal to CDAI-100	16.0%	Sandborn *et al.*[199]
Response (CDAI-100)	86	16	16.0%	
Remission	86	9	6.8%	
Adalimumab (conventional care failure)				
Response (CDAI-70)	-	N/A: Assumed equal to CDAI-100	43.0%	Adalimumab SPC[92]
Response (CDAI-100)	-	-	43.0%	
Remission	-	-	28.0%	Panaccione *et al.*[198]
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.				

Non-responders in the first and second induction period are assumed to remain in the moderate to severe category. This was noted as a criticism within the ERG report in TA352, as this assumption may not be the case in practice (e.g. a patient with a baseline CDAI score of 230 may see their score reduced by 60 points, moving them to the mild to moderate health state without being classified as a responder). However, the model does not currently allow patients to transition in this way due to a lack of efficacy data to support this.

The transition probabilities to surgery and death are applied after the above calculations. Input data for surgery and mortality are described in Sections 5.3.4 and 5.3.6, respectively.

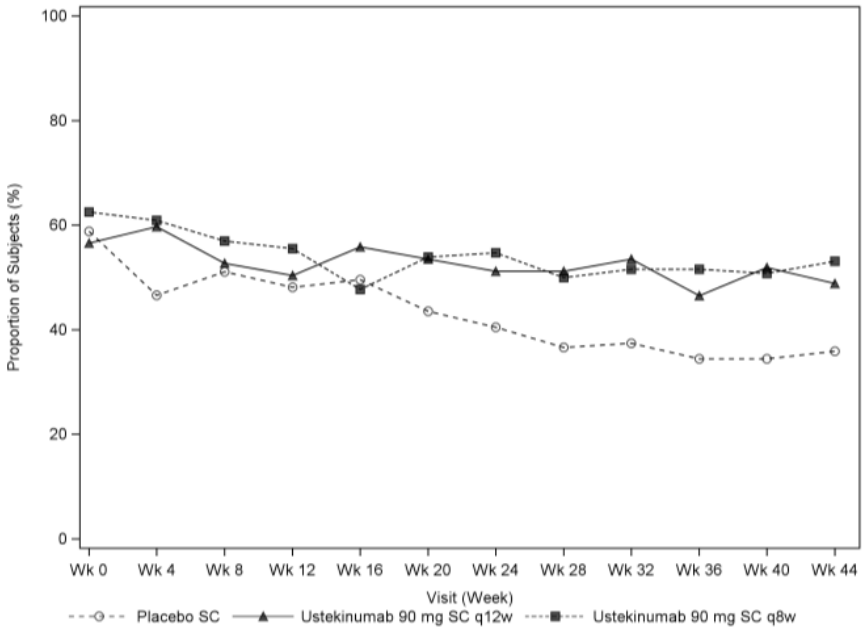
5.3.3 Efficacy: maintenance phase

The model base case uses data from the induction and treatment sequence NMA to calibrate a fixed two-week maintenance transition matrix for each treatment, which allows inclusion of maintenance data for all treatments and demonstrates important differences in treatments during maintenance identified in the NMA but remains fixed over time.

As a scenario analysis, data from the IM-UNITI study are used in the maintenance phase, which allows the production of time-varying matrices; however, this method requires an assumption of equal efficacy for all biologic treatments, which is at odds with the findings of the NMA (Section 4.10.6) and the trend seen over the duration of the maintenance phase for biologic treatments (Figure 42 to Figure 45). This scenario is included as it was suggested as an alternative approach by the ERG in TA352; however, it is unlikely to hold true.[177] In both methods, the rates of surgery (Section 5.3.4) and death (Section 5.3.6) are applied after the calculations. The model includes discontinuation due to lack of efficacy, as well as a gradual decline in efficacy following biologic treatment, described further below.

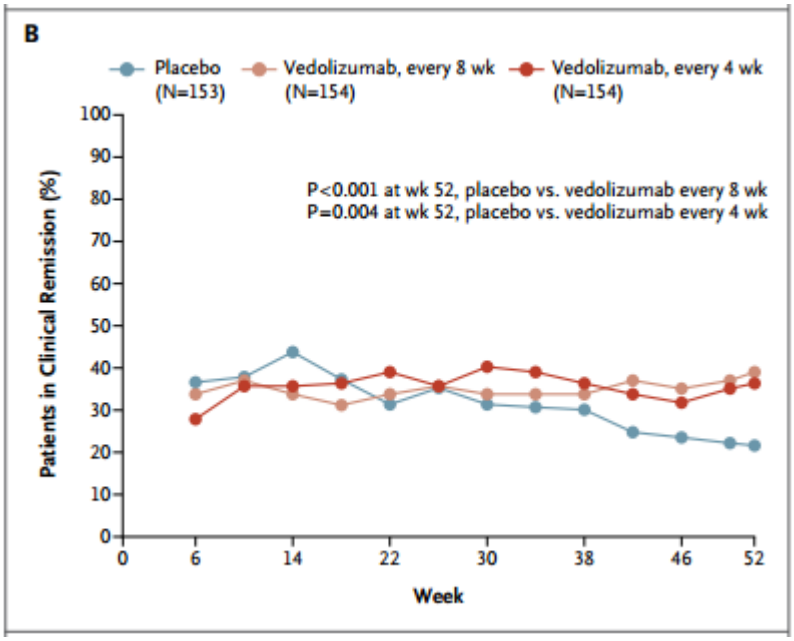
Figure 42: Proportion of patients in remission over maintenance phase – ustekinumab (IM-UNITI)

Proportion of subjects in clinical remission at each visit through Week 44; randomized subjects excluding those enrolled prior to study re-start



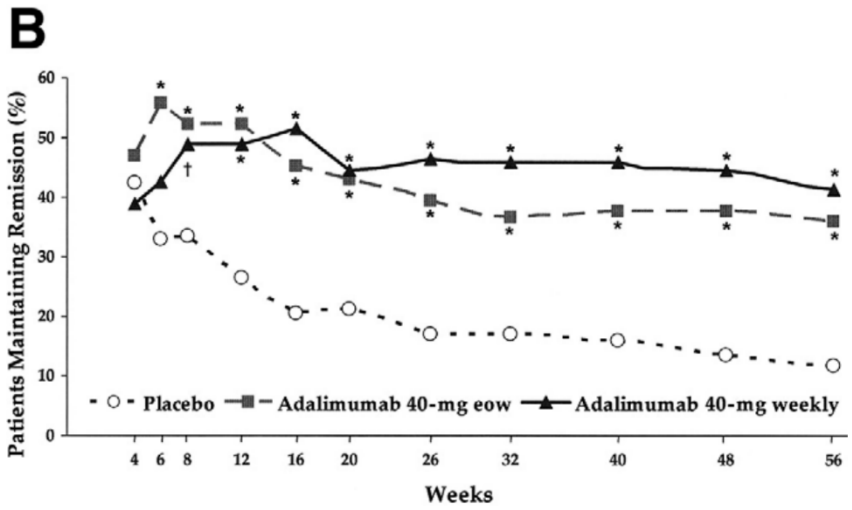
Source: IM-UNITI CSR[137]

Figure 43: Proportion of patients in remission over maintenance phase – vedolizumab (GEMINI II)



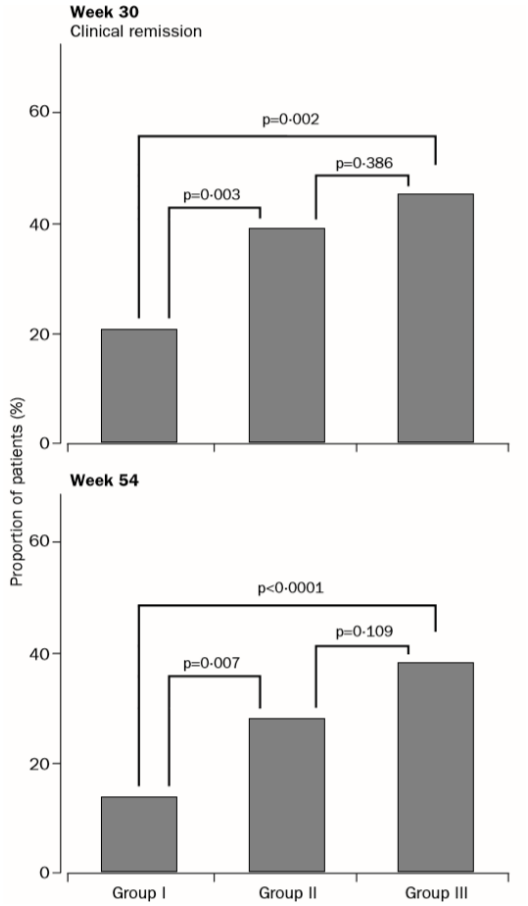
Source: Sandborn *et al.* 2013[17]

Figure 44: Proportion of patients in remission over maintenance phase – adalimumab (CHARM)



Source: Colombel *et al.* 2007[154]

Figure 45: Proportion of patients in remission over maintenance phase – infliximab (ACCENT-1)



Source: Hanauer *et al.* 2002[155]

5.3.3.1 Network meta-analysis data (base case)

NMA-based transition probabilities are derived using efficacy data from the induction and maintenance NMAs for all treatments. The method is based on that used in TA352, but with amendments to alleviate some of the concerns of the ERG.[177] The method requires estimation of both remission and CDAI-100 response. Using CDAI-100 was considered important as this was the primary definition of response within the maintenance studies. Therefore, it was not possible to include infliximab within the estimation of NMA transition matrices. Full details of the calculation of the NMA transition probabilities are given in Appendix 12.

5.3.3.2 IM-UNITI trial data (scenario analysis)

These data provide an alternative scenario for calculating maintenance transition probabilities. The scenario allows time-varying transition matrices, but assumes all biologics follow the same set of transitions. This approach for maintenance transition probabilities uses the ustekinumab CDAI-based transitions from the IM-UNITI trial for all biologic treatments. Placebo transitions are used for conventional care based on the population of patients in IM-UNITI who were re-randomised to placebo following response to ustekinumab induction. This population was felt to be the most representative of a group of patients receiving placebo, however it is noted that there is no evidence for a “true” conventional care population (i.e. a group of patients who receive placebo induction and maintenance irrespective of response status) and that this population is likely to over-predict the outcomes of a true conventional care population due to the known carry-over effect of having received and responded to ustekinumab induction therapy.

Transitions are based on data from the 4-weekly visits from the IM-UNITI study in which CDAI was collected. As the model uses a 2-week cycle length, every second cycle uses the identity matrix, which assumes patients stay in the health state they are already in – that is, there is no movement until the next observed movement. This approach has the benefit of allowing time-varying transitions during the maintenance phase; however, this may underestimate the relative efficacy of ustekinumab versus biologic comparators within the maintenance phase. Section 4.10 demonstrates the superiority of ustekinumab in the maintenance phase, and this is not captured with this method. Despite this, it is included for completeness as

this was suggested by the ERG in TA352.[177] The full list of matrices is provided in Appendix 11.

5.3.3.3 Discontinuation due to lack of efficacy

The cycle probability of patients discontinuing biologic treatment during the maintenance phase due to a lack of efficacy is built into the model. This was done using patient data from the maintenance trials of both ustekinumab (IM-UNITI)[153] and comparators (ACCENT I for infliximab and GEMINI II for vedolizumab).[17, 155]

By using the number of patients who discontinued the trial due to lack of efficacy over the total number that entered the maintenance phase, the percentage of patients who discontinued is calculated. This is then converted into an instantaneous rate followed by a per-cycle probability of discontinuation occurring using the exponential formula, given in Equation 1.

Equation 1: Exponential formula

With probability (P) over time (T), the instantaneous rate (r) is:

$$r = -[\ln(1-P)]/T$$

From r, probability (p) over time period (t) is:

$$p = 1 - \exp(-r * t)$$

Due to a lack of available data, adalimumab is assumed to have the same rate as infliximab as both share the same mode of action. Combined cycle probabilities for ustekinumab and vedolizumab are calculated using the proportion of the patients on the higher or lower dose of the treatment. The combined rate for infliximab is taken directly from the ACCENT I trial.

The cycle probabilities of discontinuation are applied to the proportion of patients in the moderate to severe health state, as it is assumed that patients will be in this state if there is loss of response. Once discontinued, patients move onto conventional care for the remainder of the time horizon or until death. This may underestimate the true proportion of patients discontinuing as the rate is applied to only patients in the moderate to severe state. However, it is not possible to know the percentage of patients in the moderate to severe state over time from the study data.

Table 41: Discontinuation due to lack of efficacy

	Number of patients	Number discontinued	% discontinued	Instantaneous rate	Cycle probability	Reference
Ustekinumab q12w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IM-UNITI CSR
Ustekinumab q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IM-UNITI CSR
Ustekinumab combined					[redacted]	Calculated
Infliximab combined*	385	31	8.05%	0.16%	0.32%	ACCENT I
Adalimumab	385	31	8.05%	0.16%	0.32%	Assumed equal to Infliximab
Vedolizumab 8 week	154	58	37.66%	1.03%	2.03%	GEMINI II
Vedolizumab 4 week	154	48	31.17%	0.81%	1.61%	GEMINI II
Vedolizumab combined					2.03%	Calculated

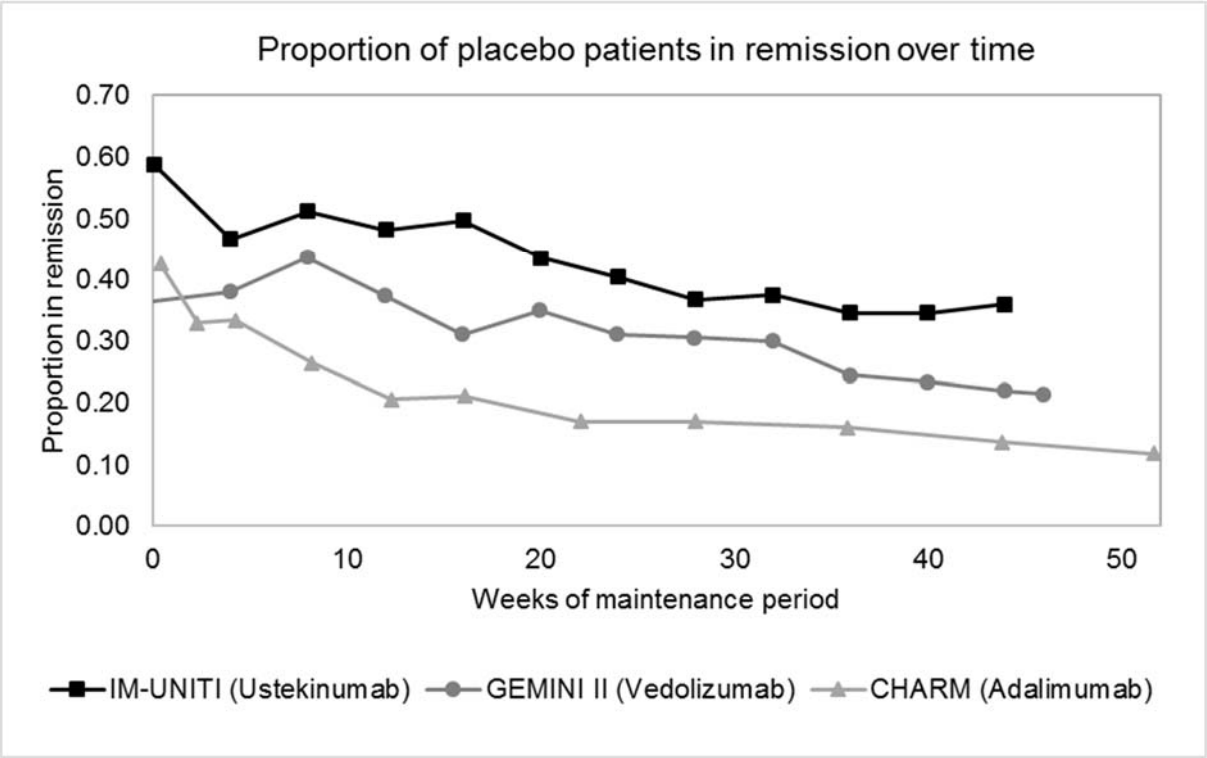
Key: CSR; clinical study report; q8w, every 8 weeks; q12w, every 12 weeks.
Note: *Infliximab included as scenario analysis only.

5.3.3.4 Biologic transitions post-completion of maintenance treatment

As previously mentioned, following the treatment period (1 year in the base case) the biologic maintenance phase ends and patients are switched to conventional care, on which they continue for the duration of the model (60 years in the base case) unless death occurs. As discussed in Section 5.2.2, the 1 year stopping rule is aligned to the NICE recommendation of existing biologics.

In the base-case analysis, rather than setting transition matrices to immediately switch from those associated with a biologic to those associated with conventional care at the end of the maintenance phase, matrices are assumed to converge over a period of time. This accounts for patients who received active treatment within the induction experiencing a gradual decline in efficacy post treatment, which occurs due to an expected carryover effect caused by the recently stopped biologic treatment. This approach was suggested in a health economic advisory board held for ustekinumab.[191] The placebo arms of the maintenance trials were used to model this decline as these patients have responded to an induction dose with active treatment in the induction phase and discontinue treatment in the maintenance because they have been randomised to the placebo arm. Figure 46 shows the number of placebo patients in remission over the maintenance phase of each treatment's publication.[17, 134, 154]

Figure 46: Proportion of placebo patients in remission during maintenance phase



Sources: Ustekinumab, IM-UNITI CSR[137]; Vedolizumab, Sandborn *et al.* 2013[17]; Adalimumab, Colombel *et al.* 2007[154]

For each biologic treatment, rate of remission graphs from the maintenance trial publications CHARM, GEMINI II and IM-UNITI were digitised using GetData Graph Digitizer to collect data on the proportion of placebo patients in remission over the trials maintenance period.[17, 134, 154] The trial structures were designed such that patients were only included within the maintenance phase having responded to induction active treatment. The change in the proportion of patients in remission over the maintenance phase was calculated for the placebo arm of each study, assuming that this either decreases or remains constant over time. These data were reweighted between 0% and 100% to calculate a percentage of patients who were in remission at the beginning of maintenance and who remained in remission at each time-point out of the percentage of patients who remained in remission at the end of maintenance for each cycle. This was used to weight matrices between conventional care and biologic treatment over time, reflecting the gradual decline in efficacy. All treatments begin the post-maintenance period with a weighting of 100% biologic:0% conventional care but have fully transitioned to a weighting of 0% biologic:100%

conventional care by Week 52. Due to a lack of available data, infliximab is assumed to be equal to adalimumab when included in scenario analysis. The resulting data are shown in Table 42.

Table 42: Biologic transitions post-maintenance phase

Week	0	2	4	6	8	10	12	14	16	18	20	22	24	
Ustekinumab	100%	100%	50%	50%	50%	50%	50%	50%	50%	50%	37%	37%	24%	
Vedolizumab	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	64%	64%	
Adalimumab	100%	100%	100%	69%	69%	69%	48%	48%	28%	28%	28%	28%	28%	
Infliximab*	100%	100%	100%	69%	69%	69%	48%	48%	28%	28%	28%	28%	28%	
Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Ustekinumab	24%	9%	9%	9%	9%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Vedolizumab	64%	64%	64%	64%	61%	61%	57%	57%	21%	21%	13%	13%	4%	0%
Adalimumab	17%	17%	17%	17%	17%	17%	17%	14%	14%	14%	14%	6%	6%	0%
Infliximab*	17%	17%	17%	17%	17%	17%	17%	14%	14%	14%	14%	6%	6%	0%
Note: *Infliximab included as scenario analysis only														

5.3.4 Surgery

The model uses an annual rate of surgery of 7%, taken from NHS Hospital Episode Statistics (HES) data.[200] The annual rate of surgery is converted into a 2-week cycle rate using the exponential formula (Equation 1), and the resulting probability for surgery is 0.28% per cycle.[190]

Due to a lack of data, post-surgery transitions from Bodger *et al.* were used (Table 43).[1] This methodology was used in TA352.[3] The transitions were only given for 8-week cycles. Therefore, an identity matrix is applied for three consecutive cycles, followed by application of the post-surgery transitions. To avoid double-counting of costs, the cost of surgery is only applied in the cycle in which transition to surgery occurs.

Table 43: Post-surgery transitions

	Remission	Mild	Moderate-severe	Surgery
Conventional care failure				
Patient numbers	105	15	12	67
Transition probabilities	0.528	0.075	0.060	0.337
TNF failure				
Patient numbers	41	6	5	26
Transition probabilities	0.526	0.077	0.064	0.333
Key: TNF, tumour necrosis factor.				

A criticism of the model in TA352 was that it does not consider repeat surgeries and, in particular, it does not consider how surgery might affect the probability of future surgeries. During model development, a version of the model was built with separate health states for post-surgical remission and post-surgical complications. However, this gave unintuitive results due to the transition probabilities. The only transition probabilities found were values from Lindsay *et al.*[187] Using these values resulted in the majority of patients moving to and remaining in remission following surgery, due to high rates of post-surgical remission in the paper which did not model a higher risk of repeat surgery. This is at odds with clinical practice, as patients are unlikely to remain in post-surgical remission due to the relapsing nature of the disease. At the advisory board held for ustekinumab, a clinical expert confirmed that around 90% of

patients will experience endoscopic recurrence within 1 year following surgery.[191] For this reason, the health states were removed from the model structure.

5.3.5 Adverse events of treatment and surgical complications

AEs of treatment and surgical complications were sourced using the same criteria as used in the NICE submission of vedolizumab.[190] AEs for inclusion were based on expert clinical opinion and were: serious infection, tuberculosis, hypersensitivity, injection site reactions and lymphoma. Individual AEs were not reported in the NMA, for several reasons including lack of comparability of definitions used in trials and heterogeneity of study design (Section 4.10). Therefore, AEs were extracted from the study publications and included in the NMA. The rates for placebo were calculated as a weighted average of the placebo rates from all trials. As the publications for ACCENT I did not report individual AEs, AEs for infliximab are taken from a 2010 publication by Colombel *et al.* that was included within the NMA conducted by Takeda for TA352.[201]

Rates were converted into a cycle rate using the exponential formula (Equation 1), taking into account the duration of each study.

The approach aims to improve the approach used in TA352, which was criticised by the ERG for not accounting for trial duration.[177] It is noted that more adverse skin reactions may be included for placebo than is the case in clinical practice due to using injected placebo in the trials. However, it is not possible to estimate the impact of this. The impact of assuming no effect of AEs is tested within scenario analyses.

The cycle rates used in the base case are given in Table 44, and a scenario is tested assessing the impact of not including AEs.

Table 44: Cycle rates of AEs

Treatment	Serious infection	Tuberculosis	Lymphoma	Hypersensitivity	Skin reactions	Source
Ustekinumab	0.34%	0.00%	0.00%	0.01%	0.75%	UNITI-1, UNITI-2 and IM-UNITI[135, 136, 153]
Vedolizumab	0.32%	0.00%	0.00%	0.00%	10.37%	GEMINI I & GEMINI II[17]
Adalimumab	0.32%	0.00 %	0.00%	0.00%	10.37%	Colombel *et al.*[154], Hanauer *et al.*[150], Rutgeerts *et al.*[202], Sandborn *et al.*[161], and Watanabe *et al.*[151]
Conventional care	0.37%	0.00%	0.00%	0.00%	1.45%	Pooled placebo data from above trials
Infliximab*	0.20%	0.00%	0.00%	0.00%	0.72%	Hanauer *et al.*[155] and Colombel *et al.*[201]
Note: *Infliximab included as scenario analysis only.						

Surgical complications are also considered within the economic analysis and are shown in Table 45. It is assumed that surgical complications have an effect on costs only, and not on HRQL, consistent with TA352.[190]

Table 45: Cycle rate of surgical complications

Adverse event	Proportion
Wound infection	2.10%
Prolonged ileus/bowel obstruction	1.15%
Intra-abdominal abscess	0.40%
Anastomotic leak	1.02%
Sources: Pooled estimates from the following studies: McLeod *et al.*[203], Milsom *et al.*[204], Zurbuchen *et al.*[205], Kusunoki *et al.*[206], Fazio *et al.*[207], Irvin *et al.*[208], Eshuis *et al.*[209], Maartenese *et al.*[210], Ikeuchi *et al.*[211], Cameron *et al.*[212], Stocchi *et al.*[213] and Funayama *et al.*[214]	

5.3.6 Mortality

All-cause mortality has been included in the model, and rates of all-cause mortality were taken from the Office for National Statistics (ONS) life tables for England and Wales, 2012–2014 (the most recent available data).[215] These rates are given by gender, and the model therefore needed to account for the ratio of male to female patients within the treated population. As the mortality rate for females is lower than males, the model population will become increasingly weighted towards females over time. The model accounts for this by referring to the prevailing ratio of males and females at the current time to calculate mortality.

A relative risk of mortality according to health state was included in the manufacturer's submission for TA352.[190] This was taken from a study by Lichtenstein *et al.* that evaluated the risk of mortality in patients with Crohn's disease treated with infliximab and non-biologic treatments: prednisone, immunomodulators and narcotic analgesics.[110] The use of these relative risks gave an advantage to treatments with higher response rates, which was criticised in the ERG report for the appraisal and was excluded from the base case preferred by the ERG and the committee.[3, 177] The ERG stated that the Lichtenstein *et al.* study found no statistically significant difference in mortality rates between infliximab-treated patients and non-infliximab-treated patients. However, using these rates in the manufacturer's model predicted biologic therapies as having lower mortality rates

than conventional care. The ERG also found that the manufacturer had applied the mortality of the patient group with unknown baseline disease severity for the surgery health state; however, no justification was given for this. Therefore, the relative risk was excluded from the model presented here. Furthermore, this approach was tested with a leading clinician in Crohn's disease who confirmed that patients with Crohn's disease should not expect any differential mortality compared to the general population. Therefore, this model considers only all-cause mortality.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

The induction and maintenance studies for ustekinumab, UNITI-1, UNITI-2 and IM-UNITI, collected HRQL data using the 36-Item Short Form Health Survey (SF-36), the Inflammatory Bowel Disease Questionnaire (IBDQ) and the CDAI which measures disease activity including patients' symptoms. HRQL data from the studies are given in Section 4.7.8.

5.4.2 Mapping

The HRQL data collected in the ustekinumab Phase III trials are not in line with the NICE reference case which refers to the EQ-5D.[168] Therefore, a range of published mapping algorithms were used to map the measures collected in the trials (SF-36, IBDQ and CDAI) onto EQ-5D values.[157, 216 217]

5.4.2.1 Methods

SF-36 to EQ-5D

An algorithm published by Rowen *et al.* was used to map SF-36 scores onto EQ-5D utility values.[216] This study used generalised least squares (GLS) regression analysis to examine the relationship between the EQ-5D utility score and the SF-36 using UK data. Predictive ability of the models was assessed using line graphs of observed versus predicted EQ-5D utility scores, mean error, mean absolute error and mean squared error. Several models were tested by Rowen *et al.* to avoid the ceiling effect, which is known to be an issue for the EQ-5D. Of the models tested, more complex models did not produce significantly better results, and therefore, the simplest model reported was used to map SF-36 to EQ-5D (Equation 2).

Equation 2: Mapping SF-36 to EQ-5D

$$EQ-5D = 0.0071 + 0.332 \times PF - 0.060 \times RP + 0.303 \times BP + 0.169 \times GH - 0.039 \times VIT + 0.115 \times SF + 0.010 \times RE + 0.237 \times MH$$

Key: BP, bodily pain; EQ-5D, EuroQol five dimensions questionnaire; GH, general health; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role physical; SF, social functioning; VIT, vitality.

IBDQ to EQ-5D

An algorithm published by Buxton *et al.* was used to map IBDQ scores onto EQ-5D utility values.[157] Again, several regressions were tested to adjust for patient demographics and clinical variables; however, more complex models did not significantly impact the results. Therefore, based on the laws of parsimony, the simplest model reported was preferred to map IBDQ to EQ-5D (Equation 3).

Equation 3: Mapping IBDQ to EQ-5D

$$EQ-5D = 0.03043 + 0.0043 \times IBDQ$$

Key: EQ-5D, EuroQol five dimensions questionnaire; IBDQ, Inflammatory Bowel Disease Questionnaire.

CDAI to EQ-5D

An algorithm published by Buxton *et al.* was used to map CDAI scores onto EQ-5D utilities.[157] The algorithm was a secondary analysis of the study; Buxton *et al.*[157] describe only a model that is unadjusted for covariates, and therefore, this model was used to map CDAI to EQ-5D (Equation 4).

Equation 4: Mapping CDAI to EQ-5D

$$EQ-5D = 0.9168 - 0.0012 \times CDAI$$

Key: EQ-5D, EuroQol five dimensions questionnaire; IBDQ, Inflammatory Bowel Disease Questionnaire.

5.4.2.2 Analyses

Univariate summaries (i.e. mean, standard deviation, minimum, median and maximum) of the utility scores were produced for all treatment arms separately (including different regimens for ustekinumab where appropriate) and for the total

population. To compare health-state values for ustekinumab versus placebo a mean difference between treatments, and a 95% confidence interval, was also produced.

Results

In general, the baseline utility and utility during maintenance were consistent across trials and across treatment arms within each mapping. The utility in the total population by health state during both induction and maintenance is summarised in Table 46. The mapped values from SF-36 scores were much lower than those from IBDQ and CDAI scores, which were more consistent with each other.

Table 46: Utility values by health state and mapping algorithm (total population)

	Statistic	EQ-5D mapped from SF-36	EQ-5D mapped from IBDQ	EQ-5D mapped from CDAI
Remission (CDAI < 150)	N	1167	1249	1250
	Mean (SD)	0.540 (0.070)	0.680 (0.130)	0.820 (0.050)
	Median	0.550	0.830	0.810
	Min, max	0.270, 0.660	0.340, 0.990	0.740, 0.970
Mild (150 ≤ CDAI < 220)	N	603	644	646
	Mean (SD)	0.480 (0.070)	0.680 (0.130)	0.700 (0.020)
	Median	0.490	0.690	0.700
	Min, max	0.260, 0.640	0.300, 0.980	0.650, 0.740
Moderate to severe (220 ≤ CDAI < 600)	N	3002	3200	3225
	Mean (SD)	0.420 (0.070)	0.550 (0.130)	0.540 (0.070)
	Median	0.800 (0.120) 0.420	0.550	0.550
	Min, max	0.220, 0.600	0.230, 0.950	0.240, 0.650

Key: CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; max, maximum; min, minimum; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

Results chosen for base case

Three published mapping algorithms were used to derive EQ-5D utility scores from SF-36, IBDQ and CDAI outcomes.[135, 136, 153] During maintenance, utility by health state showed ustekinumab treatment arms with statistically significantly better utility compared with placebo patients in some cases for SF-36 and IBDQ mappings. However, no difference between treatment arms is observed with CDAI scores, which were more frequently measured than SF-36 and IBDQ. For the purposes of

the cost-effectiveness model, pooled utility values (pooling induction and maintenance studies and pooling all treatment arms) are preferred as they give an increased sample size and present a conservative assumption that there is no difference in the utility for each health state for patients receiving ustekinumab or placebo.

The EQ-5D utility values mapped from SF-36 were much lower than the EQ-5D utility values mapped from IBDQ and CDAI scores and those published in the work by Bodger *et al.* (Table 47). The EQ-5D utility values mapped from SF-36 further lack face validity compared with the UK population norms; the utility for patients in remission (0.54) is much lower than the for those age 75+ (0.73). This does not seem reasonable when the mean baseline age of patients in the UNITI-1 and UNITI-2 trials (37 and 39) is considered.[135, 136] Given this, the EQ-5D utility values mapped from SF-36 were not considered appropriate for use within the cost-effectiveness model.

The EQ-5D utility values mapped from IBDQ and CDAI scores gave similar results to each other and both sets of results appear reasonable compared with the utility values presented by Bodger *et al.* (Table 47). Both of the mapping algorithms used were identified from the study by Buxton *et al.*[157]; this study demonstrated that there is stronger correlation between IBDQ and EQ-5D (spearman correlation coefficient 0.76) than between CDAI and EQ-5D (spearman correlation coefficient -0.62) and that the fit of the mapping algorithm is superior for IBDQ compared with CDAI (R-squared of 0.45 versus 0.29). Given this and the similarity of results between using IBDQ and CDAI scores to map EQ-5D, the mapping from IBDQ to EQ-5D is preferred for the base-case analysis.

Table 47: Bodger *et al.*: health state utilities

Health state	Utility
Remission	0.82
Mild	0.70
Moderate-severe	0.55
Surgery	0.55

5.4.3 Health-related quality-of-life studies

5.4.3.1 Methodology

Identification of studies

The strategies used to retrieve studies reporting HRQL in patients with CD from the published literature are described in Appendix 8. Justification of the methods used with reference to the decision problem are provided[146] and the rationale for the inclusion and exclusion criteria used is presented in Appendix 8.

5.4.3.2 Discussion

The SLR reported 45 studies that measured observational HRQL data in patients with CD. The included studies reported HRQL according to a variety of preference-based tools. The SLR reported various CD health states, from deep remission to severe CD.

Among the 29 longitudinal studies included in the SLR, baseline HRQL was measured using several generic and disease-specific tools. Where applicable, results from the 15 cross-sectional observational studies were used. Baseline HRQL was measured by several generic and disease-specific tools (SF-36, EQ-5D, IBDQ and SIBDQ). As specified in Appendix 8, there was a large degree of heterogeneity observed in the baseline characteristics, both across studies and across patients in the same study; CD is a chronic disease, which means that patients have received different treatment regimens, usually for years, before being included in a particular study. Despite this, HRQL results were largely comparable at baseline using each of the HRQL tools, illustrating a good degree of generalisability across the reported data. Importantly, HRQL varied at baseline according to disease severity and disease state, with a trend of higher disease severity being associated with lower HRQL.

Treatment with several agents was reported by the SLR, for example, using the SIBDQ tool. A wide range of treatments were taken by patients at baseline; however, the observational studies primarily examined treatments with anti-TNF therapies (certolizumab pegol, adalimumab, infliximab) as well as multiple combinations of TNF antagonist regimens. Treatment of patients with CD was found to improve their HRQL. Similar to pharmacological therapy, patients in need of surgical intervention

were typically associated with low HRQL, reflecting disease severity in these patients. HRQL was improved by surgical intervention in all studies identified.

HRQL was found to vary with health state, as measured by the disease-specific IBDQ score. The state of clinical remission (CDAI <150) was associated with substantial improvement in HRQL, as measured by (EQ-5D VAS, SF-36 and SHS). Where measured, patients expressed a preference for deep clinical remission; this was associated with improved IBDQ scores. Ten studies measured the statistical correlation between disease severity (measured by CDAI or HBI) and HRQL and found a good degree of negative correlation between the two.

5.4.4 Adverse reactions

Decrements in QALYs due to AEs were taken from TA352 and are shown in Table 48.[190] The weekly probabilities of each AE (Table 44) were multiplied by decrements to give the expected QALY decrement. Finally, these decrements were summed and subtracted from one to give an AE-adjusted weighting factor per cycle for each treatment, as shown in Table 49. The weighting factors were multiplied by the appropriate cycle length when calculating QALYs.

Table 48: Adverse event decrements

Adverse event	QALY decrement	Source
Serious infection	-0.52	Brown *et al.* (taken as 1 − 0.48)[218]
Tuberculosis	-0.55	Porco *et al.*, (taken as 1 − 0.45)[219]
Malignancy (including lymphoma)	-0.195	Hornberger *et al.* (taken as 1 − 0.805)[220]
Acute hypersensitivity reactions	-0.11	Beusterien *et al.*[221]
Skin site reactions	-0.03	Beusterien *et al.*[222]
Key: QALY, quality-adjusted life year.		

Table 49: Weighting factors

Treatment	Induction	Maintenance
Ustekinumab	99.72%	99.62%
Vedolizumab	99.31%	99.08%
Adalimumab	99.72%	99.62%
Conventional care	99.49%	99.32%

Infliximab*	99.38%	99.18%
Note: *Infliximab included as scenario analysis only.		

Numerous comments were made of this approach in the ERG report of TA352.[177] However, a scenario analysis was tested by the ERG to assess the impact of excluding AEs on results, and it was found that this had little impact on the cost effectiveness of vedolizumab. A scenario analysis is also tested to assess the impact on cost-effectiveness results for ustekinumab.

A study was conducted by Janssen in 2016 to obtain values specific to Crohn's disease for disutilities occurring as a result of adverse events and surgical complications. Members of the general public were given vignettes describing the moderate to severe health state (which was used as the reference state) and vignettes describing the moderate to severe state plus one of the adverse events or complications. Results are shown in Table 50. The results lack face value for some values, namely the mean utility for moderate to severe disease and the disutility or hypersensitivity. Therefore, the results are included as a scenario only.

Table 50: Results of disutility study

Health States	Disutility from reference state	SD
Moderate – severe CD TTO score (reference state)	0.70	-
Hypersensitivity	+0.06	0.18
Injection site reactions	-0.00	0.22
Serious infection	-0.07	0.16
Tuberculosis	-0.23	0.80
Lymphoma	-0.26	0.29
Bowel surgery TTO score (reference state)	0.69	-
Wound infection	-0.02	0.27
Prolonged ileus bowel obstruction	-0.11	0.29
Intra-abdominal abscess	-0.13	0.25
Anastomotic leak	-0.21	0.27
Key: CD, Crohn's disease; SD, standard deviation; TTO, time trade-off.		

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

In the base case, patients are assumed to have health-state-based utility values irrespective of treatment that are mapped from IBDQ scores (Table 46). Values were found to be similar to previously published utility analysis in Crohn's disease.[1] There is a marked difference between patients in the remission, mild and moderate to severe health states (0.80; 0.68; 0.55). This reflects the burden of symptoms associated with more severe disease such as weight loss, diarrhoea and psychological impact on general wellbeing (further details are in Appendix 10).

For the surgery health state, no trial-based utility values were available. To be able to incorporate a utility for the surgery health state in the base case, the same assumptions were used as in Bodger *et al.* whereby for 8 weeks in the surgery health state, it is assumed the first 2 weeks are spent with a utility equal to that of the moderate to severe health state, followed by 6 weeks of utility equal to the remission health state.

Scenario analyses are conducted in the model to test the impact of using CDAI mapping (Table 52) and of using health state utility values taken from Bodger *et al.* (Table 47).[1] Bodger *et al.* present QALYs as 8-week values, and they assume that the 8-week value for the surgery health state is the same as 2 and 6 weeks with health equivalent to the moderate to severe and remission health states, respectively. To calculate QALYs for the 2-week cycle in this model, it was assumed that the 2-week surgery QALY is equal to the 2-week moderate to severe disease QALY.

HRQL is assumed to decrease over time in line with general-population age-related utility decrements.[223] Coefficients for age and age-squared are shown in Table 51. As mortality is equal in all treatment arms the adjustments will have little impact.

Table 51: Age-related utility decrements

Item	Coefficient	SE	t	P > t	[95% CI]	
age	-0.0001728	0.0003737	-0.462	0.644	-0.0009053	0.0005597
age^2	-0.0000340	3.96E-06	-8.602	0	-0.0000418	-0.0000263
Key: CI, confidence interval; SE, standard error.						

Table 52: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Remission	0.800 (0.120)	0.740, 0.970	Section 5.4.2.2; Page 194	Health state utility values mapped from IBDQ to EQ-5D; best reflection of data out of measures tested; values similar to Bodger *et al.*[1]
Mild	0.680 (0.130)	0.650, 0.740	Section 5.4.2.2; Page 194	
Moderate to severe	0.550 (0.130)	0.240, 0.650	Section 5.4.2.2; Page 194	
Surgery	As for Moderate to severe		Section 5.4.5; Page 200.	Methodology used in Bodger *et al.*[1]
Serious infection	-0.52	-0.510, -0.530	Section 5.4.4; Page 198	Values utilised in TA352[190]
Tuberculosis	-0.55	-0.539, -0.561	Section 5.4.4; Page 198	
Malignancy (lymphoma)	-0.195	-0.191, -0.199	Section 5.4.4; Page 198	
Acute hypersensitivity reactions	-0.11	-0.108, -0.112	Section 5.4.4; Page 198	
Skin site reactions	-0.03	-0.029, -0.031	Section 5.4.4; Page 198	
Key: AR, adverse reaction; HS, health state.				

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

The strategies used to retrieve studies reporting cost of illness in patients with CD from the published literature are described in Appendix 9. Justification of the methods used with reference to the decision problem are provided[146] and the rationale for the inclusion and exclusion criteria used is presented in Appendix 9.

5.5.1.1 Discussion

Summary of main findings

A large proportion of the studies were retrospective and used databases most frequently to collect data.

Bassi *et al.* (2004) reported the lowest mean direct cost of £1,652 per patient estimated using patients with CD who received secondary care for over 6 months in the UK.[224] Further discussion of studies, in particular non-UK studies, is in Appendix 9.

In terms of mean total direct costs, there appeared to be two main drivers of costs across all geographic regions: the use of biologic treatments and the inclusion of surgery as a treatment. Surgery and inpatient care have traditionally been the strongest medical-related cost drivers in CD, however, more recent evidence suggests a change in cost structure, with increased costs associated with biologic therapy and a relative reduction in overall costs of surgery and hospital care.[224, 225]

Indirect cost data were reported in studies throughout Europe and the US. One of the main drivers in indirect costs was productivity losses. The employment data provided by the studies highlighted that CD sufferers are capable of maintaining full-time employment, although there are substantial losses in terms of productivity. These losses are typically in the form of absenteeism, presenteeism and sick leave.

5.5.2 Costs and resource use of intervention and comparators

Unit costs of biologic treatments were taken from the Monthly Index of Medical Specialties (MIMS) website (a database of drug prices in the UK) and are shown in Table 53.[226] The cost of the ustekinumab 130ml vial is equivalent to the 90mg cost.

Dosing information for biologic treatments was taken from the SPCs[91-93] This was combined with unit costs to calculate a cost per model cycle.

The number of injections required during the induction phase, Year 1 of the maintenance phase and Year 2+ of the maintenance phase, and the resulting cost for biologic treatments, are presented in Table 54.

Table 53: Treatment unit costs

Treatment	Dose per unit (mg)	Unit cost	Source
Ustekinumab	130	£2,147.00	MIMS[226]
	90	£2,147.00	MIMS[226]
Vedolizumab	300	£2,050.00	MIMS[226]
Infliximab (Remicade)*	100	£419.62	MIMS[226]
Infliximab (Remsima)*	100	£377.66	MIMS[226]
Infliximab (Inflectra)*	100	£377.66	MIMS[226]
Adalimumab	40	£352.14	MIMS[226]

Key: MIMS, Monthly Index of Medical Specialities.
Notes: *Infliximab included as scenario analysis only.

Table 54: Treatment costs for the induction phase and maintenance phase (based on a 6-week induction period as modelled)

Treatment	Induction		Maintenance Year 1		Average maintenance Year 2+	
	No. of administrations	Total cost	No. of administrations	Total cost	No. of administrations	Total cost
Lower dose: all treatments						
Conventional care failure						
Ustekinumab	1	[redacted]	4	£8,588	4.35	£9,339
Adalimumab	2	£2,113	25	£8804	26.09	£9187
Infliximab (Remicade)*	2	£3,357	6	£10,071	6.52	£10,944

Treatment	Induction		Maintenance Year 1		Average maintenance Year 2+	
	No. of administrations	Total cost	No. of administrations	Total cost	No. of administrations	Total cost
Infliximab (Inflectra)*	2	£3,021	6	£9,064	6.52	£9,849
Infliximab (Remsima)*	2	£3,021	6	£9,064	6.52	£9,849
TNF failure						
Ustekinumab	1	[redacted]	4	£8,588	4.35	£9,339
Vedolizumab	3	£6,150	6	£12,300	6.52	£13,366
Higher dose: all treatments						
Conventional care failure						
Ustekinumab	1	[redacted]	6	£12,882	6.52	£13,998
Adalimumab	2	£2,113	49	£17,255	52.18	£18,375
Infliximab (Remicade)*	2	£3,357	6	£20,142	6.52	£21,888
Infliximab (Inflectra)*	2	£3,021	6	£18,128	6.52	£19,699
Infliximab (Remsima)*	2	£3,021	6	£18,128	6.52	£19,699
TNF failure						
Ustekinumab	1	[redacted]	6	£12,882	6.52	£13,998
Vedolizumab	3	£6,150	11	£22,550	13.04	£26.732

Key: TNF, tumour necrosis factor; q8w, every 8 weeks; q12w, every 12 weeks.
Notes: *Infliximab included as scenario analysis only.

[redacted].

The cost of conventional care was calculated using values taken from TA352.[190] The daily costs were based on dosing and unit costs reported in the British National Formulary 2013 (Table 55).[227]

Costs were given for the 2012/13 cost year and inflated to 2014/15 values using the hospital and community health services (HCHS) index from the Personal Social Services Research Unit (PSSRU) 2015.[228] Daily costs were multiplied by usage (also given in TA352) to give a weighted total daily cost. This was used to give an average cycle cost of £30.47.

Table 55: Daily cost of conventional care

Treatment	Daily cost 2012/13	Daily cost 2014/15
Balsalazide	£0.94	£0.95
Mesalazine	£1.47	£1.49
Olsalazine	£0.71	£0.72
Sulfasalazine	£0.29	£0.29
Budesonide	£2.25	£2.28
Prednisolone	£4.86	£4.91
Azathioprine	£0.19	£0.19
Mercaptopurine	£6.95	£7.03
Methotrexate	£0.92	£0.93

Biologic treatments may have a higher dose according to SPCs. There is uncertainty over which dosing regimen for ustekinumab will be used in clinical practice. Clinician advice on interpretation of the label for ustekinumab was sought. In both populations, it was assumed that patients who responded (CDAI-100) to the induction dose are assigned to dosing every 12 weeks as per the label; patients that show a partial response (70 < CDAI < 100) continue treatment with dosing every 8 weeks. For all other treatments, it was assumed that patients begin on the lower recommended dose, as no data were found to suggest otherwise. This may favour the comparators against ustekinumab as patients with inadequate response will likely be treated with an escalated dose. Patients may dose-escalate throughout the duration of treatment due to loss of response; details are shown in Table 56.

Table 56: Starting doses and dose escalation

	Low dose	High dose	2-week probability	Details	Reference
Ustekinumab (conventional care failure)	86%	14%	2.0%	90mg every 12 weeks to 90mg every 8 weeks	IM-UNITI data[153]
Ustekinumab (TNF failure)	77%	23%			
Adalimumab	100%	0%	3.0%	40mg every 2 weeks to 40mg every week	CHARM data[154]
Vedolizumab	100%	0%	2.0%	300mg every 8 weeks to 300mg every 4 weeks	Assumed equal to ustekinumab
Infliximab – Remicade*	100%	0%	3.0%	5mg/kg every 8 weeks to 10mg/kg every 8 weeks	Assumed equal to adalimumab
Infliximab – Inflectra*	100%	0%	3.0%	Assumed equal to Remicade	Assumed equal to Remicade
Infliximab – Remsima*	100%	0%	3.0%	Assumed equal to Remicade	Assumed equal to Remicade

Key: TNF, tumour necrosis factor.
Notes: *Infliximab included as scenario analysis only.

5.5.3 Treatment administration costs

Vedolizumab, infliximab and the induction dose of ustekinumab are administered via intravenous infusion. An administration cost of £367.00 was sourced from the NHS Payment by Results tariff 2014/15 (item code: FZ37F), consistent with TA352.[190, 229] This cost is applied every time a dose is administered.

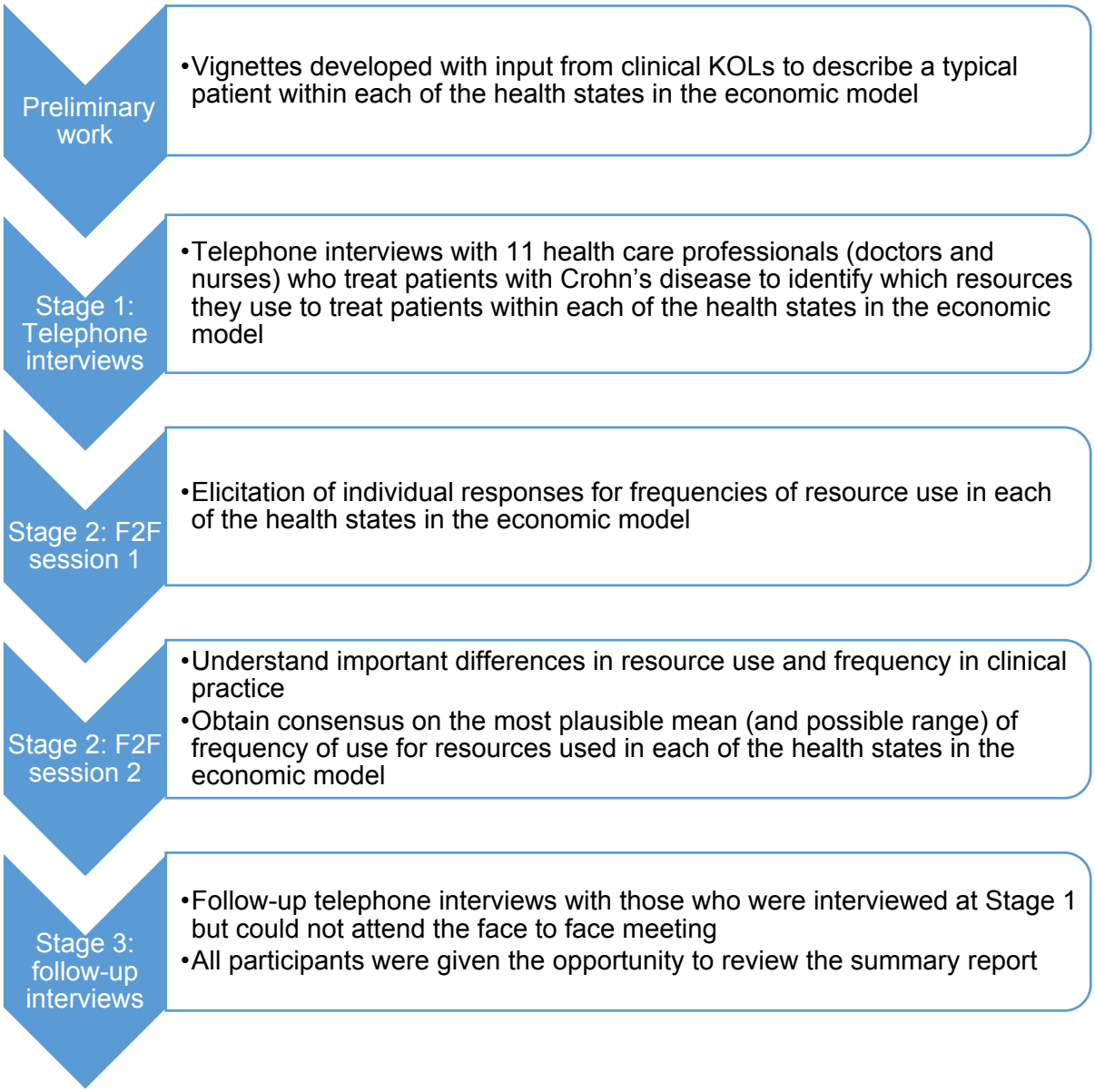
Maintenance treatment with ustekinumab and all treatments with adalimumab are administered as a subcutaneous injection. This may be administered by a nurse, self-administered (assuming no additional cost to the NHS) or, for ustekinumab, via a homecare service provided by Janssen free of charge to the NHS. An administration cost for nurse administration of £39.00 was sourced from the PSSRU 2015 report (face-to-face contact in district nursing services).[228] In the base case, no adalimumab

or ustekinumab administrations are assumed to be provided via hospital, due to the homecare service provided by Abbvie and Janssen, respectively.

5.5.4 Health-state unit costs and resource use

Estimates for resource use were gathered from a modified Delphi panel conducted by BresMed and Janssen, in which 12 clinicians estimated resource use for each model health state.[230] Information was collected in two steps. Firstly, individual telephone interviews were held to compile a list of all possible resource use items for the health states from Bodger *et al.* Following this, a face-to-face meeting was held with the clinicians to determine frequency of usage for all items. Clinicians who could not attend the face-to-face meeting were able to have a follow-up call, in which they were able to amend the upper or lower bounds of the estimates if they disagreed with the outcome of the face-to-face meeting. The process is summarised in Figure 47.

Figure 47: Process for modified Delphi panel



For the remission and mild health states, clinicians believed that there may be a difference in resource use between patients who were receiving biologic treatments and those who were not. Therefore, the frequencies for these health states were considered separately in categories named 'on biologic' and 'off biologic'.

The surgery health state was also split into categories. Clinicians felt that, when considering resource use, it was appropriate to separate surgery based on the length of stay required. Frequencies were considered for minor procedures that required only a day case stay (surgery day case), medium complexity procedures requiring a

stay of up to 5 days (surgery <5 days) and complex procedures requiring a stay of more than 5 days (surgery complex >5 days).

Full results for the CDAI-based health states are given in Appendix 13, and resulting costs per year and cycle for each CDAI-based health state are given in Table 57.

Table 57: CDAI health state cycle costs

	Remission		Mild		Moderate to severe
On/off biologic	**On**	**Off**	**On**	**Off**	
Total costs per patient per year	£1,029	£426	£5,558	£7,544	£13,568
Total costs per patient per cycle	£39.42	£16.32	£213.04	£289.18	£520.07

The estimated costs from the Delphi panel were higher than previous submissions. However, we believe that our estimates reflect the true current cost to the NHS due to the rigorous process by which the outputs were estimated. Within TA352, initial estimates were taken from Bodger *et al.* and inflated to 2012 values. These values were taken from a sample of 160 patients in 2000/2001. Therefore, estimates used in TA352 may represent outdated data. At the ACD stage, results of a survey of UK clinicians and nurses were presented that were also lower than the costs in this submission. However, the Delphi approach is more rigorous than the survey conducted in TA352. The original health state costs for TA352 and the updated values at the ACD stage are both tested in scenario analyses.

The cost of each surgical category are calculated as a weighted average of procedures in the small and large intestine, using frequencies and costs sourced from NHS reference costs 2014/2015.[231]

Table 58: Surgical procedure unit costs

Resource type	Costs	Frequency	Weighted cost	Reference
Surgery day case	£764.68	297	£997.81	NHS Reference Costs 2014/15. Day case. Currency code FZ67F Major Small Intestine Procedures, 19 years and over, with CC Score 0–1
	£1,207.00	331		NHS Reference Costs 2014/15. Day case. Currency code FZ77E Major

				Large Intestine Procedures, 19 years and over, with CC Score 0
Surgery <5 days	£4,101.46	2863	£4,035.45	NHS Reference Costs 2014/15. Elective inpatients. Currency code FZ67F Major Small Intestine Procedures, 19 years and over, with CC Score 0–1
	£3,870.24	1144		NHS Reference Costs 2014/15. Elective inpatients. Currency code FZ77E Major Large Intestine Procedures, 19 years and over, with CC Score 0
Surgery complex >5 days	£6,040.25	1352	£6,744.78	NHS Reference Costs 2014/15. Non elective inpatients. Currency code FZ66F Very Major Small Intestine Procedures, 19 years and over, with CC Score 0–1
	£9,012.71	420		NHS Reference Costs 2014/15. Non elective inpatients. Currency code FZ73F Very Complex Large Intestine Procedures with CC Score 0–2

The total cost of the surgery health state was calculated as a weighted average of the cost for each category. Proportions from a consultation with a UK clinician are used to weight the categories. It was estimated that surgery is comprised of 20% day cases, 10% <5 day stays and 70% >5 day stays. Applying the weights (Table 59) gives a per patient total resource use cost for the health state.

Table 59: Weighted surgery category costs

Surgery category	Cost	Proportion	Weighted cost
Surgery day case	£2,767.70	20.00%	£553.54
Surgery <5 days	£5,603.02	10.00%	£560.30
Surgery >5 days	£10,785.02	70.00%	£7,549.51
		Total cost:	£8,663.36

For surgery, the rate and cost of surgical complications must also be considered. The expected number of outpatient visits and extra hospital days for each complication is taken from TA352.[190] Costs were sourced from NHS Reference costs 2014/15 (Table 60).[231]

Table 60: Additional resource costs for surgical complications

Resource type	Costs	Reference
Additional hospital days	£162	NHS Reference Costs 2014/15. Elective inpatients excess bed days Currency Code FZ37P Inflammatory Bowel Disease without Interventions, with CC Score 5+
Outpatient visits	£140	NHS Reference Costs 2014/15 Outpatient attendances; Service Code 301 Gastroenterology

The rate per cycle of surgical complications is given in Table 45 (Section 5.3.5). The rates of each complication were multiplied by number of additional hospital days/outpatient visits required and the cost of each resource item to gain an expected cost per complication. The resulting complication costs were added to the weighted surgery cost above, giving the result of £8,866 per patient per surgery shown below in Table 61. The cost is applied upon patients entering the surgery health state. For the following three cycles, the cost of remission is applied.

Table 61: Total surgery cost

Costs	Additional hospital days	Outpatient visits	Risk per surgery	Weighted costs
Wound infection	4.0	1.0	2.10%	£63.89
Prolonged ileus/small bowel obstruction	4.5	1.0	1.15%	£39.17
Abdominal abscess	7.0	2.5	0.40%	£23.83
Anastomotic leak	9.5	2.5	1.02%	£75.36
Surgery			-	£8,663.36
	Total cost of surgery			**£8,865.62**

5.5.5 Adverse reaction unit costs and resource use

As described in Section 5.3.5, five AEs were included in the model: serious infection (defined as septicaemia, pneumonia, urinary tract infections, respiratory infections and bronchitis), tuberculosis, hypersensitivity, injection site reactions and lymphoma. The costs for all AEs, except for lymphoma, were sourced from NHS Reference Costs 2014/15 and are shown in Table 62.[231] The cost of lymphoma is given in

TA352 as the average of lymphoma costs from three technology appraisals of rituximab for lymphoma, and was accepted by the ERG.[177, 190] More recent values were searched for but were not identified. The cost of lymphoma for 2011/12 has been inflated to 2014/15 values using the HCHS index from the PSSRU 2015.[228] The NHS reference costs used for other AEs are consistent with TA352.[190]

Table 62: Adverse event costs

Adverse event	Cost	Source
Serious infection	£3,957	NHS Reference Costs 2014/15.[231] Average HRGs of: septicaemia, pneumonia, urinary tract infection, respiratory infection, and bronchitis
Tuberculosis	£2,650	NHS Reference Costs 2014/15.[231] Average of non-elective short and long stay tuberculosis, with CC score 0–1
Hypersensitivity	£3,337	NHS Reference Costs 2014/15.[231] Average of non-elective short-stay and long-stay pyrexia
Injection site reactions	£5,240	NHS Reference Costs 2014/15.[231] Average HRGs of skin disorders with interventions
Lymphoma	£15,399	NICE (2003)[232], NICE (2012)[193], and NICE (2011).[233] Average of lymphoma costs from three technology appraisals for rituximab (TA65, TA243, and TA226). Inflated from 2011/12 values to 2014/15 values using PSSRU 2015[228]

Key: CC, complication and comorbidity; HRG, Healthcare Resource Group; NHS, National Health Service.

5.5.6 Miscellaneous unit costs and resource use

No other costs are used in the model.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case *de novo* analysis inputs

The summary of key parameters (efficacy, utilities, treatment costs) to the cost-effectiveness model are presented in Table 63. Details of all model inputs are given in Appendix 14.

Table 63: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model controls			
Time horizon	60	0, 0 (None)	Section 5.2.2
Cycle length (weeks)	2	0, 0 (None)	Section 5.2.2
Discount rate for costs	3.50%	0.02, 0.04 (None)	Section 5.2.2
Discount rate for QALYs	3.50%	0.02, 0.04 (None)	Section 5.2.2
Mean age – Conventional care failure	39.20	13.05, 65.35 (Normal)	Section 5.3.1
Mean weight – Conventional care failure	73.41	34.11, 112.71 (Normal)	Section 5.3.1
Proportion of patients – female – Conventional care failure	0.53	0.49, 0.57 (Beta)	Section 5.3.1
Patients <55kg – Conventional care failure	0.19	0.19, 0.19 (Beta tree)	Section 5.3.1
Patients >55kg and <85kg – Conventional care failure	0.60	0.6, 0.6 (Beta tree)	Section 5.3.1
Patients >85kg – Conventional care failure	0.21	0.21, 0.21 (Beta tree)	Section 5.3.1
Mean age – TNF Failure	37.30	13.7, 60.9 (Normal)	Section 5.3.1
Mean weight – TNF Failure	69.80	34.03, 105.57 (Normal)	Section 5.3.1
Proportion of patients – female – TNF Failure	0.57	0.54, 0.61 (Beta)	Section 5.3.1
Patients <55kg – TNF Failure	0.23	0.23, 0.23 (Beta tree)	Section 5.3.1
Patients >55kg and <85kg – TNF Failure	0.59	0.59, 0.59 (Beta tree)	Section 5.3.1
Patients >85kg – TNF Failure	0.18	0.18, 0.18 (Beta tree)	Section 5.3.1
Duration of treatment	1.00	1, 3 (None)	Section 5.2.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Annual rate of surgery	0.07	0.06, 0.08 (Normal)	Section 5.3.4
Drug costs			
Unit cost: Ustekinumab 90mg	£2,147	0, 0 (None)	Section 5.5.2
Unit cost: Ustekinumab 130mg	£2,147	0, 0 (None)	Section 5.5.2
Unit cost: Adalimumab	£352	0, 0 (None)	Section 5.5.2
Unit cost: Vedolizumab	£205	0, 0 (None)	Section 5.5.2
Ustekinumab q12w proportion of patients – Conventional care failure	86%	0, 0 (None)	Section 5.5.2
Ustekinumab q12w proportion of patients – TNF failure	77%	0, 0 (None)	Section 5.5.2
Adalimumab lower dose starting proportion	100%	0, 0 (None)	Section 5.5.2
Infliximab – Remicade lower dose starting proportion	100%	0, 0 (None)	Section 5.5.2
Vedolizumab lower dose starting proportion	100%	0, 0 (None)	Section 5.5.2
Patients dose escalating in IM-UNITI	29	0, 0 (None)	Section 5.5.2
Patients dose escalating in CHARM	140	0, 0 (None)	Section 5.5.2
Dose escalation 2-week probability – Infliximab – Remicade	1%	0, 0 (None)	Section 5.5.2
Utility values			
Utility Remission IM-UNITI – IBDQ to EQ-5D	0.80	0.79, 0.81 (Beta)	Section 5.4.2.2
Utility Mild IM-UNITI – IBDQ to EQ-5D	0.68	0.67, 0.69 (Beta)	Section 5.4.2.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utility Moderate to severe IM-UNITI – IBDQ to EQ-5D	0.55	0.55, 0.55 (Beta)	Section 5.4.2.2
Age-related utility decrements age	-0.00017	0, 0 (Beta)	Section 5.4.5
Age-related utility decrements age^2	-0.00003	0, 0 (Beta)	Section 5.4.5
Disutility Serious infection	-0.52	-0.51, -0.53 (Beta)	Section 5.4.4
Disutility Tuberculosis	-0.55	-0.54, -0.56 (Beta)	Section 5.4.4
Disutility Hypersensitivity	-0.20	-0.19, -0.2 (Beta)	Section 5.4.4
Disutility Injection site reactions	-0.11	-0.11, -0.11 (Beta)	Section 5.4.4
Disutility Lymphoma	-0.03	-0.03, -0.03 (Beta)	Section 5.4.4
Induction transition probabilities			
Remission rate Conventional care failure – Ustekinumab 6mg/kg	0.35	0.29, 0.42 (Beta)	Section 5.3.2
Remission OR Conventional care failure – Ustekinumab 6mg/kg vs Adalimumab 160/80 mg	0.64	0.25, 1.53 (Normal)	Section 5.3.2
Remission OR Conventional care failure – Ustekinumab 6mg/kg vs Placebo	2.50	1.6, 3.98 (Normal)	Section 5.3.2
Remission rate TNF failure – Ustekinumab 6mg/kg	0.18	0.14, 0.24 (Beta)	Section 5.3.2
Remission OR TNF failure – Ustekinumab 6mg/kg vs Vedolizumab 300 mg	1.53	0.69, 3.39 (Normal)	Section 5.3.2
Remission OR TNF failure – Ustekinumab 6mg/kg vs Placebo	2.34	1.37, 4.08 (Normal)	Section 5.3.2
Response CDAI-100 rate Conventional care failure – Ustekinumab 6mg/kg	0.56	0.49, 0.62 (Beta)	Section 5.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Response CDAI-100 OR Conventional care failure – Ustekinumab 6mg/kg vs Adalimumab 160/80 mg	1.03	0.47, 2.2 (Normal)	Section 5.3.2
Response CDAI-100 OR Conventional care failure – Ustekinumab 6mg/kg vs Placebo	3.12	2.08, 4.68 (Normal)	Section 5.3.2
Response CDAI-100 rate – TNF failure – Ustekinumab 6mg/kg	0.34	0.28, 0.4 (Beta)	Section 5.3.2
Response CDAI-100 OR TNF failure – Ustekinumab 6mg/kg vs Vedolizumab 300 mg	1.05	0.59, 1.85 (Normal)	Section 5.3.2
Response CDAI-100 OR TNF failure – Ustekinumab 6mg/kg vs Placebo	1.87	1.26, 2.8 (Normal)	Section 5.3.2
Percentage of moderate – severe responders – Conventional care failure	[redacted]	[redacted]	Section 5.3.2
Percentage of moderate – severe responders – TNF Failure	[redacted]	[redacted]	Section 5.3.2
Ustekinumab Delayed responders – Conventional care failure – Response (CDAI-70)	0.51	0.46, 0.55 (Beta)	Section 5.3.2
Ustekinumab Delayed responders – Conventional care failure – Response (CDAI-100)	0.51	0.46, 0.55 (Beta)	Section 5.3.2
Ustekinumab Delayed responders – Conventional care failure – Remission	0.29	0.25, 0.33 (Beta)	Section 5.3.2
Ustekinumab Delayed responders – TNF failure – Response (CDAI-70)	0.51	0.46, 0.55 (Beta)	Section 5.3.2
Ustekinumab Delayed responders – TNF failure – Response (CDAI-100)	0.51	0.46, 0.55 (Beta)	Section 5.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Ustekinumab Delayed responders – TNF failure – Remission	0.29	0.25, 0.33 (Beta)	Section 5.3.2
Vedolizumab Delayed responders – Response (CDAI-70)	0.19	0.11, 0.27 (Beta)	Section 5.3.2
Vedolizumab Delayed responders – Response (CDAI-100)	0.19	0.11, 0.27 (Beta)	Section 5.3.2
Vedolizumab Delayed responders – Remission	0.10	0.05, 0.18 (Beta)	Section 5.3.2
Maintenance discontinuation			
Discontinuation due to lack of efficacy – Placebo	0.11	0.07, 0.17 (Beta)	Section 5.3.3.3
Discontinuation due to lack of efficacy – Ustekinumab q12w	[redacted]	[redacted]	Section 5.3.3.3
Discontinuation due to lack of efficacy – Ustekinumab q8w	[redacted]	[redacted]	Section 5.3.3.3
Discontinuation due to lack of efficacy – Vedolizumab q8w	0.38	0.3, 0.45 (Beta)	Section 5.3.3.3
Discontinuation due to lack of efficacy – Vedolizumab q4w	0.31	0.24, 0.39 (Beta)	Section 5.3.3.3

Key: CDAI, Crohn's Disease Activity Index; CI, confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; LY, life year; OR, odds ratio; q4w, every 4 weeks; q8w, every 8 weeks; QALY, quality-adjusted life year; TNF, tumour necrosis factor.

5.6.2 Assumptions

The list of assumptions made in the cost-effectiveness model is given below (Table 64).

Table 64: List of assumptions

Factor	Chosen values	Justification	Reference
Time horizon	60 years (lifetime)	Crohn's disease is a lifetime condition; mean age of patients is 37 (TNF failure) / 39 (Conventional care failure); value used by Bodger *et al.*	Bodger *et al.*, UNITI-1, UNITI-2.[1, 135, 136]
Cycle length	2 weeks	Cycle length chosen to allow for variable inductions	
Health effects measures	QALYs	NICE reference case	NICE 2013[168]
Discount for utilities and costs	3.5% for utilities and costs	NICE reference case	NICE 2013[168]
Perspective on outcomes	Direct health effects	NICE reference case	NICE 2013[168]
Perspective on costs	NHS	NICE reference case	NICE 2013[168]
Partial responders	Patients who partially respond (70 < CDAI < 100) in the induction phase remain in the moderate to severe health state	No available data on patients moving to mild health state	
Treatment length	Treatment lasts for 1 year in base case	Bodger *et al.* assume one or two years in their base case; vedolizumab NICE submission assumes 1 year in the base case. Majority of trials provide 1 year of data	Bodger *et al.*, TA352[1, 190]
Mortality	Same as background mortality	Relative risk given in NICE vedolizumab submission found to make unwarranted assumptions; Lichtenstein *et al.* found no statistical difference in mortality between infliximab and non-infliximab treated patients. Approach supported by KOL	Lichtenstein *et al.*, TA352 ERG report[110, 177]
AEs	Only serious AEs are relevant to the analysis	AEs for inclusion selected by UK clinical experts.	TA352[190]

Factor	Chosen values	Justification	Reference
		A literature search was conducted for AEs within the disutility study, and no further AEs were identified except for frequent AEs, which should be captured within the mild / moderate to severe health states.	
Utility values	Utility of surgery is equivalent to non-response	Consistent with assumption made by Bodger *et al.* and supported by the evidence of the disutility study.	Bodger *et al.*[1]
Maintenance transition probabilities	Maintenance transition probabilities are constant over time, but vary by treatment per the NMA	The NMA demonstrated directional differences in efficacy between treatments during maintenance; this approach to estimating transition probabilities is the best approach available to use the NMA evidence. The approach taken is consistent with, but improves upon the method used in TA352.	TA352[190]
Efficacy of conventional care	Placebo efficacy estimates can be used as a proxy for the efficacy of conventional care	Patients in clinical trials received placebo in addition to conventional treatments for CD	UNITI-1, UNITI-2, IM-UNITI[134-136]
Biosimilars for infliximab	Biosimilars have equal efficacy and AEs to Remicade®, the only difference is in acquisition cost (scenario analyses only)	Biosimilars have been recommended on the basis that they are at least as effective and as safe as the branded product; all available evidence for infliximab is for Remicade However, importantly, recent evidence from the NOR-SWITCH study suggest otherwise.	
Discontinuation from maintenance treatment	Patients in moderate-to-severe CD are assumed to discontinue from their biologic treatment during maintenance due to loss of efficacy, at rates estimated from observed data in clinical trials	This reflects how biologic treatments are used in clinical practice	

Factor	Chosen values	Justification	Reference
Efficacy following end of maintenance treatment	It is assumed that, rather than transitions immediately changing from those associated with biologic treatment to those associated with conventional care following completion of maintenance treatment, there will be a gradual convergence of transition probabilities over time	This approach was suggested at an advisory board meeting, to reflect that the efficacy of patients who have completed maintenance treatment is unlikely to immediately drop to the efficacy of conventional care on cessation of treatment. This is also supported by trial data showing that the proportion of patients in remission following induction in patients who were randomised to placebo (i.e. patients who responded to active induction) gradually declined	CHARM, GEMINI II & IM-UNITI.[17, 134, 154]
Key: AE, adverse event; KOL, key opinion leader; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALYs, quality-adjusted life years; TNF, tumour necrosis factor.			

5.7 Base-case results

Base-case results are presented for both the conventional care failure and TNF failure populations. Results are shown for the CDAI-100 response criteria and using list prices for all treatments.

Vedolizumab has a confidential patient access scheme (PAS), and biosimilar prices are variable; however, we are not privy to confidential simple patient access schemes and thus results are presented using list prices for all comparators.

5.7.1 Base-case incremental cost-effectiveness analysis results

Incremental analyses are shown for the conventional care failure population and the TNF failure population in Table 65 and Table 66, respectively.

An incremental analysis compares multiple mutually exclusive treatments against each other to find the most cost-effective treatment option out of all the available interventions. This is done in three steps:

1. Treatments are ordered from least to most expensive.
2. Check for strong dominance. Treatments are dominated if they are both costlier and less effective than another treatment included in the analysis.

3. Check for extended dominance. Treatments are extendedly dominated if an alternative treatment can provide more QALYs for a lower cost per QALY. This is because decision makers prefer a more effective treatment with a lower incremental cost-effectiveness ratio (ICER).

The results from the incremental analysis indicate that ustekinumab dominates both conventional care and adalimumab in the conventional care failure population, and that ustekinumab dominates both conventional care and vedolizumab in the TNF failure population. In addition, despite the fact that only 1 year of biologic treatment is modelled, significant QALY gains are accrued for ustekinumab compared to conventional care, with important relative gains over biologic comparators, thus strengthening the model findings. This is further confirmed in scenario analyses (Section 5.8.3).

Table 65: Base-case results: conventional care failure population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£263,053	43.0941	13.0501				Dominant	
Conventional care	£278,542	43.0941	12.6500	£15,489	0.0000	-0.4001	-	Dominated
Adalimumab	£283,762	43.0941	12.9022	£20,709	0.0000	-0.1479	£20,701	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 66: Base-case results: TNF failure population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£288,088	44.9817	12.9521				Dominant	
Conventional care	£294,600	44.9817	12.7280	£6,512	0.0000	-0.2241	-	Dominated
Vedolizumab	£302,820	44.9817	12.8179	£14,732	0.0000	-0.1342	£91,454	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TNF, tumour necrosis factor.								

5.7.1.1 Base-case incremental cost-effectiveness analysis including infliximab

Infliximab is not included in the base case due to lack of CDAI-100 induction efficacy data. However, it is included as a scenario analysis in Table 67, using the CDAI-100 outcome and assuming equal efficacy for adalimumab and infliximab, and in Table 68 using the CDAI-70 outcome. In the CDAI-100 scenario ustekinumab remains the cost-effective treatment option. In the CDAI-70 scenario ustekinumab is no longer cost-effective, and Inflectra is the cost-effective treatment option; however these results should be interpreted with caution given the limitations of the NMA outcomes for infliximab noted previously in Section 4.10.4.

Table 67: Base-case results: conventional care failure population including infliximab (CDAI-100)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£263,053	43.0941	13.0501				Dominant	
Conventional care	£278,542	43.0941	12.6500	£15,489	0.0000	-0.4001	-	Dominated
Infliximab - Inflectra	£278,693	43.0941	12.8208	£15,640	0.0000	-0.2292	£882	Dominated
Infliximab - Remsima	£278,693	43.0941	12.8208	£15,640	0.0000	-0.2292	£883	Dominated
Infliximab - Remicade	£279,698	43.0941	12.8208	£16,645	0.0000	-0.2292	£6,767	Dominated
Adalimumab	£283,762	43.0941	12.9022	£20,709	0.0000	-0.1479	£20,701	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 68: Base-case results: conventional care failure population including infliximab (CDAI-70)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£264,420	43.0941	13.0285				Dominant	
Infliximab - Inflectra	£264,476	43.0941	13.1388	£56	0.0000	0.1103	Dominant	£504
Infliximab - Remsima	£264,476	43.0941	13.1388	£0	0.0000	0.0000	Dominant	Dominated
Infliximab - Remicade	£265,930	43.0941	13.1388	£1,454	0.0000	0.0000	Dominant	Dominated
Conventional care	£278,219	43.0941	12.6555	£13,743	0.0000	-0.4833	-	Dominated
Adalimumab	£286,251	43.0941	12.8766	£21,776	0.0000	-0.2622	£36,325	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

5.7.2 Clinical outcomes from the model

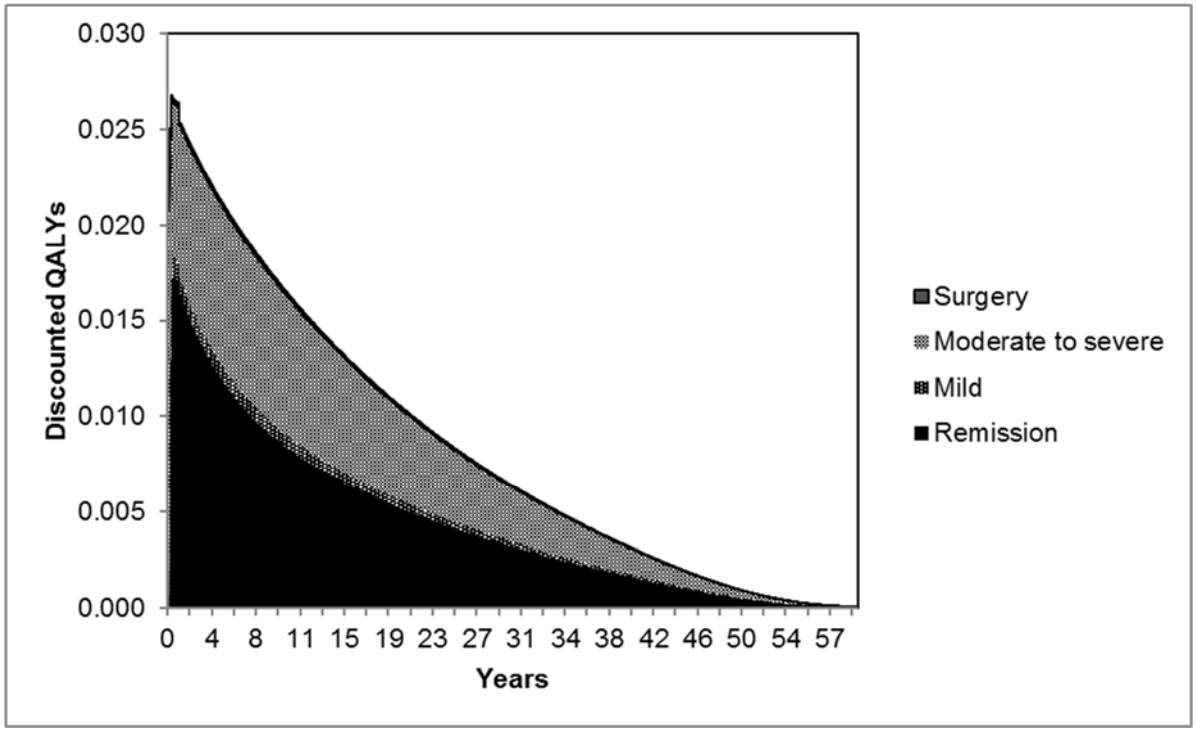
5.7.2.1 Markov trace – life years

The proportion of patients in each health state over time (Markov Trace) for all treatments are shown in Appendix 15.

5.7.2.2 Markov trace – QALYs

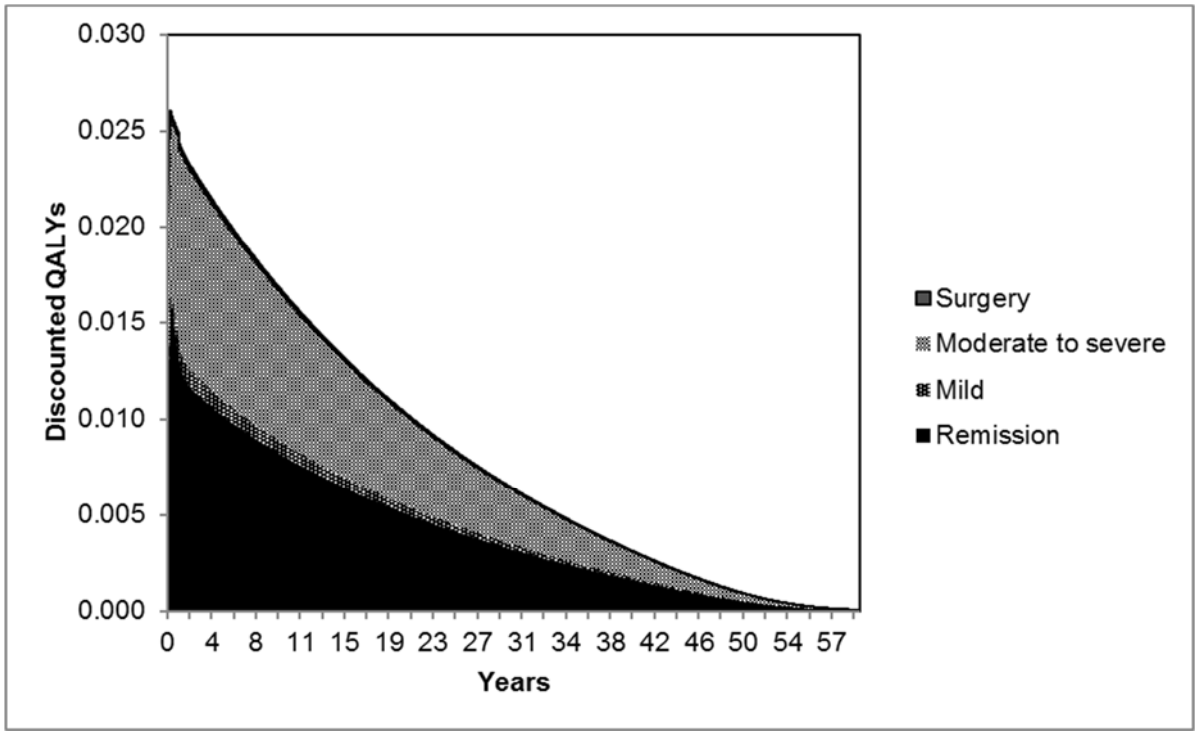
Figure 48 to Figure 53 show the split of discounted QALYs in each health state over time for the conventional care failure and TNF failure populations, respectively.

Figure 48: Markov trace QALYs: ustekinumab conventional care failure



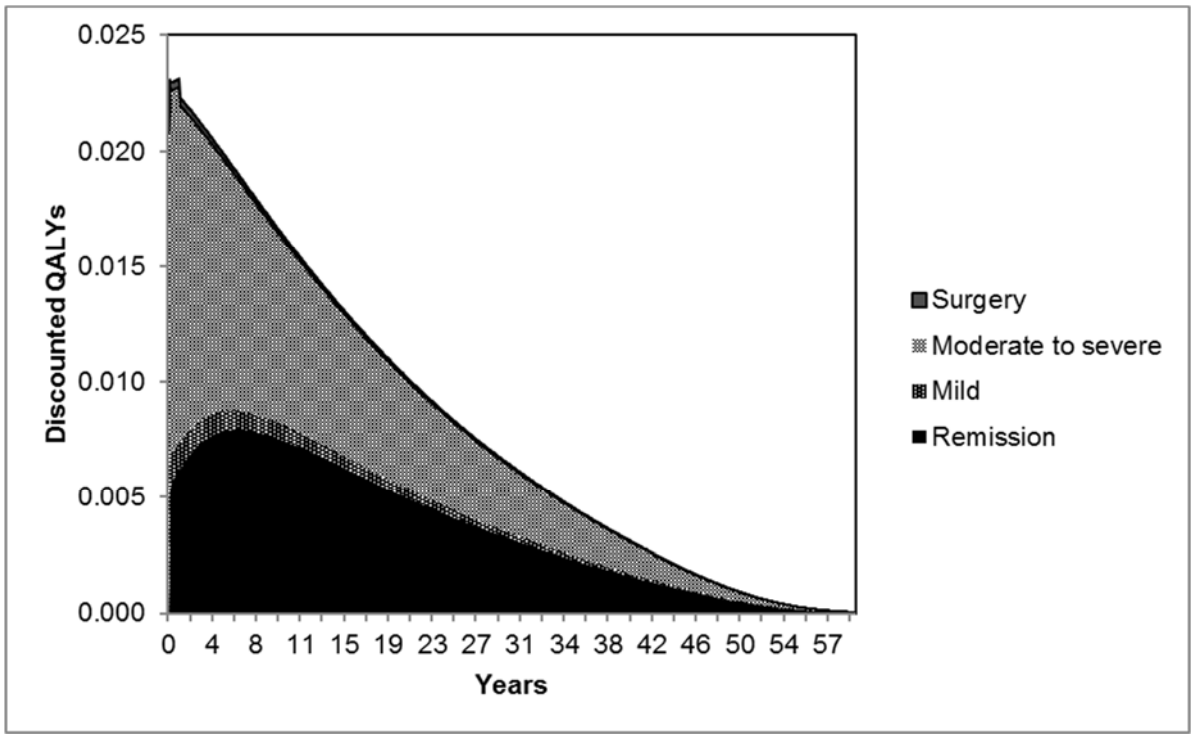
Key: QALY, quality-adjusted life year.

Figure 49: Markov trace QALYs: adalimumab conventional care failure



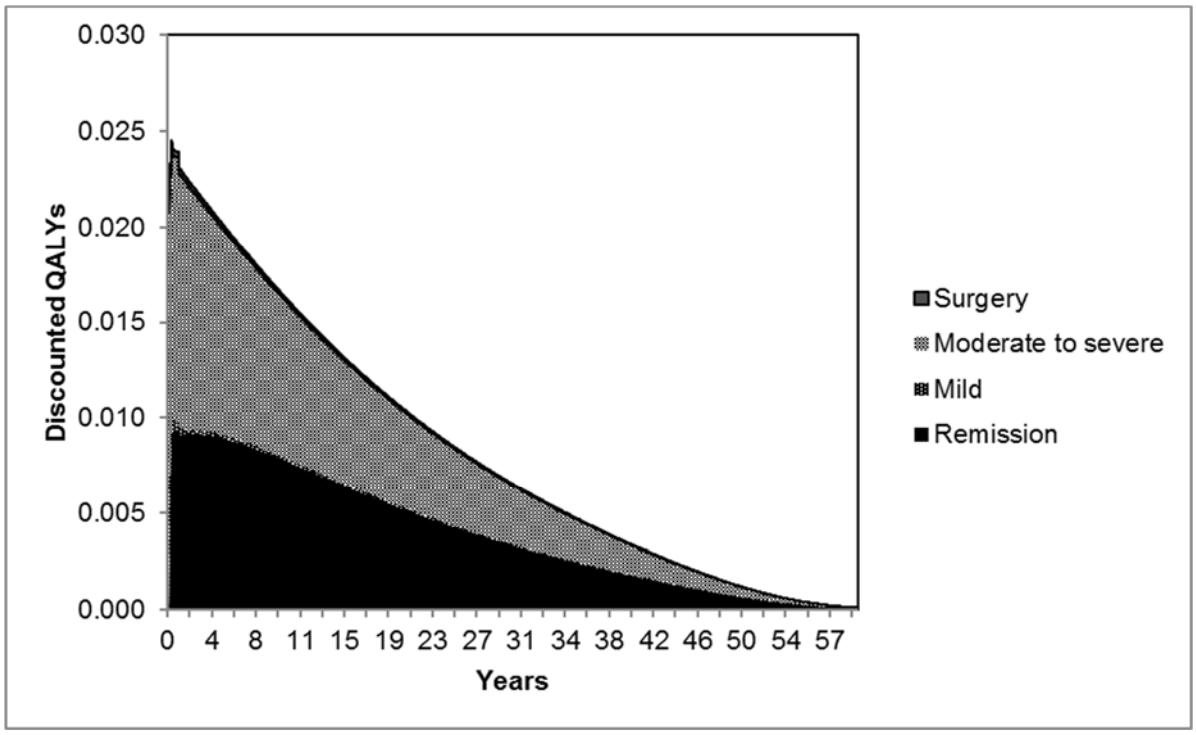
Key: QALY, quality-adjusted life year.

Figure 50: Markov trace QALYs: conventional care conventional care failure



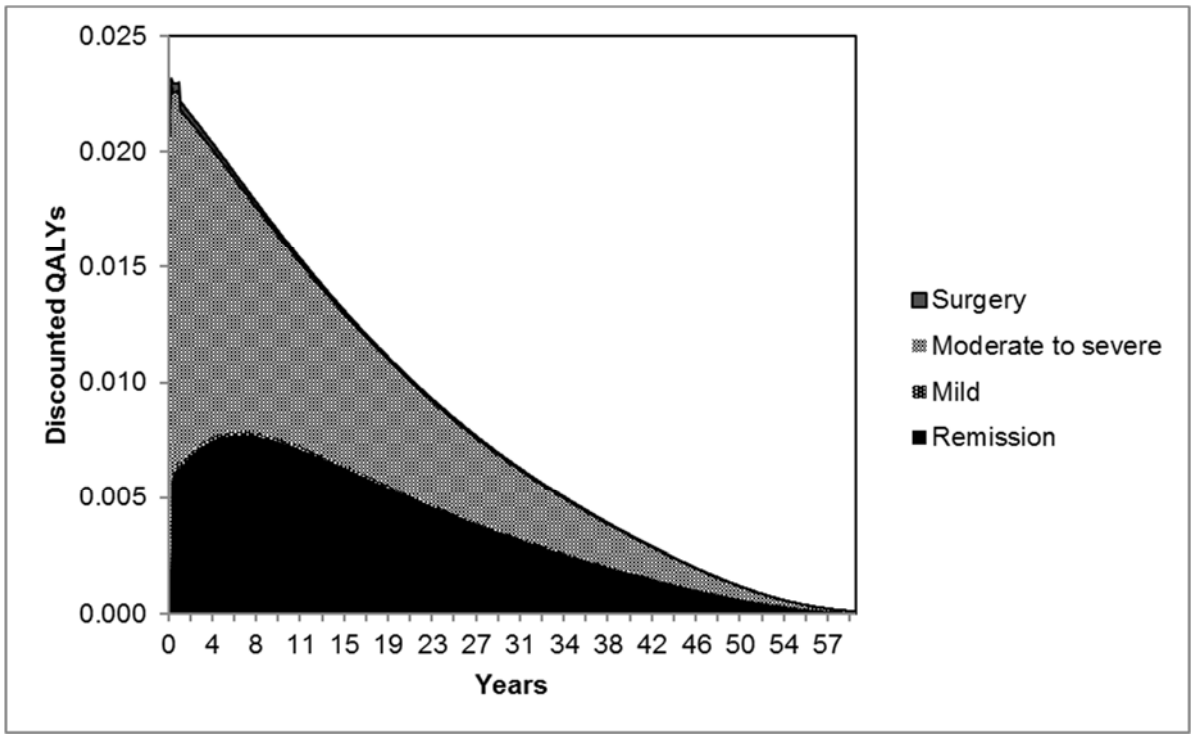
Key: QALY, quality-adjusted life year.

Figure 51: Markov trace QALYs: ustekinumab TNF failure



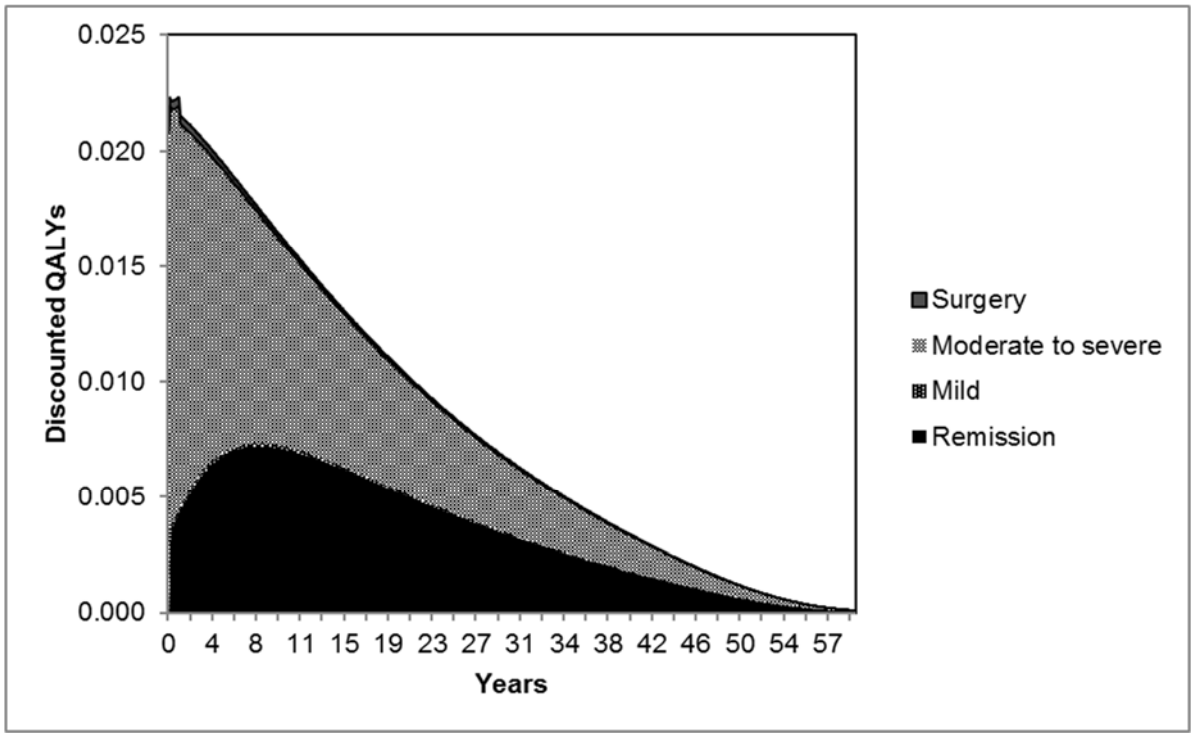
Key: QALY, quality-adjusted life year; TNF, tumour necrosis factor.

Figure 52: Markov trace QALYs: vedolizumab TNF failure



Key: QALY, quality-adjusted life year; TNF, tumour necrosis factor.

Figure 53: Markov trace QALYs: conventional care TNF failure



Key: QALY, quality-adjusted life year; TNF, tumour necrosis factor.

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 69: Ustekinumab versus conventional care – QALY gain by health state: conventional care failure population

Health state	QALY ustekinumab	QALY conventional care	Increment	Absolute increment	% absolute increment
Remission	6.8553	5.5633	1.2920	1.2920	59.16%
Mild	0.5001	0.5332	-0.0331	0.0331	1.52%
Moderate to severe	5.5663	6.4063	-0.8400	0.8400	38.46%
Surgery	0.1283	0.1472	-0.0189	0.0189	0.87%
Total	13.0501	12.6500	0.4001	2.1840	100.00%
Key: QALY, quality-adjusted life year.					

Table 70: Ustekinumab versus adalimumab – QALY gain by health state: conventional care failure population

Health state	QALY ustekinumab	QALY adalimumab	Increment	Absolute increment	% absolute increment
Remission	6.8553	6.4154	0.4399	0.4399	60.10%
Mild	0.5001	0.5018	-0.0017	0.0017	0.23%
Moderate to severe	5.5663	5.8502	-0.2838	0.2838	38.78%
Surgery	0.1283	0.1348	-0.0065	0.0065	0.89%
Total	13.0501	12.9022	0.1479	0.7319	100.00%
Key: QALY, quality-adjusted life year.					

Table 71: Ustekinumab versus conventional care – QALY gain by health state: TNF failure population

Health state	QALYs ustekinumab	QALYs conventional care	Increment	Absolute increment	% absolute increment
Remission	6.0746	5.3770	0.6977	0.6977	57.57%
Mild	0.1394	0.1191	0.0203	0.0203	1.68%
Moderate to severe	6.5873	7.0704	-0.4831	0.4831	39.86%
Surgery	0.1508	0.1616	-0.0108	0.0108	0.89%
Total	12.9521	12.7280	0.2241	1.2119	100.00%
Key: QALY, quality-adjusted life year.					

Table 72: Ustekinumab versus vedolizumab – QALY gain by health state: TNF failure population

Health state	QALYs ustekinumab	QALYs vedolizumab	Increment	Absolute increment	% absolute increment
Remission	6.0746	5.6570	0.4176	0.4176	57.07%
Mild	0.1394	0.1241	0.0153	0.0153	2.10%
Moderate to severe	6.5873	6.8795	-0.2922	0.2922	39.93%
Surgery	0.1508	0.1573	-0.0065	0.0065	0.89%
Total	12.9521	12.8179	0.1342	0.7317	100.00%
Key: QALY, quality-adjusted life year.					

Table 73: Ustekinumab versus conventional care – cost by category: conventional care failure population

Health state	Cost ustekinumab	Cost conventional care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£17,390	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£209,316	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£51,836	[redacted]	[redacted]	[redacted]
Total	£263,053	£278,542	-£15,489	£33,053	100.00%

Table 74: Ustekinumab versus adalimumab – cost by category: conventional care failure population

Health state	Cost ustekinumab	Cost adalimumab	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£27,716	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£194,020	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£62,025	[redacted]	[redacted]	[redacted]
Total	£263,053	£283,762	-£20,709	£21,443	100.00%

Table 75: Ustekinumab versus conventional care – cost by category: TNF failure population

Health state	Cost ustekinumab	Cost conventional care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£17,744	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£223,965	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£52,891	[redacted]	[redacted]	[redacted]
Total	£288,088	£294,600	-£6,512	£21,184	100.00%

Table 76: Ustekinumab versus vedolizumab – cost by category: TNF failure population

Health state	Cost ustekinumab	Cost conventional care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£29,727	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£2,190	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£218,778	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£52,124	[redacted]	[redacted]	[redacted]
Total	£288,088	£302,820	-£14,732	£14,743	100.00%

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was run on the model for both populations, using 5,000 simulations.

5.8.1.1 Tabulated results

The mean results over all the iterations were tabulated into incremental analyses for both populations. Results are given in Table 77 and Table 78 for the conventional care failure and TNF failure populations, respectively. The conclusions of the probabilistic results are similar to the deterministic results with both analyses indicating that ustekinumab is dominant against conventional care in both populations. Additionally, ustekinumab is against adalimumab in the conventional care population, and against vedolizumab in the TNF failure population.

Table 77: Probabilistic incremental analysis – conventional care failure population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Ustekinumab	£311,497	15.3543			
Conventional care	£336,148	14.9294	£24,651	-0.4249	Dominated
Adalimumab	£336,435	15.1903	£24,938	-0.1640	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Table 78: Probabilistic incremental analysis – TNF failure population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Ustekinumab	£345,941	15.5047			
Conventional care	£359,785	15.2393	£13,844	-0.2654	Dominated
Vedolizumab	£364,658	15.3525	£18,717	-0.1522	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TNF, tumour necrosis factor.					

5.8.1.2 Cost-effectiveness scatterplot

Costs and QALYs from each iteration of the PSA were plotted for all treatments. Figure 54 and Figure 55 show the results for the conventional care failure and TNF failure populations, respectively. These shown the similarities in spread of costs and QALYs for all treatment arms in the analyses.

Figure 54: Cost-effectiveness scatter plot: conventional care failure

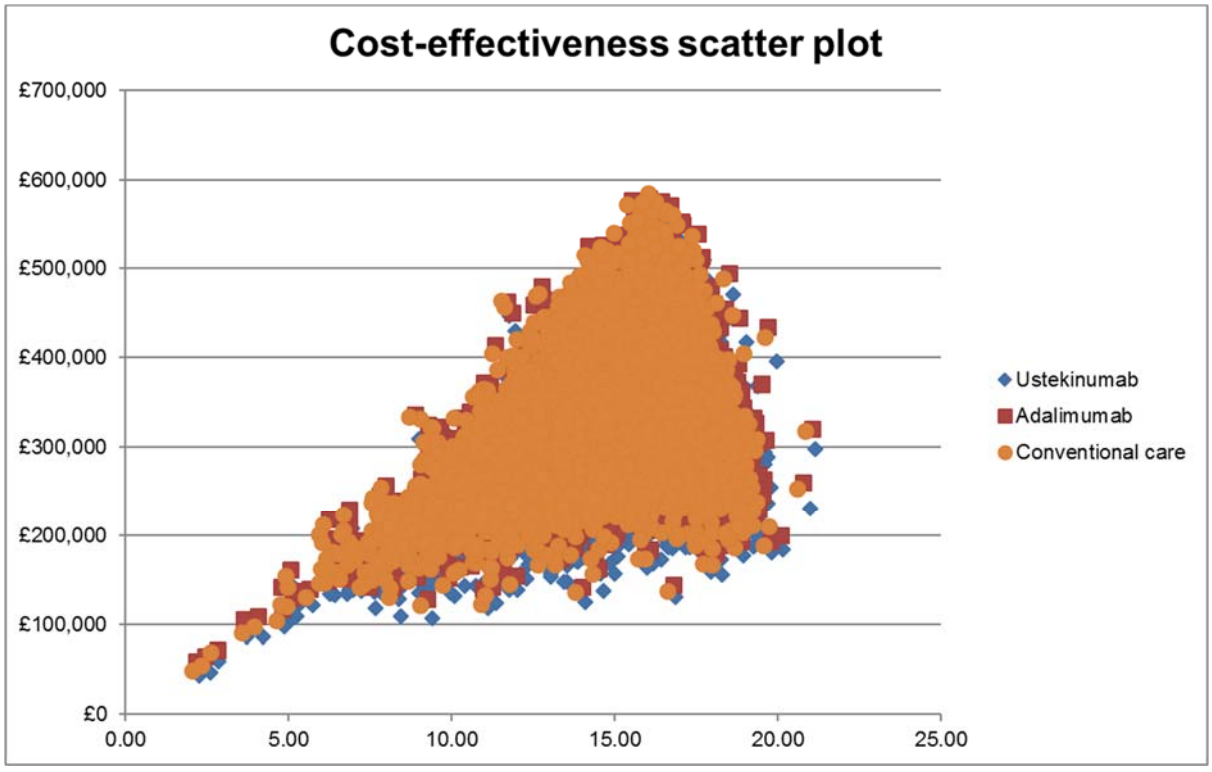
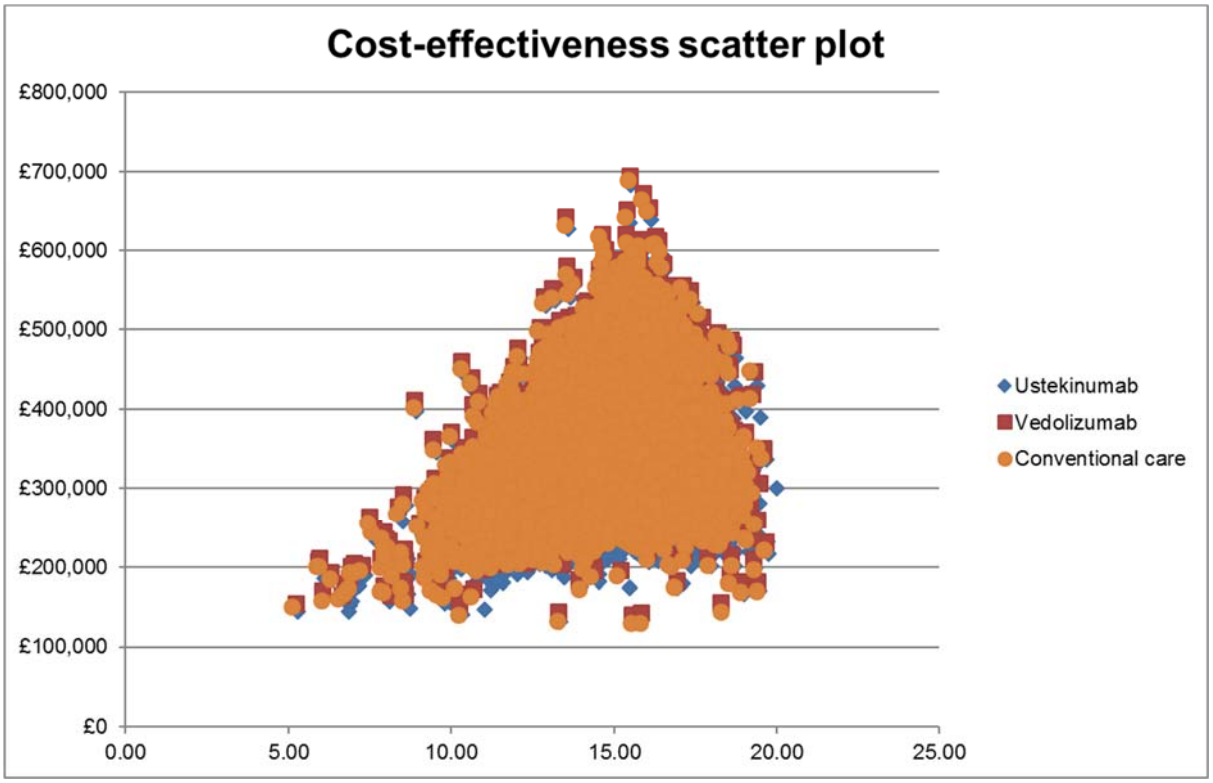


Figure 55: Cost-effectiveness scatter plot: TNF failure

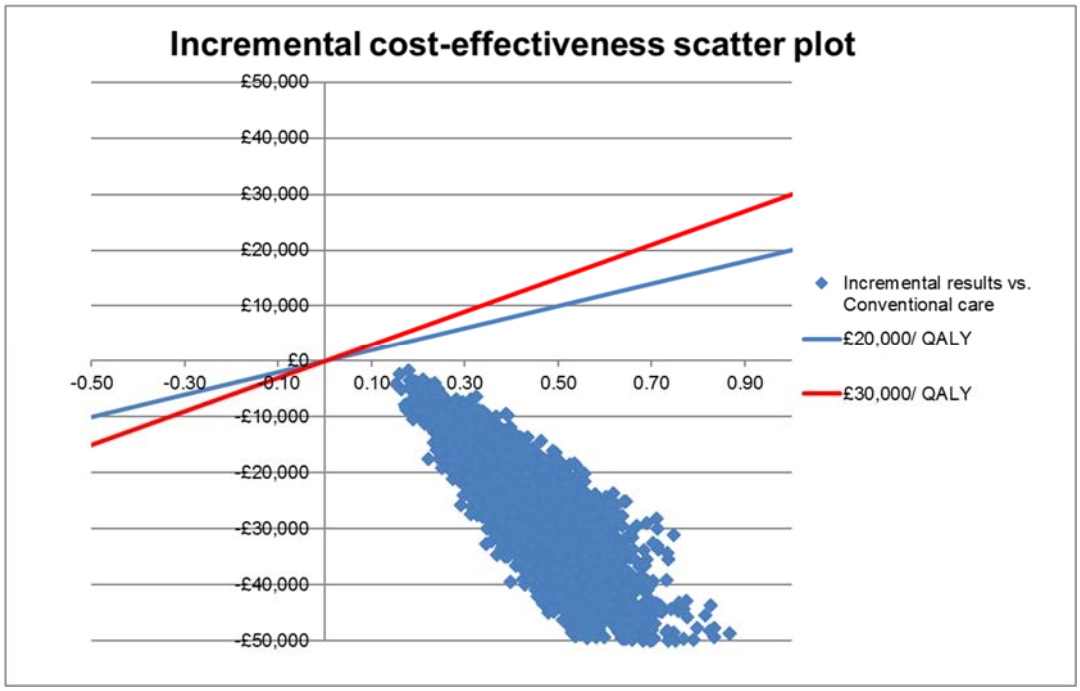


Key: TNF, tumour necrosis factor.

5.8.1.3 Pairwise cost-effectiveness scatterplot

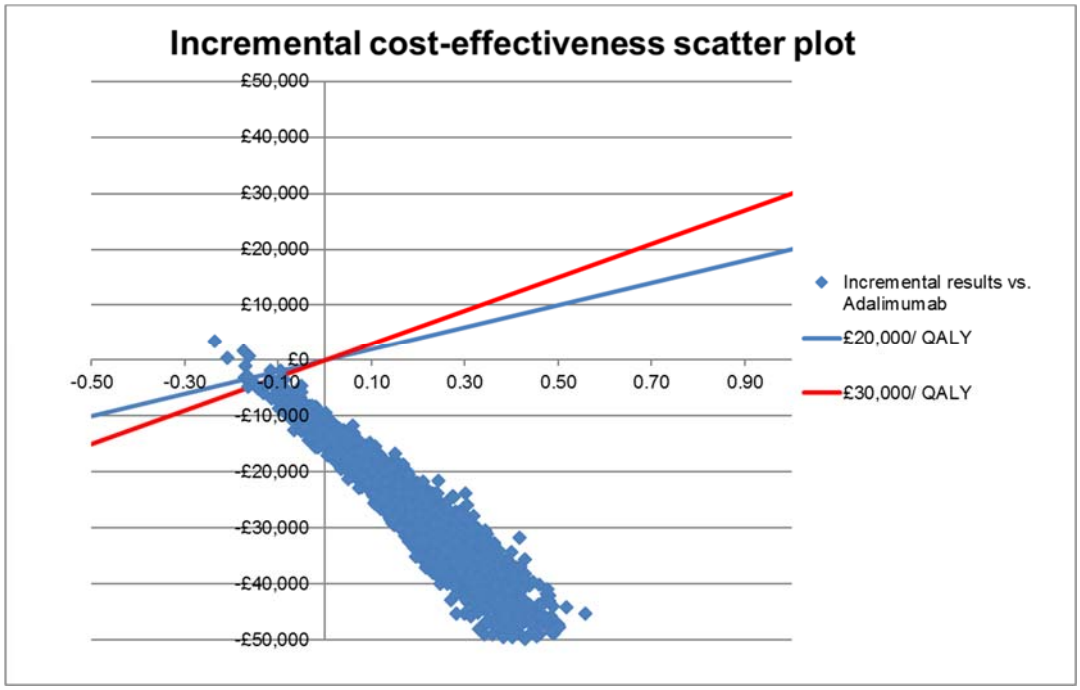
The results of each iteration were plotted on pair-wise scatter plots, showing incremental results. Figure 56 and Figure 57 show the results versus conventional care and adalimumab in the conventional care failure population, respectively. Figure 58 and Figure 59 show results in the TNF failure population versus conventional care and vedolizumab, respectively. Results indicate that for all treatments, the majority of PSA iterations result in positive incremental QALYs and negative incremental costs versus all treatments, i.e. that ustekinumab remains dominant in the majority of iterations.

Figure 56: PSA incremental scatter plot: conventional care failure population, ustekinumab versus conventional care



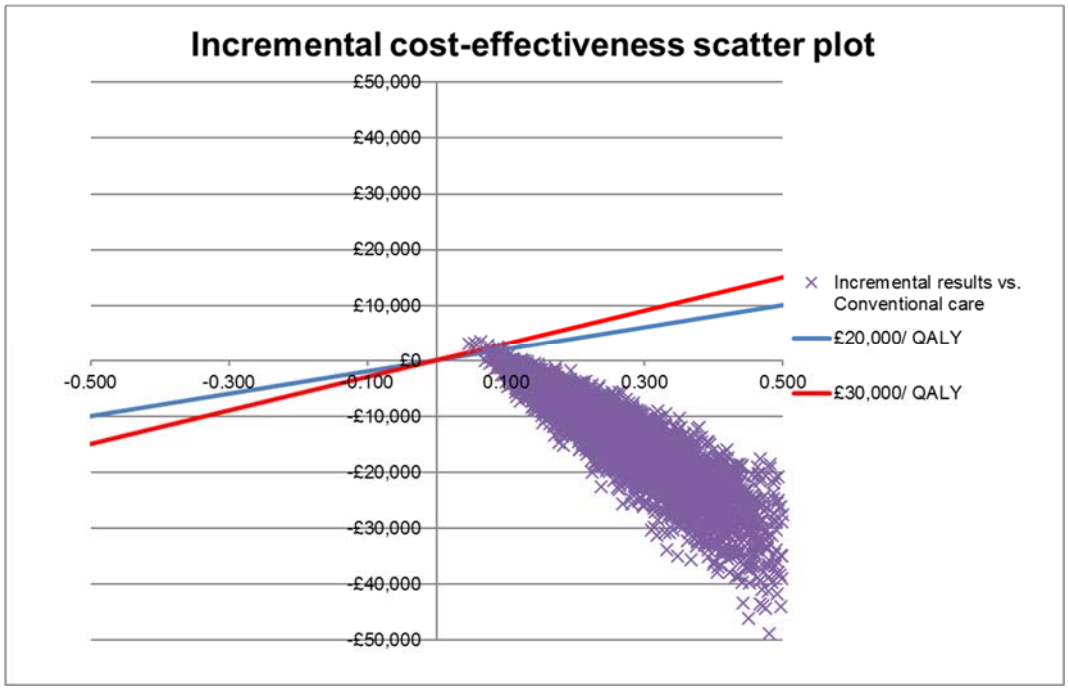
Key: PSA, probabilistic sensitivity analysis.

Figure 57: PSA incremental scatter plot: conventional care failure population, ustekinumab versus adalimumab



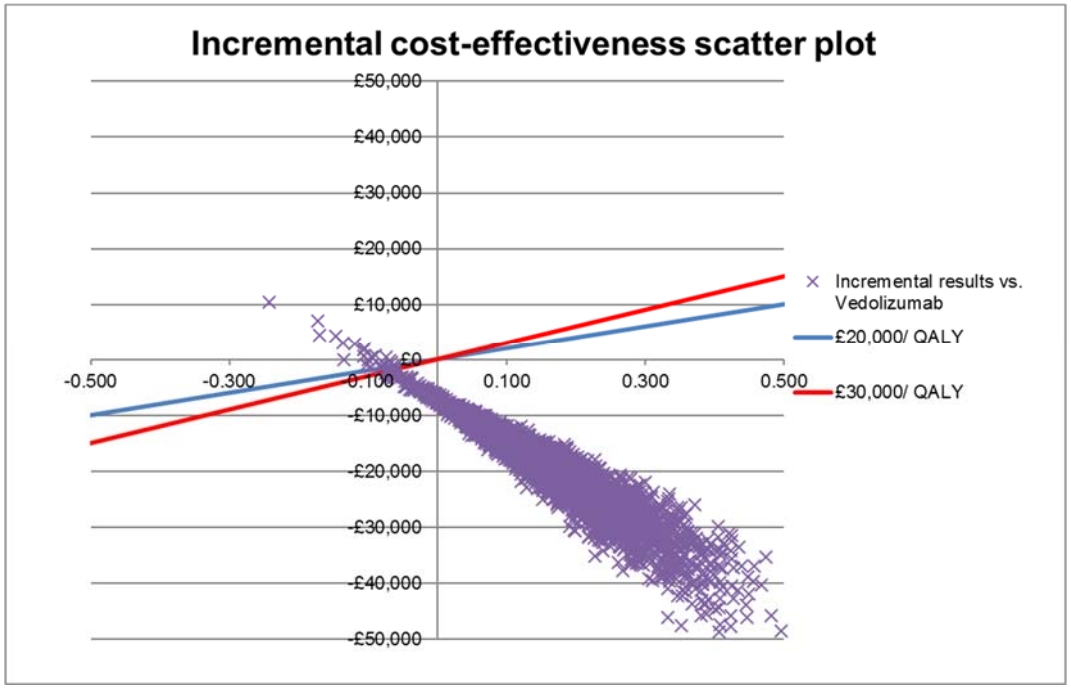
Key: PSA, probabilistic sensitivity analysis.

Figure 58: PSA incremental scatter plot: TNF failure population, ustekinumab versus conventional care



Key: PSA, probabilistic sensitivity analysis; TNF, tumour necrosis factor.

Figure 59: PSA incremental scatter plot: TNF failure population, ustekinumab versus vedolizumab



Key: PSA, probabilistic sensitivity analysis; TNF, tumour necrosis factor.

5.8.1.4 Cost-effectiveness acceptability curve

Cost-effectiveness acceptability curves (CEACs) are present in Figure 60 and Figure 61 for the conventional care failure and TNF failure populations, respectively. The results indicate that, in both populations, ustekinumab has a 100% chance of being the most cost-effective treatment available at the £30,000 WTP threshold.

Figure 60: Cost-effectiveness acceptability curve: conventional care failure

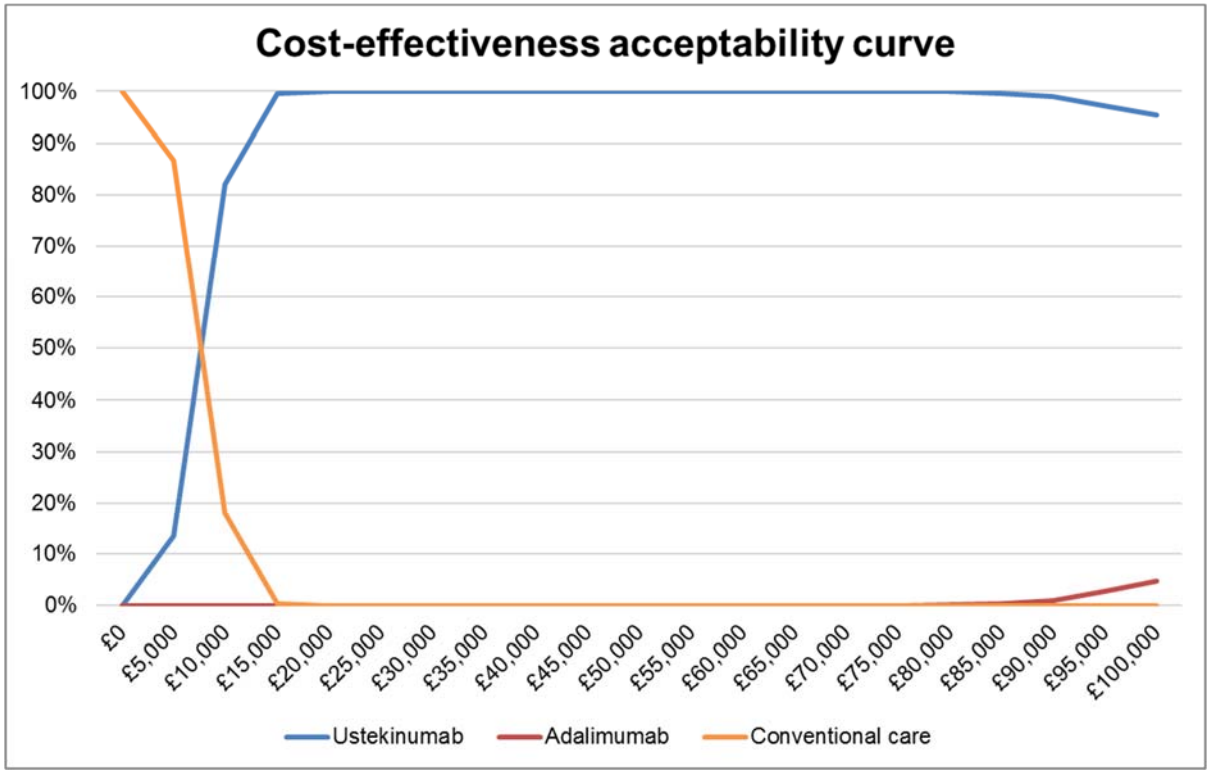
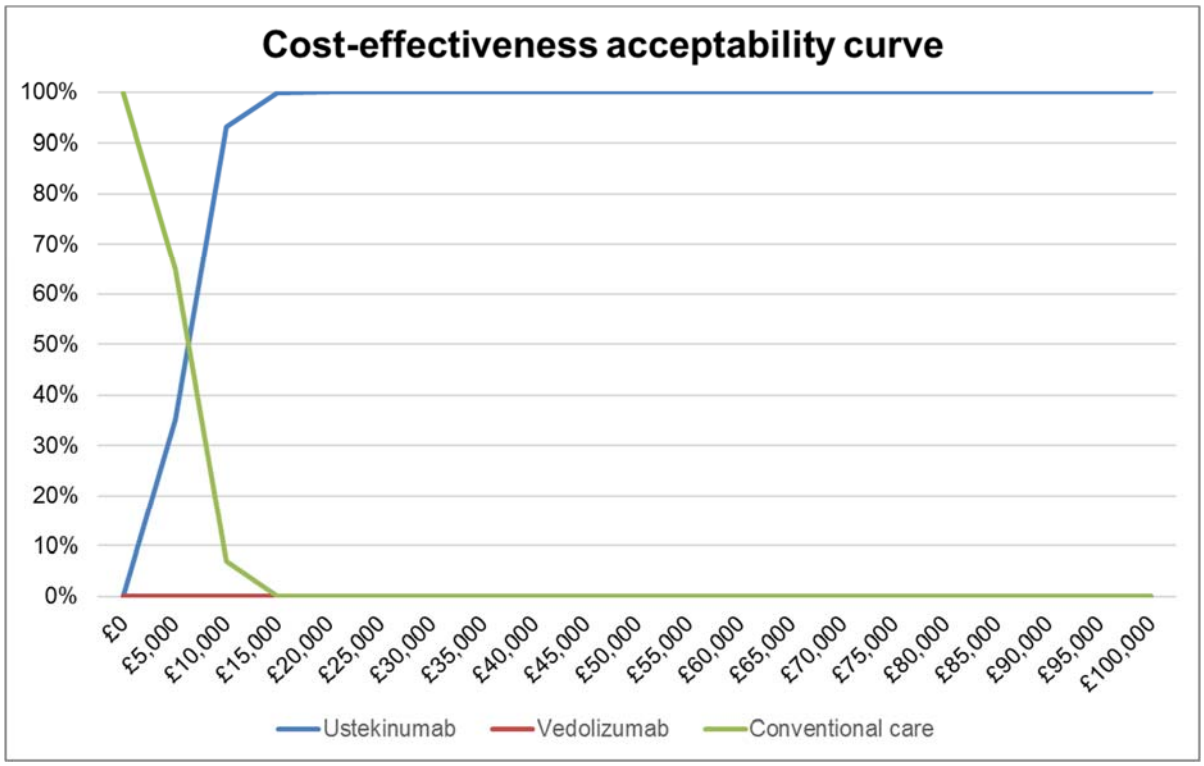


Figure 61: Cost-effectiveness acceptability curve: TNF failure



Key: TNF, tumour necrosis factor.

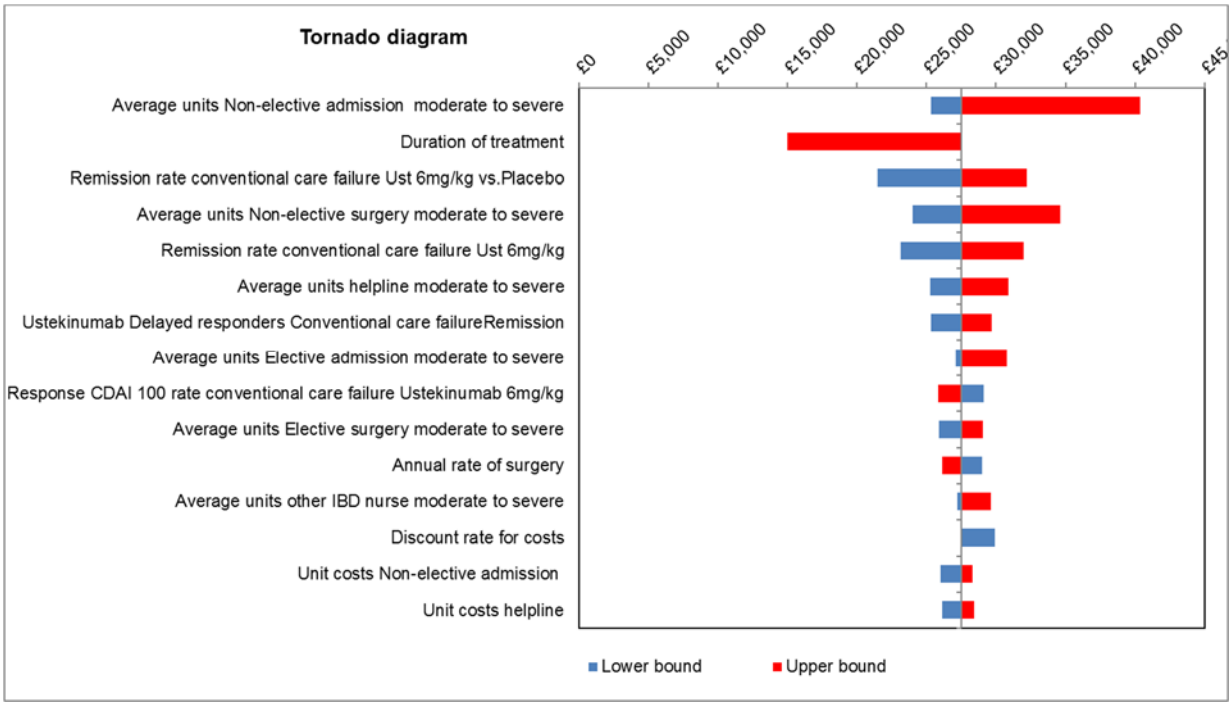
5.8.2 Deterministic sensitivity analysis

In a one-way sensitivity analysis (OWSA), variables were replaced with their upper or lower bounds. The model was then run with these values. Due to relatively small QALY gains between treatments, testing upper and lower bounds may result in ICERs moving between quadrants of the cost-effectiveness plane and can therefore be difficult to interpret. Therefore, OWSA results are shown in terms of net monetary benefit (NMB) using a WTP threshold of £30,000 as the NMB is easier to interpret where small QALY gains are concerned (NMB > £0 indicates cost-effectiveness at the specified threshold). The variables that had the biggest impact on NMB were plotted on tornado diagrams. Figure 62 and Figure 64 show the results for the conventional care failure and TNF failure populations, respectively. The results indicate that duration of biologic treatment, several resource use frequencies for the moderate to severe health state, and induction efficacy have large effects on the NMB for both populations. Figure 63 and Figure 65 show results versus adalimumab and vedolizumab in their respective populations. The results indicate that induction efficacy and resource use units for the moderate to severe health state have an

impact on both comparisons, however duration of treatment has the largest impact on NMB versus adalimumab. The results demonstrate that the NMB remains above zero (and hence ustekinumab remains cost-effective) under extreme values of all parameters, for all treatments. Influential parameters versus biologics are in line with the findings of the economic evaluation SLR (see Section 5.1.2.1)

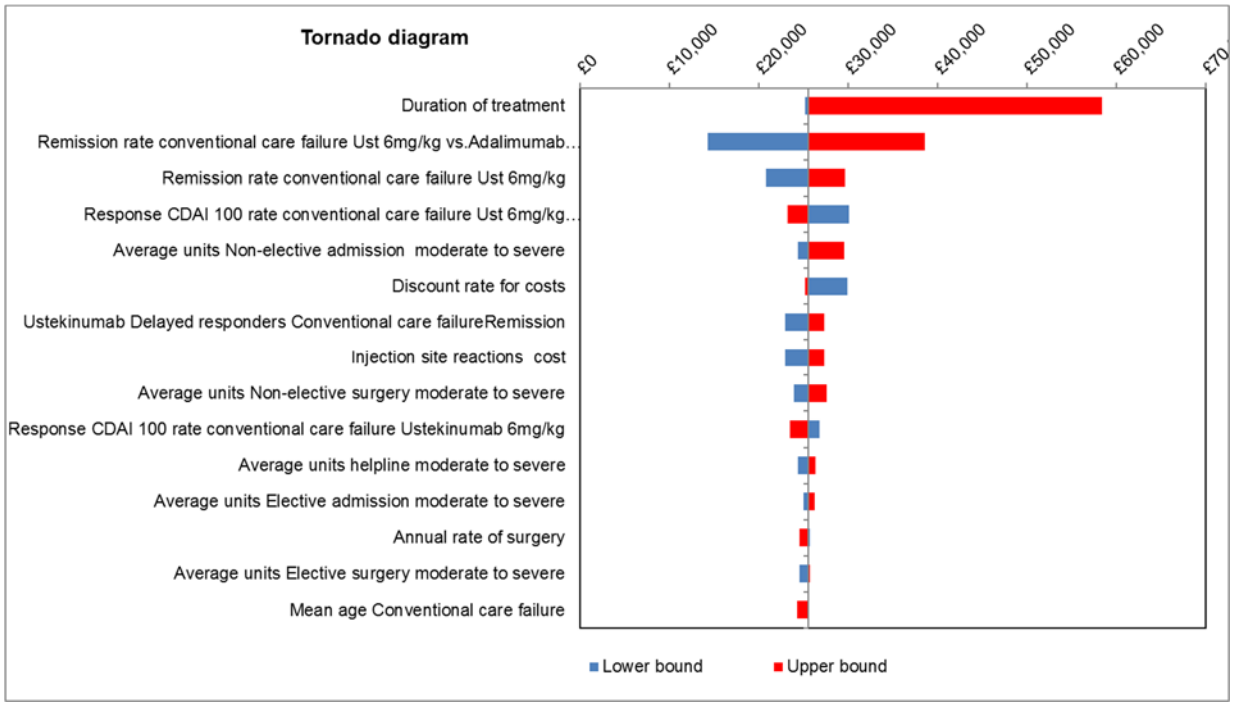
It is noted that for duration of treatment the lower bound is equal to the base case value.

Figure 62: Tornado diagram versus conventional care: conventional care failure population (base case NMB = £27,531)



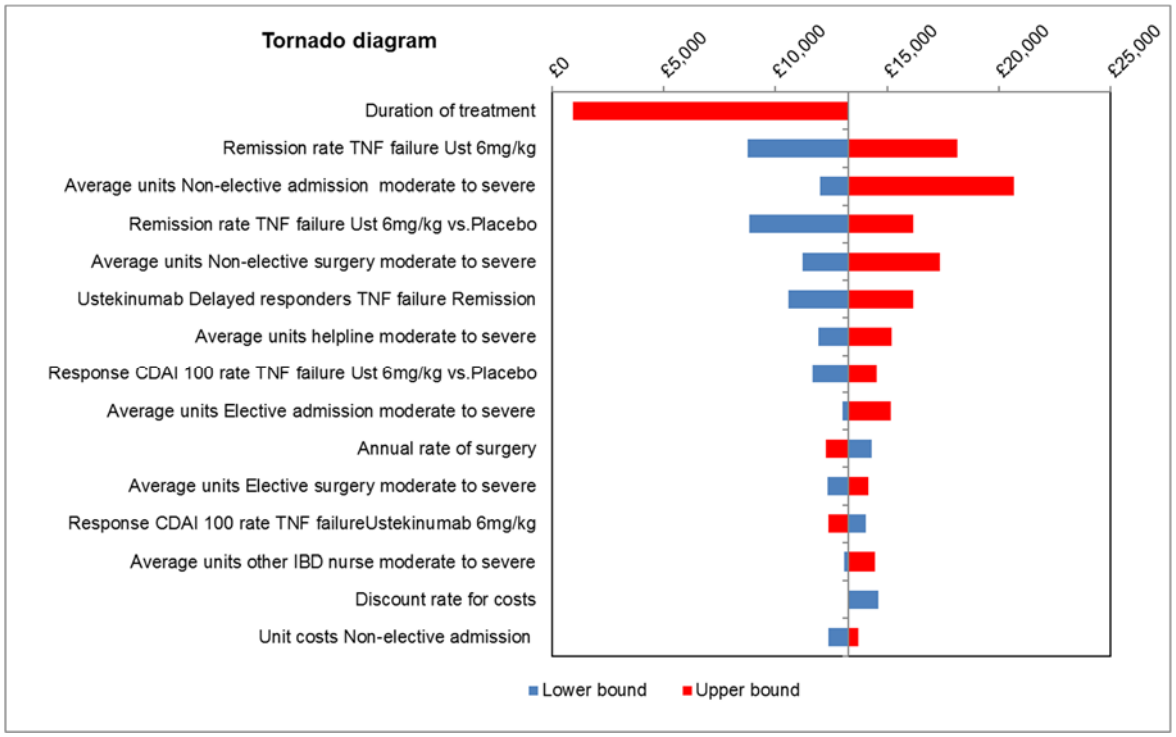
Key: IBD, inflammatory bowel disease; ust, ustekinumab.

Figure 63: Tornado diagram versus adalimumab: conventional care failure population (base case NMB = £25,557)



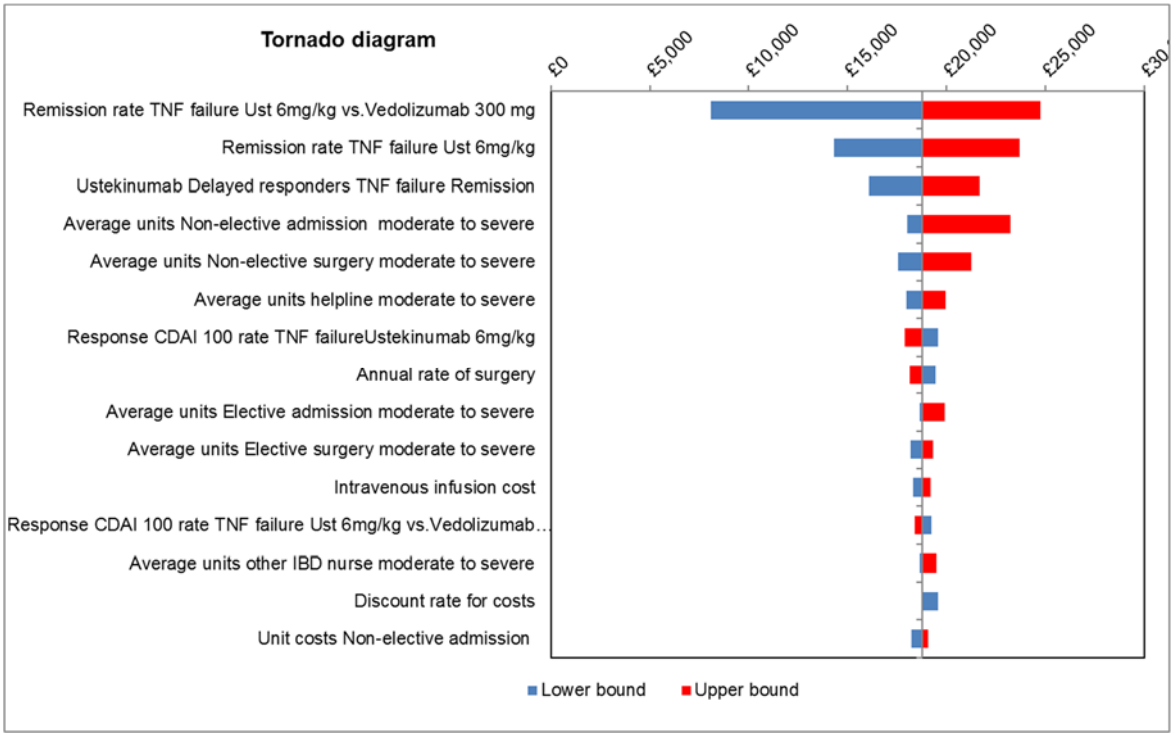
Key: IBD, inflammatory bowel disease; q8w, every 8 weeks; q812, every 12 weeks; ust, ustekinumab.

Figure 64: Tornado diagram versus conventional care: TNF failure population (base case NMB = £13,262)



Key: IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ust, ustekinumab.

Figure 65: Tornado diagram versus vedolizumab: TNF failure population (base case NMB = £18,765)



Key: IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ust, ustekinumab.

5.8.3 Scenario analysis

Many scenarios were tested within the model. The full list is presented in Table 79:

Table 79: Scenario analyses

	Scenario	Base case setting	Scenario setting	Justification
1	Base case	N/A	N/A	N/A
2	10-year time horizon	60 year time horizon	10-year time horizon	To explore the impact of alternative time horizons on the model results. 10-year time horizon was base case in TA352.
3	1-year time horizon		1-year time horizon	
4	2-year treatment duration	1-year treatment duration	2-year treatment duration	The duration of treatment is uncertain; data are available for comparison with other biologic treatments for 1 year of treatment. These scenarios explore the impact of extending the treatment duration.
5	3-year treatment duration		3-year treatment duration	

				IBD audit 2015 confirms that in practice patients may remain on biologic treatment beyond 1-year
6	No half cycle correction	Half-cycle correction applied	No half-cycle correction applied	To verify that this does not impact results given the short cycle-length used in the model.
7	Alternative utility source: IMUNITI SF-36	Utility source: IMUNITI IBDQ	Utility source: IMUNITI SF-36	To explore the impact of alternative utility values on the results of the analysis.
8	Alternative utility source: IMUNITI CDAI		Utility source: IMUNITI CDAI	
9	Alternative utility source: Bodger *et al.*		Utility source: Bodger *et al.*	
10	Response criteria: CDAI-70	Response criteria: CDAI-100	Response criteria: CDAI-70	Previous trials defined response using CDAI-70. This analysis explores the impact of assessing initial response to treatment based on CDAI-70.
11	Alternative source for resource use costs: TA352 resource use costs – original	Delphi panel resource use estimates used to derive costs.	Costs used in the original manufacturer's submission for TA352	Resource use costs were identified as a key driver of results. This explores the impact of using costs aligned with the most recent Crohn's disease NICE TA.
12	Alternative source for resource use costs: TA352 resource use costs – ACD responses		Costs used in the manufacturer's ACD response for TA352	
13	Ustekinumab dosing all q12w at start of maintenance phase	Ustekinumab dosing split between q12w and q8w at the start of maintenance based on clinician interpretation of the label	Ustekinumab dosing 100% q12w at the start of maintenance	The label for ustekinumab allows clinicians to use their judgement for dosing of ustekinumab. These scenarios explore the impact of the extreme situations.
14	Ustekinumab dosing all q8w at start of maintenance phase		Ustekinumab dosing 100% q8w at the start of maintenance	
15	No gradual decline in	Gradual decline in efficacy is	No gradual decline in efficacy is	The true impact on efficacy of biologic

	efficacy post-biologic maintenance phase	assumed following the end of the biologic maintenance phase	assumed following the end of the biologic maintenance phase	treatments following discontinuation at the end of maintenance is uncertain, this reflects the extreme and conservative scenario in which efficacy is lost immediately following cessation of treatment.
16	No dose escalation	Dose escalation is included	No dose escalation is included	To explore the impact of dose escalation on results.
17	Alternative maintenance data source: IMUNITI data	Maintenance data source: NMA transitions (calibrated)	Maintenance data source: IMUNITI transitions	To explore the impact of allowing transition probabilities to vary over time using data observed from the IMUNITI study. It is noted that this assumes that all biologic treatments have equal efficacy during maintenance which is a conservative assumption which is not in line with the results of the treatment sequence NMA.
18	AEs not included	AEs included	AEs not included	To explore the impact of AEs on the results of the analysis.
19	Adalimumab lower induction dose	Adalimumab induction dose 160/80	Adalimumab induction dose 80/40	To explore the impact of assuming the lower dose of adalimumab. It is noted that treatment sequence outcomes are only available for the 160/80 induction dose, and so the calibrated transition probabilities for the 80/40 induction dose assume the same treatment sequence outcome as for the 160/80 dose and therefore the efficacy of the 80/40 treatment sequence is likely to be over-estimated.
20	Ustekinumab induction efficacy lower bound	Ustekinumab induction efficacy (responders and	Ustekinumab induction efficacy (responders and	To explore the impact of assuming lower efficacy for ustekinumab during induction.

		remitters) based on mean	remitters) based on lower bound	
21	Disutility study included	Disutility study results used for disutilities associated with AEs and surgical complications	Disutilities due to AEs in line with TA352; no disutilities due to surgical complications	To explore the impact of an alternative source for disutilities due to AEs and the inclusion of disutilities due to surgical complications
Key: ACD, Appraisal Consultation document; AE, adverse event; CDAI, Crohn's Disease Activity Index; N/A, not applicable; q8w, every 8 weeks; q12w, every 12 weeks; SF-36; Short-form 36; TA, technology appraisal.				

Most scenarios tested did not affect the incremental cost-effectiveness decision. A few scenarios did affect the decision in both populations. A 1-year time horizon gave ICERs vs. conventional care of £55,376 and £121,408 in the conventional care failure and TNF failure populations, respectively. This is not considered to be a meaningful scenario given the chronic nature of Crohn's disease.

Using the original health state costs from TA352 gave ICERS for ustekinumab versus conventional care of £4,433 and £14,001 for the conventional care failure and TNF failure populations, respectively. Whilst ustekinumab is no longer dominant under this scenario, it remains the cost-effective treatment at a WTP threshold of £30,000 per QALY gained.

Use of a 2-year and 3-year treatment duration did not affect the decision for the conventional care population, but gave ICERs versus conventional care of £440 and £25,459, respectively, for the TNF failure population. Whilst ustekinumab is no longer dominant under this scenario, it remains the cost-effective treatment at a WTP threshold of £30,000 per QALY gained.

Using IM-UNITI transition probabilities gave ICERs for ustekinumab versus conventional care of £56,516 and £59,956 for the same populations, respectively. This scenario should be interpreted with extreme caution; as noted earlier IM-UNITI placebo arm, which portrays conventional care in this scenario, is not a true placebo arm as patients had previously received and responded to ustekinumab in the induction phase and were then randomised to placebo in the maintenance phase. The effect of ustekinumab induction coupled with longer half-life could potentially explain a smaller difference in efficacy between ustekinumab and conventional care which can be reflected in the increased ICERs.

The full results of each scenario are shown in Appendix 16.

5.8.3.1 Summary of sensitivity analyses results

The results of probabilistic and deterministic sensitivity analysis, and of pre-defined scenario testing demonstrate that ustekinumab remains dominant over comparator treatments in a range of scenarios. There are few circumstances in which the incremental result is changed.

5.8.3.2 Cost-minimisation

The results from the sensitivity indicate that a cost-minimisation approach may be more appropriate, as the ICER is subject to large differences due to the small QALY gains in the base case results. Ustekinumab is a cost-saving treatment option compared with all comparators.

A cost-minimisation analysis was conducted, using only the acquisition and administration costs of each biologic treatment (derived directly from the cost-effectiveness model). Costs of health states and adverse events were excluded as under a cost-minimisation analysis, the biologic treatments are assumed to have equal efficacy and comparable safety profiles. Conventional care has been excluded from this analysis as it is not reasonable to assume that biologic treatments and conventional care have equal efficacy.

The results of the cost-minimisation analysis in Table 80 and Table 81 indicate that ustekinumab is cost-saving versus other biologic treatments for the Conventional care failure and TNF failure populations, respectively.

Table 80: Cost-minimisation analysis: Conventional care failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
Ustekinumab	[redacted]	£367	[redacted]	
Adalimumab	£13,486	£0	£13,486	[redacted]

Table 81: Cost-minimisation analysis: TNF failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
Ustekinumab	£10,278	£367	£10,645	
Vedolizumab	£20,307	£5,138	£25,445	£14,800

The difference between treatment acquisition cost in conventional care failure and TNF failure population is due a high use of dosing every 8 weeks in TNF population as patients are at a more advanced stage of disease.

5.9 Subgroup analysis

No further subgroup analysis is presented in the submission as results are split for TNF failure and conventional care failure in the base-case results.

5.10 Validation

5.10.1 Validation of *de novo* cost-effectiveness analysis

Several amendments were made to the model based on ERG feedback from TA325. Criticisms of the model from the ERG included the list shown in Table 82, in addition to a description of the efforts made to improve upon these.

Table 82: ERG comments from TA352

ERG comment	Actions taken	Section
Patients on conventional care in the moderate to severe health state were not allowed to move to other health states in the maintenance phase – this was deemed to be overly pessimistic.	Patients allowed to make this transition.	Section 5.3.3
Surgery modelled as a single health state was considered simplistic as the probability of repeat surgery is likely to be dependent on previous surgeries. Additionally, it was felt that patients undergoing resection should be	A model version was tested in which two post-surgical health states, 'post-surgical remission' and 'post-surgical complications' were included in the model. This gave non-intuitive results and the previous structure was used.	Section 5.3.4

ERG comment	Actions taken	Section
distinguished from patients undergoing ileostomy.	Surgery costs are formulated using results from a modified Delphi panel in which different surgery types are considered based on cost, probability and requirement for resource use.	
The same induction length (8 weeks) was used for all treatments, which was not in line with the induction lengths within the relevant clinical trials.	Differential induction length used via 2-week cycle length.	Section 5.2.2
It was assumed that non-responders in the induction phase would begin the maintenance phase in the moderate to severe state.	Not possible to change this within the model structure. Structure requires fitting of two data points, 'response' and 'response' to 3 Markov-based health states.	Section 5.2.3
The ERG recognised the need to calibrate some inputs for efficacy due to the model structure; however, it felt that unjustifiable assumptions were made.	Efforts made to improve upon the calibration method used in TA352. Namely, additional parameters for Solver and same starting matrix for biologics and conventional care.	Section 5.3.3.1
It was assumed that all patients stopped treatment at 1 year, which the ERG did not feel certainty over.	Different treatment lengths tested in scenario analysis.	Section 5.8.3
The ERG stated that discontinuation due to lack of efficacy should be included within the maintenance phase of the model.	Included within maintenance phase.	Section 5.3.3.3
Within the maintenance phase placebo efficacy was calculated from all placebo patients, which included patients on active treatment in the induction phase.	Within the clinical trials, patients are only included in the maintenance if they have responded during the induction. Therefore, patients who receive placebo in the induction and maintenance ('placebo-placebo' patients) represent a subset of patients pre-disposed to respond to conventional care. Given this, patients who received ustekinumab in the induction and placebo in the maintenance were considered more reflective of the general patient population, but it is acknowledged that there are no data available for a "true" placebo treatment arm (a population of patients that received placebo induction and maintenance irrespective of response status).	Section 5.3.3.2
Key: ERG, evidence review group.		

5.10.2 Expert validation

An advisory board was held in July 2016 with three health economic experts and a leading clinician to assess model inputs and structure. The experts broadly agreed that the modelling approach was appropriate, and in particular suggested the inclusion of a gradual decline in efficacy post completion of maintenance treatment with biologics and of a second induction dose for delayed responders to biologic therapy where this is indicated in the SPC.[191]

The wording of the dosing was modified at CHMP opinion and expert clinical opinion was sought to understand how the license would be interpreted by UK clinicians. This was used to inform the percentage of patients commencing maintenance treatment on q12w and q8w dosing.

5.10.3 Quality control

The model was quality checked multiple times through internal processes at the company that built the economic model. A modeller who had not been involved in the model construction reviewed the model for coding errors or inconsistencies.

5.10.4 Comparison to trial data

Outcomes from the model at one year were compared against the outcomes predicted by the treatment sequence NMA at one year. The distribution of patients across the health states predicted by the NMA was calculated using the proportion of patients in remission and with response to treatment from the NMA and the proportion of moderate to severe responders as described in Section 5.3.2. To enable a fair comparison with the outcomes of the NMA, the following settings were changed from the model base case:

- Delayed responders were not considered as the induction and maintenance trials informing the treatment sequence NMA did not consider the impact of delayed responders to treatment
- The rate of surgery was set of 0% as the NMA did not predict the impact of surgery on the distribution of patients across the health states
- Dose-escalation was not considered for all treatments and maintenance doses were considered as separate treatment arms as the treatment

sequence NMA considered the efficacy of individual maintenance treatment regimens.

The results of this comparison are presented in Table 83.

Table 83: Comparison of model and treatment sequence NMA at 1 year

		NMA			Model		
Induction	**Maintenance**	**Remission**	**Mild**	**Moderate - Severe**	**Remission**	**Mild**	**Moderate - Severe**
Conventional care failure							
Ustekinumab 6mg/kg	Ustekinumab q12w	36.7%	[redacted]	[redacted]	34.7%	[redacted]	[redacted]
Ustekinumab 6mg/kg	Ustekinumab q8w	40.0%	[redacted]	[redacted]	37.5%	[redacted]	[redacted]
Adalimumab 160/80	Adalimumab eow	31.4%	[redacted]	[redacted]	32.7%	[redacted]	[redacted]
Adalimumab 160/80	Adalimumab weekly	36.5%	[redacted]	[redacted]	37.6%	[redacted]	[redacted]
Placebo	Placebo-placebo	18.0%	[redacted]	[redacted]	18.0%	[redacted]	[redacted]
TNF failure							
Ustekinumab 6mg/kg	Ustekinumab q12w	17.0%	[redacted]	[redacted]	17.3%	[redacted]	[redacted]
Ustekinumab 6mg/kg	Ustekinumab q8w	17.8%	[redacted]	[redacted]	17.7%	[redacted]	[redacted]
Vedolizumab 300	Vedolizumab q8w	13.2%	[redacted]	[redacted]	13.7%	[redacted]	[redacted]
Vedolizumab 300	Vedolizumab q4w	13.2%	[redacted]	[redacted]	13.0%	[redacted]	[redacted]
Placebo	Placebo-placebo	11.0%	[redacted]	[redacted]	11.0%	[redacted]	[redacted]

Key: eow, every other week; NMA, network meta-analysis; q4w, every 4 weeks, q8w, every 8 weeks; q12w, every 12 weeks.

This demonstrates that when the model is set to be comparable to the treatment sequence NMA, the model predicts the outcomes of the NMA very closely. In the conventional care population, the modelled proportion of patients in remission for ustekinumab (both doses) is lower than the proportion predicted by the NMA,

whereas for adalimumab the trend is in the opposite direction, therefore the modelled outcomes may be conservative against ustekinumab. Despite this, ustekinumab dominates adalimumab. In the TNF failure population, the model predicts a slightly higher proportion of patients in remission than the NMA for both ustekinumab and vedolizumab.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Comparison with previous modelling

The model structure is based on Bodger *et al*., used in TA187 and TA352, for which the ERG in TA352 was largely satisfied.[1, 2, 177] Where the ERG expressed concerns with the submission in TA352, efforts have been made to improve upon these.

Firstly, a relative risk of mortality, whereby patients in more severe health states were assumed to have worse mortality outcomes, was criticised by the ERG as this assumption leads to the conclusion that biologics have better survival prospects than patients on conventional care. However, the study this assumption was based on, Lichtenstein *et al*., found there was no difference between treatments in terms of mortality.[71] For this reason, the cost-effectiveness model for ustekinumab assumes no differential mortality between health states, thus presenting a more conservative assumption in the comparison versus conventional care.

Efforts were made to improve upon the methods used to calculate resource use in TA352 as resource use was one of the key drivers of the model.[3] TA352 initially included health state resource use costs from Bodger *et al*., which were initially calculated in 2000/1, and are therefore not likely to be relevant to current NHS practice. [12] Following the initial submission, the manufacturer conducted a survey with seven UK clinicians and one nurse via telephone interviews to gain updated resource use estimates. For this submission, we aimed to improve upon this by conducting a modified Delphi panel approach including 12 clinicians and nurses from centres around the UK. Clinicians and nurses were selected with the aim to provide a reflective geographical spread of the UK. The inclusion of nurses aimed to provide a different perspective from that of the clinicians. The process was run iteratively, whereby the first stage was to hold individual telephone interviews for a full list of potential resource uses for Crohn's patients. Following this, at a face-to-face

meeting, the same participants were asked to estimate the frequency of resource use individually, after which the group's responses were compared, and any areas of disagreement were discussed until a single answer was agreed upon. Participants unable to attend the face-to-face meeting had individual follow-up telephone interviews, in which they were able to view the group's responses and add to the range of credible values if they disagreed. Generally, however, at this stage, participants were largely satisfied with the responses of the group.

Within TA352, AEs were selected based upon clinical opinion. The same approach was used for this submission. The ERG criticised the methodology used in TA352 as it did not for trial length when calculating rates of adverse events.[14] Therefore, in this submission, we have adjusted for trial length in its estimation by calculating individual cycle rates for each study. For treatments with more than one trial, a weighted average of rates was calculated taking patient numbers into account.

The methods used to gain disutility values within TA352 were criticised by the ERG as these was taken from published literature not related to Crohn's disease, assuming the disutility was taken away from one, i.e. perfect health.[14] As an alternative to this method, a disutility study was undertaken in which vignettes were given to members of the general population to estimate the impact of each adverse event relative to a baseline health state of moderate to severe Crohn's disease. This method is tested as a scenario analysis.

Finally, a range of methods were used for estimating EQ-5D utilities from ustekinumab trial data to meet the NICE reference case. The chosen method, mapping from IBDQ, had the greatest correlation with EQ-5D, and had values that were consistent with published values from Bodger *et al*., as shown in Table 84.[1]

Table 84: Comparison of health state values

Health state	IBDQ to EQ-5D	Bodger *et al*. utility
Remission	0.80	0.82
Mild	0.68	0.70
Moderate-severe	0.54	0.55

5.11.2 Generalisability of the analysis

Resource use costs in the model were taken from a modified Delphi panel involving clinician and nurse gastroenterology KOLs across the UK to gain an overview of current practice; these estimates are therefore directly relevant to clinical practice in England.

5.11.3 Strengths of the economic evaluation

5.11.3.1 Previous modelling

The economic evaluation aims to improve upon previous work accepted by NICE, as detailed above.

5.11.3.2 Outcomes

The model is robust to sensitivity analyses. The PSA estimates a 100% chance of cost-effectiveness at the £30,000 cost per QALY threshold in both populations, and the OWSA shows similar outcomes. Most upper and lower bounds tested calculated ustekinumab as dominating all other treatment options in both populations.

A comprehensive list of scenarios was tested, and few affected the conclusions of the cost-effectiveness analysis; ustekinumab remained the dominant treatment in most cases.

5.11.4 Limitations of the economic evaluation

Within the model, placebo efficacy from IM-UNITI is taken from a placebo–placebo cohort of patients. That is, patients who received placebo in the induction studies and then received placebo in IM-UNITI within the non-randomised population. However, it was noted at the advisory board held in July that this may be an over-estimation of true placebo efficacy, as the criteria for entering IM-UNITI was response during the induction studies. There are no available data for a cohort of patients who received placebo during the induction and maintenance phases irrespective of response status for obvious ethical reasons. Therefore, the data available may represent a cohort of patients who are pre-disposed to respond well to placebo. In clinical practice, the absolute difference between ustekinumab and conventional care may be greater than that seen in the trial and reflected in the cost-

effectiveness modelling. Despite this limitation in favour of conventional care, ustekinumab remains dominant in this comparison.

5.11.5 Conclusions

Crohn's disease is a chronic condition, with patients generally receiving diagnosis at a young age and continuing to manage their conditions for the remainder of their lifetime. It is estimated that around 4,000 patients with Crohn's disease in the UK have failed all currently available therapies. Therefore, there is a clear unmet need for patients in the UK to have additional therapies that induce and maintain response and remission in Crohn's disease patients. Ustekinumab represents a lower patient burden than other therapies, with most patients requiring maintenance doses every 12 weeks, or every 8 weeks when the dose is escalated, compared with existing therapies with more frequent maintenance dosing (between 2 and 8 weeks). Further, ustekinumab has the benefit of convenient subcutaneous maintenance dosing compared to infused maintenance of infliximab or vedolizumab.

Ustekinumab is cost saving compared to vedolizumab and conventional care in the TNF failure population, and is cost saving against adalimumab and conventional care in the conventional care failure population. Factors likely contributing to the cost savings are [redacted] and the free home administration of SC maintenance ustekinumab provided by Janssen.

Ustekinumab has proven to be safe, effective and cost effective. The budget impact model demonstrates that ustekinumab is likely to be cost saving to the NHS.

6 Assessment of factors relevant to the NHS and other parties

6.1 Patient Population

The 2017 general population of England and Wales is estimated to be approximately 66,024,730, and it is estimated that the prevalence rate of Crohn's disease is 0.20%.[16, 234] Therefore, at the beginning of 2017, the total number of people suffering from Crohn's disease in England and Wales was estimated to be 132,049. It was estimated that 40% of patients with Crohn's disease have moderate to severely active Crohn's disease.[16] As per the assumptions made in the NICE costing statement for TA352, approximately 50% of these patients are eligible for biologic treatment.[16] Of these patients, approximately 50% (13,205) were estimated to have previously failed conventional care, and 50% (13,205) previously failed an anti-TNF agent. [16]

Given a projected incidence rate of 0.01%, and a projected increase in the general population over the 5-year period, there will be an increase in the number of Crohn's disease patients eligible for treatment each year. [16] Table 85 shows the 5-year projected eligible patient population for ustekinumab, without considering mortality.

Table 85: 5-year projection of ustekinumab eligible patients

	2017	2018	2019	2020	2021
Conventional care failure	13,865	14,530	15,200	15,874	16,553
TNF failure	13,865	14,530	15,200	15,874	16,553
Key: TNF, tumour necrosis factor.					

6.2 Treatment options

The treatment options that are assessed in the budget impact model are dependent on the population sub-group, as per the cost effectiveness analysis. Patients who have previously failed conventional care are eligible for ustekinumab, in addition to adalimumab, infliximab (Remicade), approved infliximab biosimilars Inflectra and Remsima and conventional care. Adalimumab efficacy is used for infliximab values due to lack of suitable infliximab data. Patients who are in the TNF failure subgroup

can be treated with ustekinumab, vedolizumab or conventional care, in line with recent guidance.[3] However, it was noted that in practice, adalimumab is used as a second line treatment following infliximab. This is reflected in the market shares, though it is noted that evidence was taken from the conventional care failure population to calculate adalimumab results, due to a lack of data within the TNF failure population.

The proportion of patients who remain alive each year in the budget impact analysis (Table 86) were calculated using mortality rates in line with the cost effectiveness analysis.

Table 86: Proportion of population who remain alive over time

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Proportion of patients alive	1.000	0.999	0.997	0.996	0.994

In line with the cost effectiveness analysis, it is assumed that there is no difference in mortality between treatments in each population (cross reference mortality section). The proportions do differ between the populations because of differences in both age and the percentage of patients that are male/female in the sub-groups.

6.3 Market share estimates

Market share estimates were applied to the eligible patient population to calculate patient numbers by treatment across the 5-year period. Table 87 and Table 88 reflect the market shares of available treatment options in a world without and with ustekinumab for conventional care failure patients, respectively.

Table 87: World without ustekinumab market share estimates – Conventional care failure population

	2017	2018	2019	2020	2021
Adalimumab	49.00%	48.00%	47.00%	46.00%	45.00%
Infliximab - Remicade	21.90%	19.90%	17.90%	15.90%	13.90%
Infliximab - Inflectra	17.19%	18.69%	20.19%	21.69%	23.19%
Infliximab - Remsima	11.91%	13.41%	14.91%	16.41%	17.91%
Conventional care	0.00%	0.00%	0.00%	0.00%	0.00%

Table 88: World with ustekinumab market share estimates – Conventional care failure population

	2017	2018	2019	2020	2021
Ustekinumab	1.00%	4.00%	6.00%	8.00%	10.00%
Adalimumab	48.00%	44.00%	44.00%	42.00%	40.00%
Infliximab - Remicade	21.90%	19.90%	14.90%	11.90%	8.90%
Infliximab - Inflectra	17.19%	18.69%	20.19%	21.69%	23.19%
Infliximab - Remsima	11.91%	13.41%	14.91%	16.41%	17.91%
Conventional care	0.00%	0.00%	0.00%	0.00%	0.00%

Table 89 and Table 90 represent market shares for the TNF failure population without and with ustekinumab, respectively.

Table 89: World without ustekinumab market share estimates – TNF failure population

	2017	2018	2019	2020	2021
Vedolizumab	40.00%	40.00%	40.00%	40.00%	40.00%
Adalimumab	60.00%	60.00%	60.00%	60.00%	60.00%
Conventional care	0.00%	0.00%	0.00%	0.00%	0.00%

Table 90: World with ustekinumab market share estimates – TNF failure population

	2017	2018	2019	2020	2021
Ustekinumab	5.00%	15.00%	30.00%	45.00%	60.00%
Vedolizumab	35.00%	30.00%	25.00%	15.00%	5.00%
Adalimumab	60.00%	55.00%	45.00%	40.00%	35.00%
Conventional care	0.00%	0.00%	0.00%	0.00%	0.00%

6.4 Results

Table 91 and Table 92 show the net budget impact of ustekinumab for the conventional care failure TNF failure populations, respectively. The implementation

of ustekinumab results in a saving of £231,123 and £4,752,249 in Year 1 and a total cumulative saving across the 5 years of £664,719 and £9,780,324 for the conventional care failure and TNF failure populations, respectively.

Table 91: Net budget impact – Conventional care failure

	Year 1	Year 2	Year 3	Year 4	Year 5
Net budget impact in year	-£231,123	-£52,260	-£89,282	-£130,604	-£161,450
Cumulative net budget impact	-£231,123	-£283,383	-£372,665	-£503,269	-£664,719

Table 92: Net budget impact – TNF failure

	Year 1	Year 2	Year 3	Year 4	Year 5
Net budget impact in year	-£4,752,249	-£552,553	-£984,366	-£1,450,180	-£2,040,976
Cumulative net budget impact	-£4,752,249	-£5,304,802	-£6,289,168	-£7,739,348	-£9,780,324

7 References

1. Bodger K, Kikuchi T and Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Aliment Pharmacol Ther*. 2009; 30(3):265-74.

2. National Institute for Health and Care Excellence (NICE). TA187: Infliximab (review) and adalimumab for the treatment of Crohn's disease. 2010. Available at: https://www.nice.org.uk/guidance/ta187. Accessed: 16 April 2015.

3. National Institute for Health and Care Excellence (NICE). TA352: Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. 2015. Available at: https://www.nice.org.uk/guidance/ta352. Accessed: 12 December 2015.

4. Sandborn W, Feagan B, Gasink C, et al. A Phase 3, randomized, multicenter, double-blind, placebo-controlled, study of ustekinumab maintenance therapy in moderate-severe crohn's disease patients: results from IM-UNITI. British Society of Gastroenterology (BSG) Annual Meeting 2016. Liverpool, England. 20 - 23 June 2016 2016. OC-057.

5. Sandborn W, Feagan B, Gasink C, et al. A Phase 3, randomized, multicenter, double-blind, placebo-controlled, study of ustekinumab maintenance therapy in moderate-severe crohn's disease patients: results from IM-UNITI. Digestive Disease Week (DDW) 2016. San Diego, CA, USA. 21 - 24 May 2016 2016. 768.

6. Liu Z, Yadav PK, Xu X, et al. The increased expression of IL-23 in inflammatory bowel disease promotes intraepithelial and lamina propria lymphocyte inflammatory responses and cytotoxicity. *J Leukoc Biol*. 2011; 89(4):597-606.

7. Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology*. 1997; 112(4):1169-78.

8. Berrebi D, Besnard M, Fromont-Hankard G, et al. Interleukin-12 expression is focally enhanced in the gastric mucosa of pediatric patients with Crohn's disease. *Am J Pathol*. 1998; 152(3):667-72.

9. Parrello T, Monteleone G, Cucchiara S, et al. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. *J Immunol*. 2000; 165(12):7234-9.

10. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science*. 2006; 314(5804):1461-3.

11. Moon CM, Shin DJ, Son NH, et al. Genetic variants in the IL12B gene are associated with inflammatory bowel diseases in the Korean population. *J Gastroenterol Hepatol*. 2013; 28(10):1588-94.

12. Vermeire S, Van Assche G and Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. *Inflamm Bowel Dis*. 2004; 10(5):661-5.

13. Wang K, Zhang H, Kugathasan S, et al. Diverse genome-wide association studies associate the IL12/IL23 pathway with Crohn Disease. *Am J Hum Genet*. 2009; 84(3):399-405.

14. Davidson NJ, Hudak SA, Lesley RE, et al. IL-12, but not IFN-gamma, plays a major role in sustaining the chronic phase of colitis in IL-10-deficient mice. *J Immunol*. 1998; 161(6):3143-9.

15. Neurath MF. IL-23: a master regulator in Crohn disease. *Nat Med*. 2007; 13(1):26-8.

16. National Institute for Health and Care Excellence (NICE). TA352. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Costing report. 2015. (Updated: 26 August 2015) Available at: https://www.nice.org.uk/guidance/ta352/costing. Accessed: 15 October 2016.

17. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013; 369(8):711-21.

18. Lichtenstein GR, Waters HC, Kelly J, et al. Assessing Drug Treatment Preferences of Patients with Crohn's Disease. *The Patient: Patient-Centered Outcomes Research*. 2010; 3(2):113-23.

19. Baumgart DC and Sandborn WJ. Crohn's disease. *Lancet*. 2012; 380(9853):1590-605.

20. Kalla R, Ventham NT, Satsangi J and Arnott ID. Crohn's disease. *BMJ*. 2014; 349:g6670.

21. Bewtra M, Su C and Lewis JD. Trends in hospitalization rates for inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol*. 2007; 5(5):597-601.

22. Davis KL, Mody R, Rubin DT and Wang C-C. Mo1326 Association Between Suboptimal Therapy and Health Care Costs in Inflammatory Bowel Disease. *Gastroenterology*. 2013; 144(5):S-637-S-8.

23. Dretzke J, Round J, Edlin R, et al. Use of tumour necrosis factor alpha (TNF α) inhibitors adalimumab and infliximab for Crohn's disease. 2008. Available at: https://www.nice.org.uk/guidance/ta187/documents/assessment-report2. Accessed: 11 October 2016.

24. Loftus EV, Jr., Schoenfeld P and Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther*. 2002; 16(1):51-60.

25. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997; 337(15):1029-35.

26. D'Inca R and Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol*. 2014; 7:151-61.

27. Onali S, Calabrese E and Pallone F. Measuring disease activity in Crohn's disease. *Abdom Imaging*. 2012; 37(6):927-32.

28. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lemann score. *Inflamm Bowel Dis*. 2011; 17(6):1415-22.

29. Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet*. 2016; 387(10014):156-67.

30. Thia KT, Sandborn WJ, Harmsen WS, et al. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology*. 2010; 139(4):1147-55.

31. Henriksen M, Jahnsen J, Lygren I, et al. Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). *Scand J Gastroenterol*. 2007; 42(5):602-10.

32. Gower-Rousseau C, Vasseur F, Fumery M, et al. Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry (EPIMAD). *Dig Liver Dis*. 2013; 45(2):89-94.

33. Lakatos L, Kiss LS, David G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002-2006. *Inflamm Bowel Dis*. 2011; 17(12):2558-65.

34. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol*. 2007; 5(12):1430-8.

35. Munkholm P, Langholz E, Davidsen M and Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol*. 1995; 30(7):699-706.

36. Wolters FL, Russel MG, Sijbrandij J, et al. Phenotype at diagnosis predicts recurrence rates in Crohn's disease. *Gut*. 2006; 55(8):1124-30.

37. Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. *Gastroenterology*. 1999; 117(1):49-57.

38. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012; 142(1):46-54 e42; quiz e30.

39. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol*. 2015; 12(4):205-17.

40. Talley NJ, Abreu MT, Achkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol*. 2011; 106 Suppl 1:S2-25; quiz S6.

41. Bernstein CN and Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. *Gut*. 2008; 57(9):1185-91.

42. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol*. 2006; 3(7):390-407.

43. Franke A, McGovern DP, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet*. 2010; 42(12):1118-25.

44. Umeno J, Asano K, Matsushita T, et al. Meta-analysis of published studies identified eight additional common susceptibility loci for Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2011; 17(12):2407-15.

45. Lerebours E, Gower-Rousseau C, Merle V, et al. Stressful life events as a risk factor for inflammatory bowel disease onset: A population-based case-control study. *Am J Gastroenterol*. 2007; 102(1):122-31.

46. Barclay AR, Russell RK, Wilson ML, et al. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *J Pediatr*. 2009; 155(3):421-6.

47. Gent AE, Hellier MD, Grace RH, et al. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet*. 1994; 343(8900):766-7.

48. Aamodt G, Bukholm G, Jahnsen J, et al. The association between water supply and inflammatory bowel disease based on a 1990-1993 cohort study in southeastern Norway. *Am J Epidemiol*. 2008; 168(9):1065-72.

49. Hou JK, Abraham B and El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol*. 2011; 106(4):563-73.

50. Seksik P, Nion-Larmurier I, Sokol H, et al. Effects of light smoking consumption on the clinical course of Crohn's disease. *Inflamm Bowel Dis*. 2009; 15(5):734-41.

51. Jones DT, Osterman MT, Bewtra M and Lewis JD. Passive smoking and inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol*. 2008; 103(9):2382-93.

52. Sartor RB and Mazmanian SK. Intestinal Microbes in Inflammatory Bowel Diseases. *Am J Gastroenterol Suppl*. 2012; 1(1):15-21.

53. Martinez-Medina M, Aldeguer X, Gonzalez-Huix F, et al. Abnormal microbiota composition in the ileocolonic mucosa of Crohn's disease patients as revealed by polymerase chain reaction-denaturing gradient gel electrophoresis. *Inflamm Bowel Dis*. 2006; 12(12):1136-45.

54. Mannon PJ, Fuss IJ, Mayer L, et al. Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med*. 2004; 351(20):2069-79.

55. Lichtenstein GR, Hanauer SB, Sandborn WJ and Practice Parameters Committee of American College of G. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009; 104(2):465-83; quiz 4, 84.

56. Glickman RM. *Inflammatory bowel disease: ulcerative colitis and Crohn's disease*. New York, NY: McGraw-Hill, 1998, p. 1633-45.

57. Goh J and O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2003; 17(3):307-20.

58. Schalamon J, Mayr JM and Hollwarth ME. Mortality and economics in short bowel syndrome. *Best Pract Res Clin Gastroenterol*. 2003; 17(6):931-42.

59. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013; 145(5):996-1006.

60. Lakatos PL, David G, Pandur T, et al. IBD in the elderly population: results from a population-based study in Western Hungary, 1977-2008. *J Crohns Colitis*. 2011; 5(1):5-13.

61. Selinger CP, Andrews JM, Titman A, et al. Long-term follow-up reveals low incidence of colorectal cancer, but frequent need for resection, among Australian patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2014; 12(4):644-50.

62. Freeman HJ. Natural history and long-term clinical course of Crohn's disease. *World J Gastroenterol*. 2014; 20(1):31-6.

63. Helzer JE, Chammas S, Norland CC, et al. A study of the association between Crohn's disease and psychiatric illness. *Gastroenterology*. 1984; 86(2):324-30.

64. Kappelman MD, Moore KR, Allen JK and Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Dig Dis Sci*. 2013; 58(2):519-25.

65. Lix LM, Graff LA, Walker JR, et al. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. *Inflamm Bowel Dis*. 2008; 14(11):1575-84.

66. Castillo-Cejas MD, Robles V, Borruel N, et al. Questionnaries for measuring fatigue and its impact on health perception in inflammatory bowel disease. *Rev Esp Enferm Dig*. 2013; 105(3):144-53.

67. Stark RG, Reitmeir P, Leidl R and Konig HH. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. *Inflamm Bowel Dis*. 2010; 16(1):42-51.

68. Casellas F, Alcala MJ, Prieto L, et al. Assessment of the influence of disease activity on the quality of life of patients with inflammatory bowel disease using a short questionnaire. *Am J Gastroenterol*. 2004; 99(3):457-61.

69. Calvet X, Gallardo O, Coronas R, et al. Remission on thiopurinic immunomodulators normalizes quality of life and psychological status in patients with Crohn's disease. *Inflamm Bowel Dis*. 2006; 12(8):692-6.

70. Iglesias M, Vazquez I, Barreiro-de Acosta M, et al. Health related quality of life in patients with Cohn s disease in remission. *Rev Esp Enferm Dig*. 2010; 102(11):624-30.

71. Lichtenstein GR, Yan S., Bala, M., Hanauer, S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. 2004; (0002-9270 (Print)).

72. Stjernman H, Granno C, Jarnerot G, et al. Short health scale: a valid, reliable, and responsive instrument for subjective health assessment in Crohn's disease. *Inflamm Bowel Dis*. 2008; 14(1):47-52.

73. McDermott E, Keegan D, Byrne K, et al. The Short Health Scale: a valid and reliable measure of health related quality of life in English speaking inflammatory bowel disease patients. *J Crohns Colitis*. 2013; 7(8):616-21.

74. Hoivik ML, Bernklev T, Solberg IC, et al. Patients with Crohn's disease experience reduced general health and vitality in the chronic stage: ten-year results from the IBSEN study. *J Crohns Colitis*. 2012; 6(4):441-53.

75. Feagan BG, Sandborn WJ, Hass S, et al. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. *Am J Gastroenterol*. 2007; 102(12):2737-46.

76. Lazzaro C, Cappello M, Cortelezzi C, et al. Health-Related Quality of Life in Italian Patients With Moderate and Severe Crohn's Disease: Interim Results from the Sole Study. *Value Health*. 2014; 17(7):A570-1.

77. Piercy J, Ozbay AB, Roughley A, et al. Tu1256 Comparison of Ulcerative Colitis With Crohn's Disease From the Perspective of Patient Burden. *Gastroenterology*. 2015; 148(4):S-839.

78. Shafran I, Burgunder P and Fakih F. Certolizumab pegol as treatment for Crohn's disease in a community IBD practice: P-51. *Inflamm Bowel Dis*. 2011; 17:S27.

79. Mudter J, Neurath MF, von Arnauld de la Perriére P, et al. P233 Adalimumab produces high responder and remission rates and has an independent effect on quality of life in Crohn's disease patients. *J Crohns Colitis*. 2012; 6(Supplement 1):S102.

80. Floyd DN, Langham S, Severac HC and Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. *Dig Dis Sci*. 2015; 60(2):299-312.

81. Bernklev T, Moum B, Moum T and Inflammatory Bowel South-Eastern Norway Group of G. Quality of life in patients with inflammatory bowel disease: translation, data quality, scaling assumptions, validity, reliability and sensitivity to change of the Norwegian version of IBDQ. *Scand J Gastroenterol*. 2002; 37(10):1164-74.

82. Ren WH, Lai M, Chen Y, et al. Validation of the mainland Chinese version of the Inflammatory Bowel Disease Questionnaire (IBDQ) for ulcerative colitis and Crohn's disease. *Inflamm Bowel Dis*. 2007; 13(7):903-10.

83. Huang H, Leong RW, Ko Y and Kariyawasam VC. Pilot validation study of the international classification of functioning, disability and health score: a novel measure of disability in Crohn's disease. *J Gastroenterol Hepatol*. 2012; 27:105-6.

84. van der Have M, van der Aalst KS, Kaptein AA, et al. Determinants of health-related quality of life in Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014; 8(2):93-106.

85. Yarlas A, White M, Ingham M, et al. Evidence of content validity and psychometric properties of SF-36 for measuring health-related quality of life of patients with Crohn’s disease. 11th Congress of ECCO. Amsterdam, The Netherlands. 16-19 March 2016. P229.

86. Yu AP, Cabanilla LA, Wu EQ, et al. The costs of Crohn's disease in the United States and other Western countries: a systematic review. *Curr Med Res Opin*. 2008; 24(2):319-28.

87. Mandel MD, Balint A, Lovasz BD, et al. Work disability and productivity loss in patients with inflammatory bowel diseases in Hungary in the era of biologics. *Eur J Health Econ*. 2014; 15 Suppl 1:S121-8.

88. Odes S, Vardi H, Friger M, et al. Effect of phenotype on health care costs in Crohn's disease: A European study using the Montreal classification. *J Crohns Colitis*. 2007; 1(2):87-96.

89. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis*. 2010; 4(1):28-62.

90. National Institute for Health and Care Excellence (NICE). NICE Pathways: Crohn's disease overview. 2016. (Updated: 17 May 2016) Available at: http://pathways.nice.org.uk/pathways/crohns-disease. Accessed: 10 October 2016.

91. European Medicines Agency (EMA). Summary of Product Characteristics. Vedolizumab summary of product characteristics. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002782/WC500168528.pdf. Accessed: 10 October 2016.

92. European Medicines Agency (EMA). Summary of Product Characteristics. Adalimumab summary of product characteristics. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf. Accessed: 10 October 2016.

93. European Medicines Agency (EMA). Summary of Product Characteristics. Infliximab summary of product characteristics. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf. Accessed: 10 October 2016.

94. Farrokhyar F, Swarbrick ET, Grace RH, et al. Low mortality in ulcerative colitis and Crohn's disease in three regional centers in England. *Am J Gastroenterol*. 2001; 96(2):501-7.

95. Crohn's & Colitis UK. Crohn's Disease. 2013. (Updated: 2013) Available at: https://www.crohnsandcolitis.org.uk/about-inflammatory-bowel-disease/crohns-disease. Accessed: 15 October 2016.

96. Garcia Rodriguez LA, Gonzalez-Perez A, Johansson S and Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther*. 2005; 22(4):309-15.

97. Seagroatt V and Goldacre MJ. Crohn's disease, ulcerative colitis, and measles vaccine in an English population, 1979-1998. *J Epidemiol Community Health*. 2003; 57(11):883-7.

98. Stone MA, Mayberry JF and Baker R. Prevalence and management of inflammatory bowel disease: a cross-sectional study from central England. *Eur J Gastroenterol Hepatol*. 2003; 15(12):1275-80.

99. Rubin GP, Hungin AP, Kelly PJ and Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther*. 2000; 14(12):1553-9.

100. Bardhan KD, Simmonds N, Royston C, et al. A United Kingdom inflammatory bowel disease database: making the effort worthwhile. *J Crohns Colitis*. 2010; 4(4):405-12.

101. World Gastronenterology Organisation (WGO). WGO Guidelines: Inflammatory bowel disease. 2015. (Updated: August 2015) Available at: http://www.worldgastroenterology.org/guidelines/global-guidelines/inflammatory-bowel-disease-ibd/inflammatory-bowel-disease-ibd-english. Accessed: 6 October 2016.

102. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol*. 2015; 110(9):1324-38.

103. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2011; 60(5):571-607.

104. Gomollon F, Dignass A, Annese V, et al. 3. EUROPEAN Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis*. 2016.

105. Vavricka SR, Schoepfer AM, Scharl M and Rogler G. Steroid use in Crohn's disease. *Drugs*. 2014; 74(3):313-24.

106. Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology*. 1984; 86(2):249-66.

107. Singleton JW, Law DH, Kelley ML, Jr., et al. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. *Gastroenterology*. 1979; 77(4 Pt 2):870-82.

108. Schoon EJ, van Nunen AB, Wouters RS, et al. Osteopenia and osteoporosis in Crohn's disease: prevalence in a Dutch population-based cohort. *Scand J Gastroenterol Suppl*. 2000; (232):43-7.

109. Buckley LM. Calcium and Vitamin D3Supplementation Prevents Bone Loss in the Spine Secondary to Low-Dose Corticosteroids in Patients with Rheumatoid Arthritis. *Annals of Internal Medicine*. 1996; 125(12):961.

110. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol*. 2006; 4(5):621-30.

111. Munkholm P, Langholz E, Davidsen M and Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut*. 1994; 35(3):360-2.

112. Faubion WA, Jr., Loftus EV, Jr., Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001; 121(2):255-60.

113. Ho GT, Chiam P, Drummond H, et al. The efficacy of corticosteroid therapy in inflammatory bowel disease: analysis of a 5-year UK inception cohort. *Aliment Pharmacol Ther*. 2006; 24(2):319-30.

114. Papi C, Festa V, Leandro G, et al. Long-term outcome of Crohn's disease following corticosteroid-induced remission. *Am J Gastroenterol*. 2007; 102(4):814-9.

115. Lopez-Martin C, Chaparro M, Espinosa L, et al. Adverse events of thiopurine immunomodulators in patients with inflammatory bowel disease. *Gastroenterol Hepatol*. 2011; 34(6):385-92.

116. Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006; 130(3):940-87.

117. Warman JI, Korelitz BI, Fleisher MR and Janardhanam R. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. *J Clin Gastroenterol*. 2003; 37(3):220-5.

118. Avallone EV, Pica R, Cassieri C, et al. Azathioprine treatment in inflammatory bowel disease patients: type and time of onset of side effects. *Eur Rev Med Pharmacol Sci*. 2014; 18(2):165-70.

119. Martinez F, Nos P, Pastor M, et al. Adverse effects of azathioprine in the treatment of inflammatory bowel disease. *Rev Esp Enferm Dig*. 2001; 93(12):769-78.

120. McDonald JW, Tsoulis DJ, Macdonald JK and Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev*. 2012; 12:CD003459.

121. Lemann M, Zenjari T, Bouhnik Y, et al. Methotrexate in Crohn's disease: long-term efficacy and toxicity. *Am J Gastroenterol*. 2000; 95(7):1730-4.

122. Chande N, Tsoulis DJ and MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2013; (4):CD000545.

123. Ben-Horin S and Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther*. 2011; 33(9):987-95.

124. Billioud V, Sandborn WJ and Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol*. 2011; 106(4):674-84.

125. Ha C and Kornbluth A. Vedolizumab as a Treatment for Crohn’s Disease and Ulcerative Colitis. *Gastroenterol Hepatol*. 2014; 10(12):793-800.

126. Gniadecki R, Bang B, Bryld LE, et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol*. 2015; 172(1):244-52.

127. Strober BE, Bissonnette R, Fiorentino D, et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). *J Am Acad Dermatol*. 2016; 74(5):851-61 e4.

128. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Eur Acad Dermatol Venereol*. 2016; 30(7):1148-58.

129. Neovius M, Arkema EV, Olsson H, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. *Ann Rheum Dis*. 2015; 74(2):354-60.

130. Warren RB, Smith CH, Yiu ZZ, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol*. 2015; 135(11):2632-40.

131. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014; 147(3):618-27 e3.

132. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med*. 2012; 367(16):1519-28.

133. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England Journal of Medicine*. 2016; 375(20):1946-60.

134. Janssen Research and Development. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease (44-Week Clinical Study Report). (EDMS-ERI-97847519, 1.0) 9 November 2015. Data on file.

135. Janssen Research and Development. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy (UNITI 1). (EDMS-ERI-65460596) 17 September 2015. Data on file.

136. Janssen Research and Development. A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease (UNITI 2). (EDMS-ERI-86643187, 1.0) 13 October 2015. Data on file.

137. Sands B, Gasink C, Jacobstein D, et al. Efficacy and Safety of Dose Adjustment and Delayed Response to Ustekinumab in Moderate–Severe Crohn's Disease Patients: Results From the IM-UNITI Maintenance Study. United European Gastronenterology (UEG) Week 2016. Vienna, Austria. 15-19 October 2016. Presentation 5.

138. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for Induction and Maintenance of Endoscopic Healing in Patients with Crohn's Disease. United European Gastronenterology (UEG) Week 2016. Vienna, Austria. 15-19 October 2016. Presentation 104.

139. Rutgeerts P, Gasink C, Blank M, et al. A multicenter, double-blind, placebo-controlled Phase 3 study of ustekinumab, a human IL-12/23p40 monoclonal antibody, in moderate-severe crohn's disease refractory to anti-TNFα: UNITI-1. 11th Congress of European Crohn's and Colitis Organisation (ECCO). Amsterdam, The Netherlands. 16 - 19 March 2016 2016. OP014.

140. Gregor JC, McDonald JW, Klar N, et al. An evaluation of utility measurement in Crohn's disease. *Inflamm Bowel Dis*. 1997; 3(4):265-76.

141. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics*. 1999; 15(2):141-55.

142. Walters SJ and Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. *Health and Quality of Life Outcomes*. 2003; 1(1):4.

143. Ware JE, Snow KK, Kosinski M and Gandek B. *SF-36 Health Survey Manual and Interpretation Guide* Boston: The Health Institute, New England Medical Center, 1993.

144. Ware JE. User's Manual for the SF-36v2 Health Survey. 1994, p.Pages 81-4.

145. Janssen Research and Development. Abbreviated health technology assessment report of ustekinumab maintenance of efficacy in crohn's disease through 2 years (IM-UNITI). (EDMS-ERI-132762380, 1.0) 25 October 2016. Data on file.

146. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. 2015. (Updated: January 2015) Available at: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies. Accessed: 10 October 2016.

147. D'Haens G, Vermiere S, Lambrecht G, et al. Drug-concentration versus symptom-driven dose adaptation of Infliximab in patients with active Crohn's disease: a prospective, randomised, multicentre trial (Tailorix). 11th Congress of European Crohn's and Colitis Organisation (ECCO). Amsterdam, The Netherlands. 16 - 19 March 2016 2016. OP0029.

148. Matsumoto T, Motoya S, Watanabe K, et al. Comparison of adalimumab monotherapy and a combination with azathioprine for patients with Crohn's disease: a prospective, multicentre, open-labelled clinical trial (DIAMOND study). 11th Congress of European Crohn's and Colitis Organisation (ECCO). Amsterdam, The Netherlands. 16 - 19 March 2016 2016. OP011.

149. D'Haens G, Feagan B, Colombel JF, et al. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. *Gastroenterology*. 2012; 143(6):1461-9.

150. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006; 130(2):323-33; quiz 591.

151. Watanabe M, Hibi T, Lomax KG, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. *J Crohns Colitis*. 2012; 6(2):160-73.

152. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007; 146(12):829-38.

153. Sandborn W, Gasink C, Blank M, et al. O-001 A Multicenter, Double-Blind, Placebo-Controlled Phase3 Study of Ustekinumab, a Human IL-12/23P40 mAB, in Moderate-Service Crohn's Disease Refractory to Anti-TFNalpha: UNITI-1. *Inflamm Bowel Dis*. 2016; 22 Suppl 1:S1.

154. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007; 132(1):52-65.

155. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002; 359(9317):1541-9.

156. Thia KT, Sandborn WJ, Lewis JD, et al. Defining the optimal response criteria for the Crohn's disease activity index for induction studies in patients with mildly to moderately active Crohn's disease. *Am J Gastroenterol*. 2008; 103(12):3123-31.

157. Buxton MJ, Lacey LA, Feagan BG, et al. Mapping from disease-specific measures to utility: an analysis of the relationships between the Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's disease and measures of utility. *Value Health*. 2007; 10(3):214-20.

158. Neeman T. Statistical Review: Chimeric Monoclonal Antibody (cA2) to Tumor Necrosis Factor for Inflammatory Bowel Disease (Crohn's Disease). Food and Drug Administration Center for Biologics Evaluation and Research. 1998. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107710.pdf. Accessed: 10 October 2016.

159. Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. *Gut*. 2012; 61(2):229-34.

160. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health*. 2011; 14(4):417-28.

161. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007; 56(9):1232-9.

162. Bonovas S, Moja L and Danese S. In the Presence of Conceptual Heterogeneity, Results of Network Meta-analysis Comparing Therapies in Crohn's Disease Need to Be Interpreted With Caution. *Gastroenterology*. 2015; 148(7):1483-4.

163. Dias S, Sutton AJ, Welton NJ and Ades AE. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. Report by the Decision Support Unit. 2011. (Updated: April 2012) Available at: http://www.nicedsu.org.uk/TSD3%20Heterogeneity.final%20report.08.05.12.pdf. Accessed: 11 October 2016.

164. Thorlund K, Druyts E, Toor K and Mills EJ. Comparative efficacy of golimumab, infliximab, and adalimumab for moderately to severely active ulcerative colitis: a network meta-analysis accounting for differences in trial designs. *Expert Rev Gastroenterol Hepatol*. 2015; 9(5):693-700.

165. Abrams K. Evaluating complex interventions using multi-phase nested trial designs-Management of urinary incontinence across the primary/secondary care interface. *Controlled Clinical Trials.* 360 Park Ave South, New York, NY 10010-1710 USA.: Elsevier Science Inc, 2003.

166. Pacou M, Mesana L, Gauthier A, et al. Indirect treatment comparison of ustekinumab versus other biologics in moderate to severe crohn’s disease: A 1-year treatment sequence analysis. ISPOR 19th Annual Congress. Vienna, Austria. 29 Octobe 2 November 2016. PSY9.

167. Dias S, Welton NJ, Sutton AJ and Ades AE. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Report by the Decision Support Unit. 2011. (Updated: September 2016) Available at: http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%202Sep2016v2.pdf. Accessed: 11 October 2016.

168. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed: 11 October 2016.

169. Lunn DJ, Thomas A, Best N and Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput*. 2000; 10:325-37.

170. Bucher HC, Guyatt GH, Griffith LE and Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997; 50(6):683-91.

171. Hindryckx P, Baert F, Hart A, et al. Clinical trials in luminal Crohn's disease: a historical perspective. *J Crohns Colitis*. 2014; 8(11):1339-50.

172. Su C, Lichtenstein GR, Krok K, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology*. 2004; 126(5):1257-69.

173. Dretzke J, Edlin R, Round J, et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-alpha) inhibitors, adalimumab and infliximab, for Crohn's disease. *Health Technol Assess*. 2011; 15(6):1-244.

174. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*. 2015; 148(2):344-54 e5; quiz e14-5.

175. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther*. 2014; 39(12):1349-62.

176. Singh S, Garg SK, Pardi DS, et al. Comparative efficacy of biologic therapy in biologic-naive patients with Crohn disease: a systematic review and network meta-analysis. *Mayo Clin Proc*. 2014; 89(12):1621-35.

177. Rafia R, Scope A, Harman S, et al. Vedolizumab for the treatment of adults with moderately to severely active Crohn’s disease: A Single Technology Appraisal. 2014. Available at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/133650/ERGReport-13-128-01.pdf. Accessed: 11 October 2016.

178. Naessens D, Johanns J and Gasink C. Different induction response criteria do not influence 1-year response and remission rates of ustekinumab 90mg q8w in Phase III program. United European Gastronenterology (UEG) Week 2016. Vienna, Austria. 15-19 October 2016.

179. Sostegni R, Daperno M, Scaglione N, et al. Review article: Crohn's disease: monitoring disease activity. *Aliment Pharmacol Ther*. 2003; 17 Suppl 2:11-7.

180. de Dombal FT and Softley A. IOIBD report no 1: Observer variation in calculating indices of severity and activity in Crohn's disease. International Organisation for the Study of Inflammatory Bowel Disease. *Gut*. 1987; 28(4):474-81.

181. Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology*. 2002; 122(2):512-30.

182. Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut*. 2014; 63(1):88-95.

183. Jones J, Loftus EV, Jr., Panaccione R, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2008; 6(11):1218-24.

184. Williet N, Sandborn WJ and Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2014; 12(8):1246-56 e6.

185. Ghosh S, Sands B, De Villiers W, et al. A pooled safety analysis from the ustekinumab Crohn's disease and psoriatic disease Phase 2 and 3 clinical trial programs. United European Gastronenterology (UEG) Week 2016. Vienna, Austria. 15-19 October 2016.

186. Erim DO, Mahendraratnam N, Okafor PN and Wheeler SB. The Value of Vedolizumab as Rescue Therapy in Moderate-Severe Crohn's Disease Patients with Adalimumab Non-response in the USA. *J Crohns Colitis*. 2015; 9(8):669-75.

187. Lindsay J, Punekar YS, Morris J and Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease--modelling outcomes in active luminal and fistulizing disease in adults. *Aliment Pharmacol Ther*. 2008; 28(1):76-87.

188. Blackhouse G, Assasi N, Xie F, et al. Canadian cost-utility analysis of initiation and maintenance treatment with anti-TNF-alpha drugs for refractory Crohn's disease. *J Crohns Colitis*. 2012; 6(1):77-85.

189. Best WR, Becktel JM, Singleton JW and Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976; 70(3):439-44.

190. Takeda Pharmaceuticals. Vedolizumab for the for the treatment of adult patients with moderately to severely active Crohn's disease. Manufacturer's submission to the National Institute for Health and Care Excellence. 2014. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag461. Accessed: 16 April 2015.

191. Janssen Research and Development. Ustekinumab for Crohn's disease: Health economic model advisory board. July 2016.

192. Royal College of Physicians. National clinical audit of biological therapies: UK inflammatory bowel disease (IBD) audit. 2015. Available at:

https://www.rcplondon.ac.uk/projects/outputs/national-clinical-audit-report-biological-therapies-adult-report-2015. Accessed: 21 November 2016.

193. National Institute for Health and Care Excellence (NICE). TA243: Rituximab for the first-line treatment of stage III-IV follicular lymphoma: (review of NICE technology appraisal guidance 110). 2012. Available at: https://www.nice.org.uk/guidance/ta243. Accessed: 16 April 2015.

194. National Institute for Health and Care Excellence (NICE). Introducing biosimilar versions of infliximab: Inflectra and Remsima. 2015. (Updated: 31 July 2015) Available at: http://www.biosimilars-nederland.nl/wp-content/uploads/2015/08/NICE-Adoption-Resource-Biosimilar-Infliximab-2015_07_31.pdf. Accessed: 16 October 2016.

195. Jørgensen K, Olsen I, Goll G, et al. Biosimilar infliximab (ct-p13) is not inferior to originator infliximab: results from the 52-week randomized nor-switch trial. United European Gastronenterology (UEG) Week 2016. Vienna, Austria. 15-19 October 2016. LB15.

196. Royal College of Physicians. National clinical audit of biological therapies: UK inflammatory bowel disease (IBD) audit. 2013. (Updated: August 2013) Available at: http://www.rcplondon.ac.uk/sites/default/files/national_clinical_audit_report_of_biological_therapies_-_adult_report._29_august_2013.pdf. Accessed: 8 May 2015.

197. Takeda Pharmaceuticals. Final clinical study report C13007 Randomized, placebo-controlled, blinded, multicenter evaluation of induction and maintenance therapy in patients with moderate to severe CD. 2012. Data on file.

198. Panaccione R, Sandborn W, Colombel J, et al. Impact of Adalimumab therapy after 12 Weeks In patients with Crohn's Disease who were non res ponders at week4: P-0059. *Inflamm Bowel Dis*. 2008; 14:S28.

199. Sandborn W, Feagan B, Reinisch W, et al. P497 Efficacy of continued vedolizumab therapy in patients with Crohn's disease who did not respond to vedolizumab induction therapy at week 6. European Crohn's and Colitis Organisation. Copenhagen, Denmark. 20-22 February 2014 2014. P497.

200. Spoor W. Hospital Episode Statistics (HES) admitted patient care data set 2011-2014. 2015. (Updated: 28 January 2015) Available at: http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22Hospital+Episode+Statistics%2C+Admitted+patient+care+-+England%22&area=&size=10&sort=Relevance. Accessed: 16 October 2016.

201. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010; 362(15):1383-95.

202. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012; 142(5):1102-11 e2.

203. McLeod RS, Wolff BG, Ross S, et al. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. *Dis Colon Rectum*. 2009; 52(5):919-27.

204. Milsom JW, Hammerhofer KA, Bohm B, et al. Prospective, randomized trial comparing laparoscopic vs. conventional surgery for refractory ileocolic Crohn's disease. *Dis Colon Rectum*. 2001; 44(1):1-8; discussion -9.

205. Zurbuchen U, Kroesen AJ, Knebel P, et al. Complications after end-to-end vs. side-to-side anastomosis in ileocecal Crohn's disease--early postoperative results from a randomized controlled multi-center trial (ISRCTN-45665492). *Langenbecks Arch Surg*. 2013; 398(3):467-74.

206. Kusunoki M, Ikeuchi H, Yanagi H, et al. A comparison of stapled and hand-sewn anastomoses in Crohn's disease. *Dig Surg*. 1998; 15(6):679-82.

207. Fazio VW, Marchetti F, Church M, et al. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. *Ann Surg*. 1996; 224(4):563-71; discussion 71-3.

208. Irvin TT, Goligher JC and Johnston D. A randomized prospective clinical trial of single-layer and two-layer inverting intestinal anastomoses. *Br J Surg*. 1973; 60(6):457-60.

209. Eshuis EJ, Slors JF, Stokkers PC, et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. *Br J Surg*. 2010; 97(4):563-8.

210. Maartense S, Dunker MS, Slors JF, et al. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. *Ann Surg*. 2006; 243(2):143-9; discussion 50-3.

211. Ikeuchi H, Kusunoki M and Yamamura T. Long-term results of stapled and hand-sewn anastomoses in patients with Crohn's disease. *Dig Surg*. 2000; 17(5):493-6.

212. Cameron JL, Hamilton SR, Coleman J, et al. Patterns of ileal recurrence in Crohn's disease. A prospective randomized study. *Ann Surg*. 1992; 215(5):546-51; discussion 51-2.

213. Stocchi L, Milsom JW and Fazio VW. Long-term outcomes of laparoscopic versus open ileocolic resection for Crohn's disease: follow-up of a prospective randomized trial. *Surgery*. 2008; 144(4):622-7; discussion 7-8.

214. Funayama Y, Fukushima K, Shibata C, et al. Early postoperative results of novel procedure of side-to-side isoperistaltic ileocolonic anastomosis for Crohn’s disease—randomized controlled trial. 47th Annual Meeting of the Society for Surgery of the Alimentary Tract (SSAT). LA, California., USA. 20-24 May 2006 2006.

215. Office for National Statistics. Life Tables for England and Wales, 2011 to 2013. 2014. Available at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-365199. Accessed: 04 March 2016.

216. Rowen D, Brazier, J., Roberts, J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Value Health*. 2007; (1477-7525 (Electronic)).

217. Janssen Research and Development. Utility Mapping and Analysis for Ustekinumab in Crohn’s Disease: Report. 11 October 2016. Data on File.

218. Brown RE, Hutton J and Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. *Pharmacoeconomics*. 2001; 19(11):1091-102.

219. Porco TC, Lewis B, Marseille E, et al. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. *BMC Public Health*. 2006; 6(1471-2458 (Electronic)):157.

220. Hornberger J, Reyes C, Lubeck D and Valente N. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. *Leuk Lymphoma*. 2008; 49(2):227-36.

221. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes*. 2010; 8(1477-7525 (Electronic)):50.

222. Beusterien KM, Szabo SM, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer*. 2009; 101(3):387-9.

223. Ara R and Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010; 13(5):509-18.

224. Bassi A, Dodd S, Williamson P and Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut*. 2004; 53(10):1471-8.

225. van der Valk ME, Mangen M-JJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. *Gut*. 2014; 63(1):72-9.

226. Monthly Index of Medical Specialities (MIMS). 2015. Available at: http://www.mims.co.uk/. Accessed: 16 April 2015.

227. Joint Formulary Committee. British National Formulary, 66 Edition. 2013. Available at: https://www.medicinescomplete.com/about/. Accessed: 16 April 2015.

228. Curtis L. Unit Costs of Health and Social Care 2015. 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php. Accessed: 16 April 2016.

229. Department of Health (DoH). Payment by Results in the NHS: Tariff for 2013 to 2014. 2013. Available at: https://www.gov.uk/government/publications/payment-by-results-pbr-operational-guidance-and-tariffs. Accessed: 16 April 2015.

230. Janssen Research and Development. Ustekinumab for Crohn's disease: medical resource use Delphi panel. September 2016.

231. National Health Service. Department of Health Reference Costs 2014-15. 2015. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed: 27 March 2016.

232. National Institute for Health and Care Excellence (NICE). TA65: Rituximab for aggressive non-Hodgkin's lymphoma. 2003. Available at: https://www.nice.org.uk/guidance/ta65. Accessed: 16 April 2015.

233. National Institute for Health and Care Excellence (NICE). TA226: Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma. 2011. Available at: https://www.nice.org.uk/guidance/ta226. Accessed: 8 May 2015.

234. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2015. 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/latest. Accessed: 11 November 2016.

8 Appendices

Appendix 1: EPAR, CHMP and SmPC and patient population (Sections 2.2 and 3.4)

Appendix 2: Search strategies used to identify relevant RCTs (Section 4.1)

Appendix 3: Summary of CERTIFI Phase II study (Section 4.2)

Appendix 4: Additional data from the UNITI trial programme (Sections 4.5, 4.7 and 4.8)

Appendix 5: Additional information from the NMA (Section 4.10)

Appendix 6: Additional safety data from pooled analysis of long-term ustekinumab use across indications (Section 4.12)

Appendix 7: Search for cost-effectiveness studies (Section 5.1)

Appendix 8: Search strategy for measurement and valuation of health effects (Section 5.4.3)

Appendix 9: Cost and healthcare resource identification, measurement and valuation (Section 5.5.2)

Appendix 10: Calculation of CDAI score given by Dretzke *et al.*

Appendix 11: IM-UNITI transition matrices

Appendix 12: Network meta-analysis transition matrices

Appendix 13: Resource use outputs from Delphi panel

Appendix 14: Summary of inputs used in the economic model

Appendix 15: Markov trace for life years

Appendix 16: Scenario analysis

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy ID843

Dear company,

The Evidence Review Group, ScHARR – University of Sheffield, and the technical team at NICE have looked at the submission received on 24 November 2016 from Janssen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **5 January** 2017. Your response and any supporting doDMdm¬Docs/Appraisals https://appraisals.nice.org.uk/request/22599

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted], Technical Lead [redacted]. Any procedural questions should be addressed to [redacted] Project Manager [redacted]

Yours sincerely

Zoe Charles

Technical Advisor – Technology Appraisals

Centre for Health Technology Evaluation

Encl. checklist for confidential information

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

Section A: Clarification on effectiveness data

NMA-based analyses (section 4.10 of the company submission)

A1. **Priority question:** It is the ERG's understanding that the treatment sequence analysis combines data from induction and maintenance phases of therapy. This exploratory method was considered to reduce inherent bias associated with the analysis of long-term relative treatment effect estimates for ustekinumab.

In this analysis, maintenance data for the placebo arms of comparator trials included in the NMA were imputed using individual patient data from IM-UNITI; adjustment was made for the proportion of responder-non-remitters and remitters at the end of the induction phase.

Below is the ERG's interpretation on how the analyses were carried out. Please confirm that the following description is correct.

Steps in treatment sequence analysis:

The inputs in the treatment sequence analysis were as follows:

1. CDAI-70 rates at week 6 (for ustekinumab and vedolizumab) or week 4 (for both TNF inhibitors), which was done to optimise the comparability of ustekinumab with the other biologics at **induction**.
2. CDAI-100 or CDAI<150 data at the end of **maintenance** for active treatments.

Imputation step

3. Placebo-placebo arm of IM-UNITI were estimated using a weighted average of placebo rates in the two sub-populations (convention care failure and TNF-failure). The imputation methods are explained in figures 28 & 29 on pages 128 and 129 of the company submission).

ERGs interpretation of placebo-placebo imputation:

The 1-year placebo rates for conventional failure patients (figure 28) are re-estimated for each comparator trial using IM-UNITI placebo-placebo results at the end of maintenance (1-year) which are then weighted according to the proportions of responder's non-remitters and remitters from the different biologic comparator trials. The imputed 1 year response rate is calculated using the formula in figure 28.

For example:

To impute the 1 year response [responders (CDAI-100) non-remitter] rate, two sets of data were used:

1. The proportion of patients who at the end of induction data who are responder (CDAI-100) non-remitters and the proportion of remitters. These data are sourced from the relevant induction trials and for UNITI 2 would be 13% and 20 % respectively.

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

2. End of maintenance (1-year) placebo response rates among induction responders (CDAI-100) non remitters – 56% and placebo response rates among induction remitters (CDAI under 150) – 63%. The rates were estimated/imputed using IM UNITI data.

Using the formula presented in the Figure 28:

The imputed 1 year response (responders non-remitter) rate for conventional care failure placebo patients is = ((56%*13%)+(63%*20%))/(13%+20%) = 60%

The same formula is used for the anti-TNF failure patients (figure 29).

The imputed placebo-to-placebo rates for comparators' data only were specified as data inputs and modelled on a log of the odds-odds scale (logit transformation) [Appendix 5 (Pg. 92-93)] and data for the active treatments were modelled on a binary scale, as in the base case analysis.

Finally, the process for estimating the inputs for the treatment sequence analysis are reported in **Error! Reference source not found.** Where the relative probability of achieving response based on the re-randomisation criterion was multiplied by the conditional probability of maintaining response (obtained from maintenance trials for active treatment arms and estimated via the weighted average for placebo arms).

A2. **Priority Question:** Please provide the placebo-placebo imputed data for the responder's non-remitters and responders in the maintenance phase (figures 28 & 29) that were used in the treatment sequence analysis.

A3. **Priority Question:** The ERG understands that the placebo-placebo group data included only those patients who had exhibited a response to placebo in the induction trial. Are there data for patients who continued on placebo regardless of response? The CONSORT diagram (Figure 11 page 81 of the company submission) implies that some patients who did not respond to placebo in the induction trials were followed for the duration of the maintenance trial, please provide any follow-up data for these patients if it exists.

A4. The company submission compares active treatment response to different variations of 'placebo group' during the IM-UNITI trial. It is not made clear in every instance whether this refers to: the non-randomised placebo-placebo population; the ustekinumab responders randomised to placebo; or both groups pooled together. Please will you clarify this and comment on how appropriate each of these groups is as a comparator and why they were used selectively on different occasions.

A5. **Priority Question:** Please provide the annotated WinBUGS models/codes for all network meta-analyses (induction, maintenance treatment sequence analysis (including the code for imputing placebo-placebo), performed for each subgroup, and all data inputs used in these analyses and the source of these inputs (e.g. induction phase, UNITI-1 trial).

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

A6. **Priority Question:** The methods section mentions that both fixed and random effects models were considered for the NMA, but it is not clear which model was used from the results presented on Page 132-141 of the main submission, and Page 77-91 of Appendix 5. Please clarify whether these results were each generated from a fixed or random effects model, and please provide the results of both models in each case.

A7. Please provide the SUCRA plots for the treatments included in the NMA, as these have not been presented in the results on pages 132-141.

Clinical trial evidence

A8. **Priority Question**: From reading the submission and checking the CSR we understand that the population in UNITI-2 whilst being (almost) 100% patients who have not demonstrated failure/intolerance to TNF antagonist therapy, includes around 30% patients who have previously received (and presumably responded to anti-TNFs) and 70% who are anti-TNF naïve. Data for this 'truly naïve' population have been included in sensitivity analyses of the NMA (sequence analysis). As the decision problem includes this conventional care- only failure population please can you provide (in a table) the results for the primary outcome and main secondary outcomes (including endoscopic results) for this sub-group?

A9. In table 19 (page 107) of the company submission, the endoscopic results are presented at week 8, but baseline measures are not reported. Please provide baseline scores for SES-CD, and numbers of patients in the different response states for UNITI-1 and UNITI-2 separately. On page 110 of the company submission, pre-planned and post-hoc analyses of endoscopic data from the maintenance trial are referred to. Please provide the details of these analyses and the results.

A10. For Inflammatory biomarkers, please tabulate more detailed results for CRP/Faecal calprotein/ Faecal lactoferrin including:

- the mean at baseline in the two trials; the number of patients in UNITI-1 and UNITI-2 with abnormal biomarkers at baseline;
- the actual proportions of patients in both trials with normalised biomarkers at week 8 for each trial;
- the mean biomarkers at week 8 for each trial

A11. Figure 20 page 106 of the company submission provides the proportion of patients in clinical remission throughout the IM-UNITI study extension. Please provide absolute numbers of patients in clinical remission over time. Please clarify whether these data are available by previous anti-TNF status (failed, intolerant, experienced but not failed, or truly naïve).

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

A12. The term used to define responders is not consistent in pages 124-148 in the main submission. Two terms were used: “responders” and “responders non remitters”. Please clarify whether these are the same term used to define the participants who achieved CDAI <100 or <70 (in respect to criteria used for achieving response) but did not achieve CDAI under 150.

A13. Please clarify which results for ‘conventional care failure’ in Appendix 5 refer to the full UNITI-2 trial or the ‘truly anti-TNF-naïve’ population.

Sensitivity analysis

A14. The sensitivity analysis and results across subgroups analysis by induction study and by induction dose used different approaches to handling missing data, but it is unclear which approaches were used in the presented results within Tables 16 and 17 in the appendix. Please confirm if there were any differences generated by the two methods?

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** A number of resource items listed in Appendix 13 appear to have a frequency of zero. Is this correct?

B2. **Priority Question:** There are missing monitoring costs in the submission namely for A&E attendances, iron infusion, and virtual clinic. Please confirm that the costs listed in the executable model are correct.

B3. **Priority Question:** There appears to be a discrepancy between estimated total monitoring costs for each health state and the figures listed in Table 57 (pg. 209 of the company submission). This problem affects all health state costs with the exception of remission off a biologic. Please check the implementation of monitoring costs and revise as necessary.

B4. **Priority Question:** It appears that the monitoring costs in the model include additional surgical costs. See Rows 57, 58 and 62 on the “Resource Use costs” sheet. These have non-zero frequency in the mild and moderate/severe health states. This seems to imply double counting of surgery costs as this is also modelled as a separate health state. Please comment on whether this is in fact the case and provide a justification for these costs.

B5. **Priority Question**: There appears to be an error in the calculation of the proportion of patients who are moderate/severe responders in the model. This is calculated correctly in Cell P22 (Calc_Ustekinumab sheet) and is applied correctly in P34. In the subsequent transitions contained in row 35, however, this proportion is calculated as $\gamma(1-\beta+\beta\gamma)$ when in fact it should be should be $\frac{\beta\gamma}{1-\beta}$. Please confirm the error and rectify the affected calculations (note this problem may also affect other calculation sheets).

B6. **Priority Question:** In a number of transitions calculations in the model, the MOD function is being used cycle through week 38 to 44 transition, see for example Q35, Calc_Ustekinumab sheet. Please explain why this is the case and justify.

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

B7. **Priority Question:** The maintenance transition probabilities for patients on all treatment show surprisingly little movement and appear to be inconsistent with presented clinical results. For example, there is nearly a 90% probability that a patient who achieves remission following induction with ustekinumab will maintain that remission for a further 44 weeks based on the transition probabilities used in the model (this applies to both TNF naive and TNF experienced populations). However, Table 16 on page 91 of the company submission suggests that the probability is only about 60% (56% for q12w and 67% for q8w). Please comment on this inconsistency. It would seem to suggest that the maintenance transitional probabilities are overestimating the probability of patients retaining remission in the maintenance period.

B8. **Priority Question:** Please provide the Excel spread sheet which was used to generate the maintenance transition probabilities (page 297 of the company submission - Appendix 12) so that the ERG can see clearly how these were generated and can generate alternative transition probabilities in a way consistent with the company approach.

B9. **Priority Question:** Please provide further clarification on whether the Patient Access Scheme (PAS) will still be applied for patients for whom re-treatment is required, i.e. would a patient who achieves remission on ustekinumab and later relapses be subject to PAS pricing in a second induction phase with ustekinumab?

B10. **Priority Question:** Please provide further details of the table and page numbers in which the data on delayed responders quoted in table 40 on Page 178 of the company submission is found in the IM-UNITI CSRs. If it is not in the CSR please provide the source data.

B11. **Priority Question:** Please clarify which model was compared with the NMA in Table 83 on Page 249 of the company submission.

B12. Some details of the concomitant therapies used in the UNITI trials are presented in the CSRs. If any further information on the therapies used is available, please provide this information, for example dose of concomitant therapies and greater detail on drugs used.

Scenario analyses

Please carry out further scenario analyses (see questions below) and where possible please ensure that it is possible to carry out all of these scenarios together as well as separately so the ERG can incorporate multiple alternative assumptions in any alternative base-case.

B13. **Priority Question:** Please provide a modified version of the IM-UNITI maintenance transitions scenario in which the transitions for the placebo arm are generated from the patients randomised to placebo at the induction phase (this should ideally include both placebo responders and non-responders). The ERG feels that this group would better represent the conventional care patients than patients re-randomised to placebo in IM-UNITI and avoid the issues highlighted on page 182 of the company submission.

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)300 323 0140

B14. **Priority Question:** Please provide a scenario analysis incorporating the actual components of conventional therapy utilised in the different arms of the UNITI trials during the induction and maintenance phases.

B15. **Priority Question:** Please provide a scenario analysis incorporating the sensitivity analysis using truly naive patients from UNITI 2 into the economic model.

Section C: Textual clarifications and additional points

Literature Searching

C1: On Page 6 of Appendix 2 of the company submission, CINAHL is listed as one of the databases searched for the clinical effectiveness review, but no strategy has been provided. If this database was indeed searched, please provide the search strategy.

C2: Please provide the search strategy used for clinicaltrials.gov and the WHO meta-registry.

C3: In the original set of searches conducted in July 2015 (Pages 7-10 of Appendix 2 of the company submission), please clarify why terms for ustekinumab or Stelara are not included in the search strategies.

C4: Please clarify whether line 30 of the MEDLINE search strategy (Table 1, page 9 of Appendix 2 of the company submission) should read “#29 NOT #28”, rather than “#28 NOT #28” as is written.

C5: In the EMBASE.com search strategy (Table 4 of Appendix 2 of the company submission), please clarify which fields were searched for line 2, line 4, and line 31.

C6: Please clarify how many records were retrieved from the searches of CDSR, DARE, and HTA. Results were only presented from CENTRAL in Tables 3 and 5 in Appendix 2 of the company submission.

C7: In the PRISMA flow diagram for the update to the review conducted in October 2016, papers identified through database searching are reported as n=1324 in Figure 1 of Appendix 2. This does not correspond with the search results in Tables 4 & 5, showing 1075 found from MEDLINE and EMBASE, and 135 from CENTRAL, totalling 1210.Please clarify.

C8: In the EMBASE search strategy found in Table 34 of Appendix 7 on Page 155, please clarify whether lines 50-52 are relevant to the search, or have these been included by mistake.

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy ID843

Janssen are pleased to have the opportunity to provide clarification on the above submission. Every effort has been made to answer all questions herein and to provide additional requested analyses. Janssen would like to thank the Committee for allowing extra time requested by Janssen on account of Christmas holidays.

Janssen have addressed both priority and non-priority questions in the order presented below and have interpreted these questions as best as we are able and apologise if the data presented is not what was required.

It is important to note that additional data on concomitant medication use was requested; however very limited data on concomitant therapies are available beyond those that were already presented in the CSRs.

During the course of developing the responses, Janssen detected minor inconsistencies within the submission and appendices. Janssen have addressed those inconsistencies in an erratum (please refer to section D) and the updated results section are presented in Appendix 1. It is important to note that the updated results do not change the overall conclusion contained original submission.

The following notation is used: information submitted under 'commercial in confidence (CIC)' is highlighted in turquoise, and all information submitted under 'academic in confidence (AIC)' in yellow.

Encl. checklist for in confidence information

Encl. Excel files of requested data: There are several Excel files accompanying this document that contain requested data. File keys for each Excel file are contained within this document, all these files are CIC.

Section A: Clarification on effectiveness data

NMA-based analyses (section 4.10 of the company submission)

A1. **Priority question:** It is the ERG's understanding that the treatment sequence analysis combines data from induction and maintenance phases of therapy. This exploratory method was considered to reduce inherent bias associated with the analysis of long-term relative treatment effect estimates for ustekinumab.

In this analysis, maintenance data for the placebo arms of comparator trials included in the NMA were imputed using individual patient data from IM-UNITI; adjustment was made for the proportion of responder-non-remitters and remitters at the end of the induction phase.

Below is the ERG's interpretation on how the analyses were carried out. Please confirm that the following description is correct.

Steps in treatment sequence analysis:

The inputs in the treatment sequence analysis were as follows:

1. *CDAI-70 rates at week 6 (for ustekinumab and vedolizumab) or week 4 (for both TNF inhibitors), which was done to optimise the comparability of ustekinumab with the other biologics at* ***induction****.*
2. *CDAI-100 or CDAI<150 data at the end of* ***maintenance*** *for active treatments.*

Imputation step

3. *Placebo-placebo arm of IM-UNITI were estimated using a weighted average of placebo rates in the two sub-populations (convention care failure and TNF-failure). The imputation methods are explained in figures 28 & 29 on pages 128 and 129 of the company submission).*

ERGs interpretation of placebo-placebo imputation:

The 1-year placebo rates for conventional failure patients (figure 28) are re-estimated for each comparator trial using IM-UNITI placebo-placebo results at the end of maintenance (1-year) which are then weighted according to the proportions of responder's non-remitters and remitters from the different biologic comparator trials. The imputed 1 year response rate is calculated using the formula in figure 28.

For example:

To impute the 1 year response [responders (CDAI-100) non-remitter] rate, two sets of data were used:

1. *The proportion of patients who at the end of induction data who are responder (CDAI-100) non-remitters and the proportion of remitters. These data are sourced from the relevant induction trials and for UNITI-2 would be 13% and 20 % respectively.*

2. *End of maintenance (1-year) placebo response rates among induction responders (CDAI-100) non remitters – 56% and placebo response rates among induction remitters (CDAI under 150) – 63%. The rates were estimated/imputed using IM UNITI data.*

Using the formula presented in the Figure 28:

*The imputed 1 year response (responders non-remitter) rate for conventional care failure placebo patients is = ((56%*13%)+(63%*20%))/(13%+20%) = 60%*

The same formula is used for the anti-TNF failure patients (figure 29).

The imputed placebo-to-placebo rates for comparators' data only were specified as data inputs and modelled on a log of the odds-odds scale (logit transformation) [Appendix 5 (Pg. 92-93)] and data for the active treatments were modelled on a binary scale, as in the base case analysis.

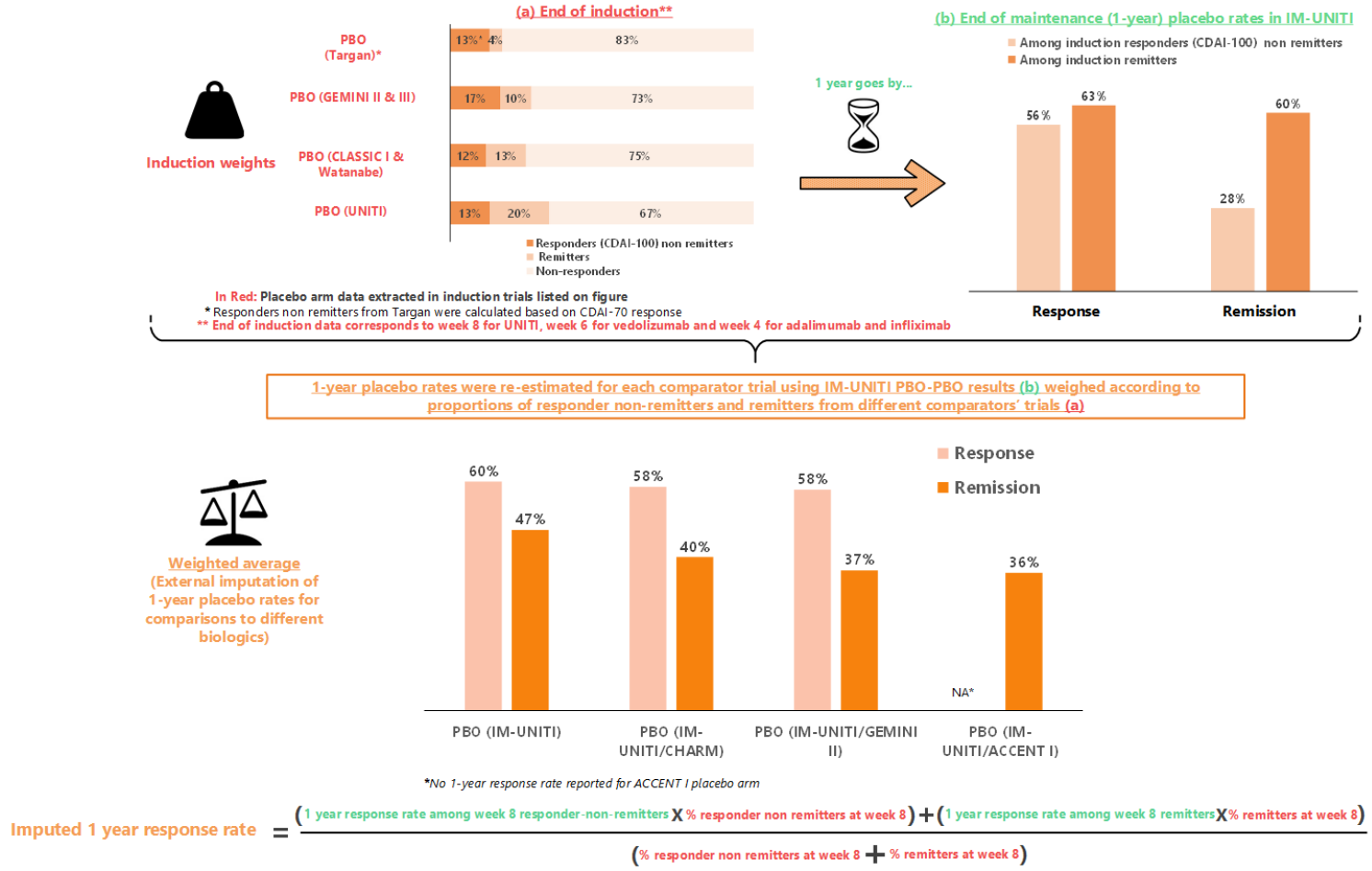
Finally, the process for estimating the inputs for the treatment sequence analysis are reported in figures 30 & 31 Where the relative probability of achieving response based on the re-randomisation criterion was multiplied by the conditional probability of maintaining response (obtained from maintenance trials for active treatment arms and estimated via the weighted average for placebo arms).

We confirm that in general the ERG's description is accurate; however, we would like to make two additional clarifications to aid the ERG's understanding of the analysis:

With respect to the imputation step 3 of the treatment sequence analysis, the ERG has stated "*Placebo-placebo arm of IM-UNITI were estimated using a weighted average of placebo rates in the two sub-populations (convention care failure and TNF-failure). The imputation methods are explained in figures 28 & 29 on pages 128 and 129 of the company submission).*"

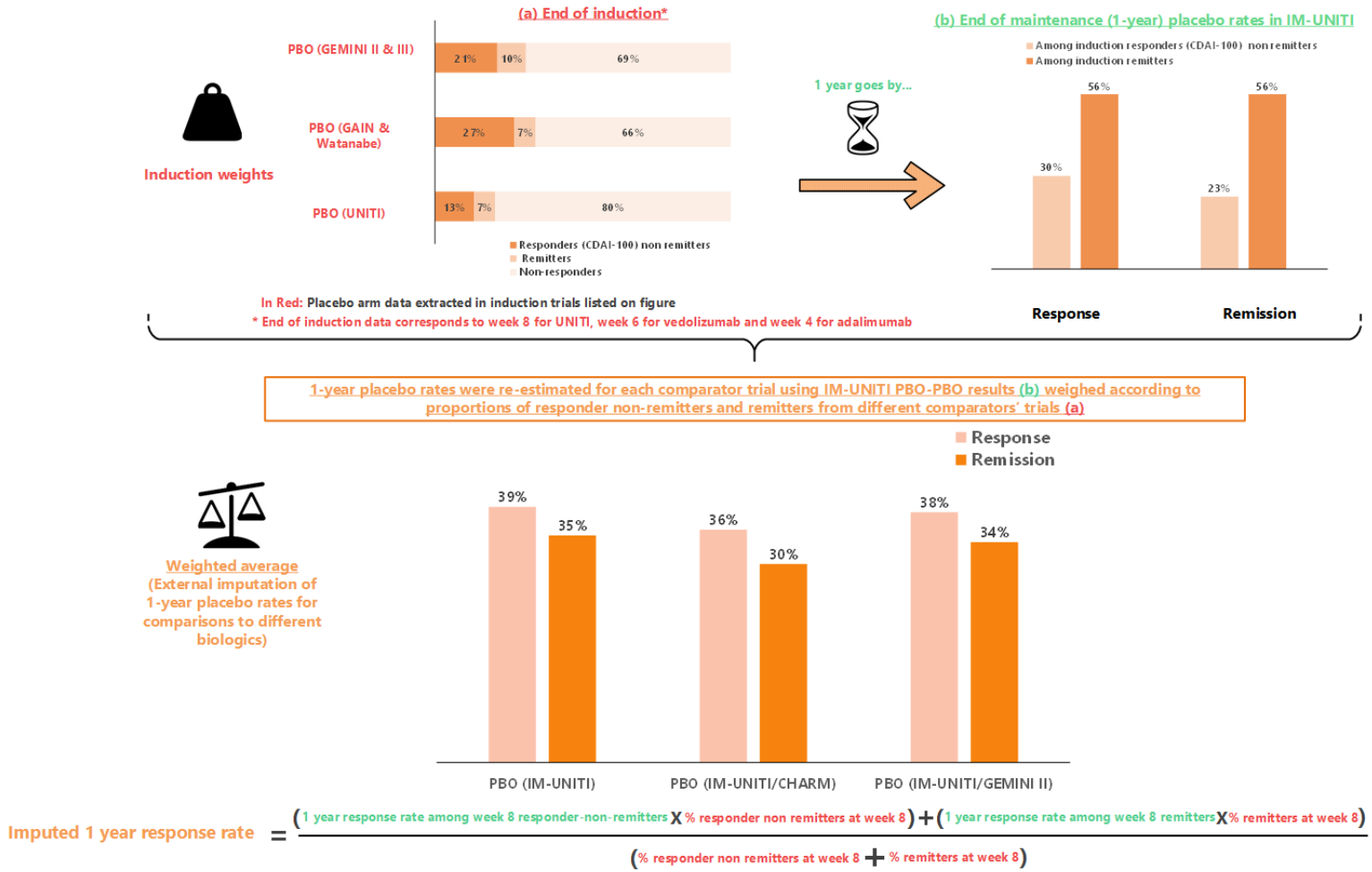
To clarify on this point, each subpopulation has its own weighted average placebo rate, calculated using the placebo-to-placebo arm data from IM-UNITI, adjusted for the proportions of "responders non-remitters" and remitters at the end of induction, by subpopulation. Proportions of "responders non-remitters" and remitters at the end of induction are different for each treatment and sub-population, as shown in section "(a) End of induction**" at the top left corner of Figures 28 and 29 on Pages 128 and 129 of the company submission. These figures are presented below in Figure 1 and Figure 2 for ease of review.

Figure 1: Conventional care failure population – placebo-placebo maintenance arm imputation



Key: CDAI, Crohn's Disease Activity Index; PBO, placebo.

Figure 2: TNF failure population – placebo-placebo maintenance arm imputation



Key: CDAI, Crohn's Disease Activity Index; PBO, placebo; TNF, tumour necrosis factor.

Furthermore, the ERG's final paragraph states "*Finally, the process for estimating the inputs for the treatment sequence analysis are reported in figures 30 & 31 Where the relative probability of achieving response based on the re-randomisation criterion was multiplied by the conditional probability of maintaining response (obtained from maintenance trials for active treatment arms and estimated via the weighted average for placebo arms).*"

To further clarify on this point, we would like to confirm that in the base case analysis, both the placebo-placebo and active treatment data were modelled on a binary scale. The imputed placebo-to-placebo rates for comparators' data only were specified as data inputs and modelled on a log of the odds-odds scale only for the sensitivity analysis. The goal of this sensitivity analysis was to incorporate additional uncertainty around the imputed placebo-placebo rates.

A2. **Priority Question:** Please provide the placebo-placebo imputed data for the responder's non-remitters and responders in the maintenance phase (figures 28 & 29) that were used in the treatment sequence analysis.

Table 1 reports data from the placebo-placebo IM-UNITI individual patient data used in the treatment sequence analysis for the responder non-remitters and responders in the maintenance phase. For example, the end of maintenance response rate in TNF-failure patients among patients who were responder non-remitters at the end of induction is 30%.

Table 1: Placebo-placebo imputed data for the responders non-remitters and responders in the maintenance phase, as used in the treatment sequence analysis

Response/remission status at end of induction	Response/remission status at end of maintenance	Population	Imputed probability
Responder non-remitters at the end of induction (Week 8)	Responders at the end of maintenance	TNF failure patients	30.00%
		Conventional care failure patients	56.00%
	Remitters at the end of maintenance	TNF failure patients	23.33%
		Conventional care failure patients	28.00%
Remitters at the end of induction (Week 8)	Responders at the end of maintenance	TNF failure patients	56.25%
		Conventional care failure patients	62.50%
	Remitters at the end of maintenance	TNF failure patients	56.25%

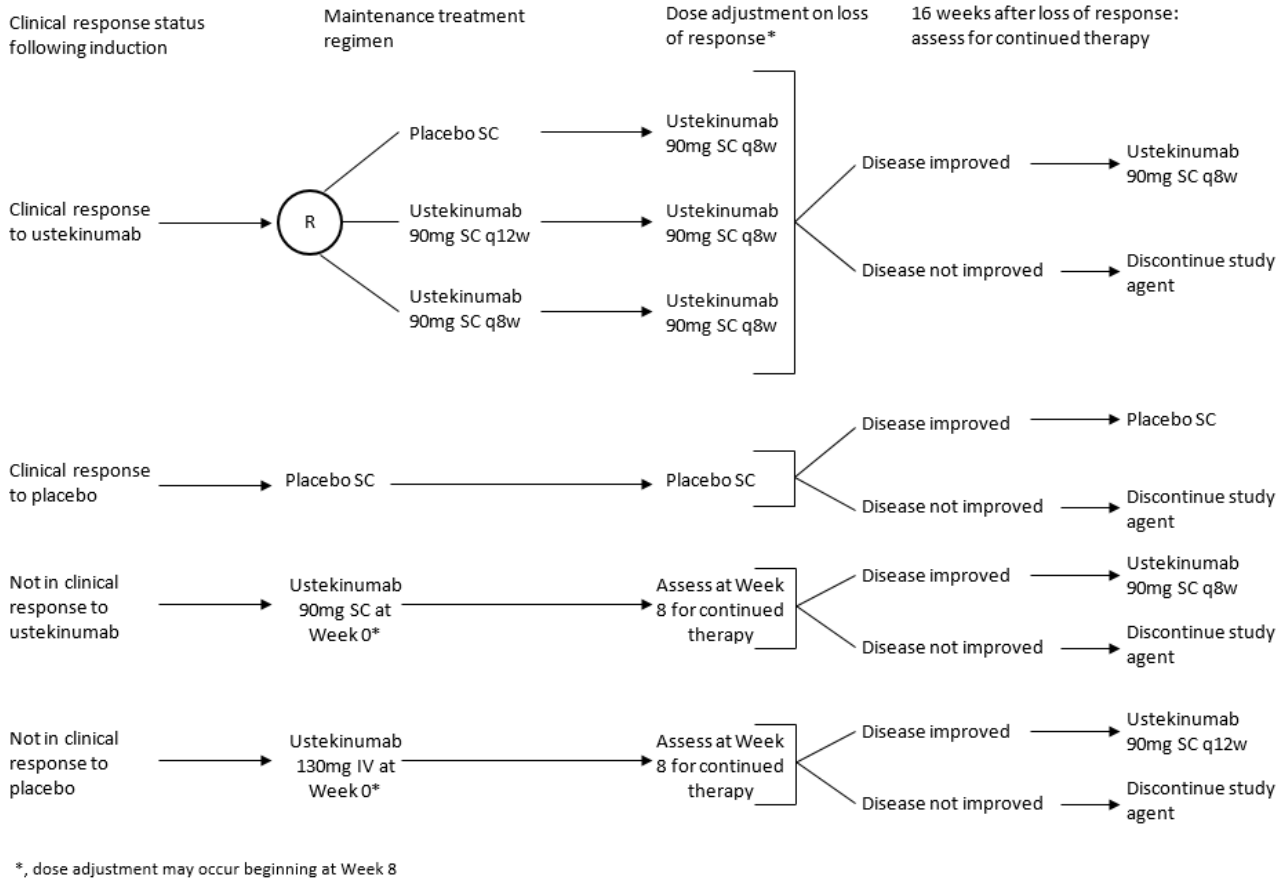
		Conventional care failure patients	60.00%
Key: TNF, tumour necrosis factor.			

A3. **Priority Question:** The ERG understands that the placebo-placebo group data included only those patients who had exhibited a response to placebo in the induction trial. Are there data for patients who continued on placebo regardless of response? The CONSORT diagram (Figure 11 page 81 of the company submission) implies that some patients who did not respond to placebo in the induction trials were followed for the duration of the maintenance trial, please provide any follow-up data for these patients if it exists.

There were no patients who continued to receive placebo regardless of response in the IM-UNITI trial. Patients treated with placebo in IM-UNITI were either ustekinumab responders from UNITI-1 or UNITI-2 randomised to placebo, or responders to placebo in UNITI-1 or UNITI-2 who continued to receive placebo. The breakdown of the different treatment pathways into the IM-UNITI trial was presented in Figure 7 on Page 62 of the main submission dossier. This figure incorrectly stated that in the final pathway patients "not in clinical response to ustekinumab" went on to receive ustekinumab 130mg at Week 0 of the IM-UNITI study. This should have stated patients not in clinical response to placebo would follow this pathway. A corrected version of this figure has been re-presented in Figure 3 for ease of review. We apologise for any confusion this typographical error may have caused in the interpretation of the study pathways and subsequent CONSORT diagrams. For final clarification, the "non-responders to placebo IV induction" arm of the CONSORT diagram therefore presents data for patients who were treated with ustekinumab 130mg IV at Week 0 of IM-UNITI.

The GEMINI II trial is the only trial which has followed up patients who did not respond to placebo and who continued to receive placebo during maintenance.[1] The published data demonstrate that in a small population of 69 patients who were non-responders to placebo at Week 6 and who continued to receive placebo for one year of maintenance, the proportions of patients with clinical remission and CDAI-100 response at 52 weeks were 7.2% in both cases. This demonstrates that the long-term probability of responding to placebo is very low for patients who do not initially respond to placebo.

Figure 3: Study populations of IM-UNITI



Key: IV, intravenous; R, randomisation; SC, subcutaneous; q8w, every 8 weeks; q12w, every 12 weeks.
Note: to maintain the blind for the non-randomised patients, both IV and SC administrations were given to all patients not in clinical response following induction.
Source: IM-UNITI CSR.[2]

To further aid understanding of the trial pathways, these are described in further detail below:

- Patients who responded to ustekinumab induction in the UNITI-1 or UNITI-2 trials and progressed into the IM-UNITI trial were randomised to receive:
    - Ustekinumab 90mg SC every 12 weeks;
    - Ustekinumab 90mg SC every 8 weeks; or
    - Placebo.
- Patients who were in clinical response to placebo in either of the UNITI-1 or UNITI-2 trials continued to receive placebo in the IM-UNITI trial.

- Patients who were not in response to ustekinumab in the UNITI-1 or UNITI-2 trials received ustekinumab 90mg at Week 0 of the IM-UNITI trial. They were assessed at Week 8; with responders continuing to receive ustekinumab 90mg every 8 weeks and non-responders discontinuing the study. This treatment schedule is in line with the license indication for ustekinumab (as reported in Section 2.3 of the main submission).
- Patients not in clinical response to placebo induction in the UNITI-1 or UNITI-2 trials received ustekinumab 130mg IV administration at Week 0. Patients who achieved clinical response at Week 8 initiated ustekinumab 90mg SC at Week 8 and then q12w thereafter through to Week 32, otherwise they were discontinued from further study agent administration.

A4. The company submission compares active treatment response to different variations of 'placebo group' during the IM-UNITI trial. It is not made clear in every instance whether this refers to: the non-randomised placebo-placebo population; the ustekinumab responders randomised to placebo; or both groups pooled together. Please will you clarify this and comment on how appropriate each of these groups is as a comparator and why they were used selectively on different occasions.

Unless specified (in Section 4.7.6 [Page 94] of the main submission), results from the IM-UNITI trial were presented for the randomised component of the trial. Therefore, with the exception of Section 4.7.6 (Page 94), the placebo group referred to was made up of patients who had responded to ustekinumab induction in the UNITI-1 or UNITI-2 trial who were then randomised to receive placebo in IM-UNITI (ustekinumab-placebo patients). Data from the IM-UNITI trial were presented for the randomised component as these were the primary analysis groups for the trial. This population is referred to as the randomised placebo group. Data from the non-randomised component of the IM-UNITI trial that were considered relevant to the decision problem were presented in Section 4.7.6 (Page 94). This included data for patients who had responded to placebo induction in the UNITI-1 or UNITI-2 trial and continued to receive placebo in IM-UNITI (placebo-placebo patients). This population is referred to as the non-randomised pure placebo group. Data across these two groups, that is, the randomised placebo group (ustekinumab-placebo patients) and the non-randomised pure placebo group (placebo-placebo patients), were not pooled for any clinical trial analyses.

Neither of these groups provide data for a true placebo arm, that is, patients who receive placebo induction and maintenance irrespective of response status. The non-randomised placebo group positively selects patients who respond well to conventional care and thus provides data for an exclusive and small subgroup of patients who do not represent the general patient population. The randomised placebo group, while subject to its own limitations of potential 'carryover effect' of biologic induction treatment, is therefore considered a more appropriate comparator set as it consists of a broader group of patients.

The randomised placebo group also provides data in line with placebo groups of other maintenance trials for biologic treatment of Crohn's disease that also consist of patients who had responded to induction therapy.

Within the NMA sections (Section 4.10, Page 110) the placebo group used in the treatment sequence analysis is the placebo-placebo treatment sequence, utilising data from the non-randomised placebo group, but adjusted for the proportions of "responders non-remitters" and remitters at the end of induction using a weighted average of placebo rates in these two subpopulations (Page 125 of the main submission dossier). The rationale for this is that "Placebo" rates in maintenance trials are not true placebo rates, as they are conditional on the rates of patients having responded to induction with different biologics and having been re-randomised to a placebo arm in maintenance and heterogeneity was observed between the placebo rates. Randomisation is not maintained in the NMA after re-randomisation because randomised placebo groups of the trials were replaced by the non-randomised placebo group of IM-UNITI, adjusted for the proportions of responders and remitters at the end of induction. The inclusion criteria and placebo rates of induction trials were similar, suggesting a similarity between patient populations included in the different induction trials. Thus, after the induction, placebo response and remission rates were imputed across trials using patients induced by placebo and (conditional upon response) continued on placebo in the IM-UNITI trial[2] (i.e. the only available data from a placebo-to-placebo arm). Despite the methodological limitations associated with this approach, it is considered here as an alternative method to synthesise the maintenance data providing that patients' characteristics are comparable across trials.

A5. **Priority Question:** Please provide the annotated WinBUGS models/codes for all network meta-analyses (induction, maintenance treatment sequence analysis (including the code for imputing placebo-placebo), performed for each subgroup, and all data inputs used in these analyses and the source of these inputs (e.g. induction phase, UNITI-1 trial).

The WinBUGS code for the induction and treatment sequence base case analysis is presented below. The same code was used for all endpoints and for both conventional care failure and TNF failure subgroups.

Induction and treatment sequence analysis WinBUGS models: Base case analysis

```
# Binomial likelihood, logit link
# Fixed effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)     # vague priors for all trial baselines
   for (k in 1:na[i]) {       # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
      rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
```

```
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
    }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
 # pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:nt) {
#or[1,(c+1)] <- exp(d[c+1])
          for (k in 1:nt) {
                    or[k,c] <- exp(d[c] - d[k])
                    lor[k,c] <- (d[c]-d[k])
                    prob.lor[k,c]<-step(d[c] - d[k])
          }
}

# ranking on relative scale
for (k in 1:nt) {
          rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
#          rk[k] <- rank(d[],k) # assumes events are "bad"
          best[k] <- equals(rk[k],1)
          for (j in 1:nt){hist[j,k]<-equals(rk[k],j)}
}

for (i in 1:ns){
AbsTrEf[i]<- mu[i]*equals(t[i,1],1)
Nref[i]<- 1*equals(t[i,1],1)
}
meanmu<-sum(AbsTrEf[])/sum(Nref[])
mean<-exp(meanmu)/(1+exp(meanmu))


}


}                                   # *** PROGRAM ENDS
```

The WinBUGS code for the treatment sequence sensitivity analysis incorporating uncertainty around the placebo-placebo imputation is presented below. The same code was used for all endpoints and for both conventional care failure and TNF failure subgroups.

Treatment sequence analysis WinBUGS model: Sensitivity analysis code for incorporating placebo-placebo imputation uncertainty

```
# Binomial likelihood, logit link
# Fixed effects model (sensitivity analyses only conducted for FE model)

model{                    # *** PROGRAM STARTS

# log odds model for arm 1
for(i in 1:ns){           # LOOP THROUGH STUDIES

prec[i] <- pow(SE[i],-2)
LOD[i] ~ dnorm(delta[i],prec[i])
delta[i] <- mu[i] + d[t[i,1]] - d[t[i,1]]
```

```
}

# Binomial model for arms 2 and 3
for(i in 1:ns){               # LOOP THROUGH STUDIES

   mu[i] ~ dnorm(0,.001)
   for (k in 2:na[i])  {      # LOOP THROUGH ARMS

      r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood

# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
    }
   }
d[1]<-0    # treatment effect is zero for reference treatment

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
 # pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2

for (c in 1:nt) {
          for (k in 1:nt) {
                    or[k,c] <- exp(d[c] - d[k])
                    lor[k,c] <- (d[c]-d[k])
                    prob.lor[k,c]<-step(d[c] - d[k])
          }
}

temp1 <- r[1,1]
temp2 <- n[1,1]
}      # *** PROGRAM ENDS
```

The data used in the induction phase analysis are presented in Table 2, the data used in the treatment sequence analysis are presented in Table 3 and the data used in the treatment sequence sensitivity analysis incorporating uncertainty around the placebo-placebo imputation are presented in Table 4.

Table 2: Induction phase analysis data

Source	Subpopulation	Treatment	N	CDAI-70 (n)	CDAI-100 (n)	CDAI< 150 (n)
Targan 1997	Conventional care failure	Placebo	24	4		1
Targan 1997	Conventional care failure	Infliximab 5	27	22		13
Targan 1997	Conventional care failure	Placebo	24	4		1
Targan 1997	Conventional care failure	Infliximab 5	26	16		7
CLASSIC I	Conventional care failure	Placebo	74	27	19	9

CLASSIC I	Conventional care failure	Adalimumab 160/80	76	45	38	27
CLASSIC I	Conventional care failure	Adalimumab 80/40	75	44	30	18
GEMINI II	TNF failure	Placebo	70	20	16	3
GEMINI II	TNF failure	Vedolizumab 300	105	37	25	11
GEMINI II	Conventional care failure	Placebo	77	30	22	7
GEMINI II	Conventional care failure	Vedolizumab 300	112	61	42	20
GEMINI III	TNF failure	Placebo	157	50	35	19
GEMINI III	TNF failure	Vedolizumab 300	158	79	62	24
GEMINI III	Conventional care failure	Placebo	50	18	12	6
GEMINI III	Conventional care failure	Vedolizumab 300	51	25	20	16
UNITI-1	TNF failure	Placebo	247	75	53	22
UNITI-1	TNF failure	Ustekinumab 130	245	113	84	40
UNITI-1	TNF failure	Ustekinumab 6	249	109	84	46
UNITI-2	Conventional care failure	Placebo	209	81	60	37
UNITI-2	Conventional care failure	Ustekinumab 130	209	123	108	60
UNITI-2	Conventional care failure	Ustekinumab 6	209	135	116	73
UNITI-1	TNF failure	Placebo	247	72	50	18
UNITI-1	TNF failure	Ustekinumab 130	245	105	82	39
UNITI-1	TNF failure	Ustekinumab 6	249	119	94	52
UNITI-2	Conventional care failure	Placebo	209	92	67	41
UNITI-2	Conventional care failure	Ustekinumab 130	209	121	99	64
UNITI-2	Conventional care failure	Ustekinumab 6	209	139	121	84
GAIN	TNF failure	Placebo	166	56	41	12

GAIN	TNF failure	Adalimumab 160/80	159	82	61	34
CERTIFI	TNF failure	Placebo	132	38	31	14
CERTIFI	TNF failure	Ustekinumab 6	131	62	52	16
Watanabe 2012	TNF failure	Placebo	13	5	2	1
Watanabe 2012	TNF failure	Adalimumab 80/40	20	10	9	2
Watanabe 2012	TNF failure	Adalimumab 160/80	19	12	8	5
Watanabe 2012	Conventional care failure	Placebo	10	2	2	2
Watanabe 2012	Conventional care failure	Adalimumab 80/40	14	10	8	4
Watanabe 2012	Conventional care failure	Adalimumab 160/80	14	11	7	6

Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.

Table 3: Treatment sequence analysis data

Induction phase data source	Maintenance phase data source	Subpopulation	Treatment	Treatment sequence analysis inputs		
				N	CDAI-100 (n)	CDAI<150 (n)
CLASSIC I and Watanabe pooled data	CHARM	Conventional care failure	Placebo-Placebo	84	17	12
CLASSIC I and Watanabe pooled data	CHARM	Conventional care failure	Adalimumab 160 80 - adalimumab 40 eow	90	26	23
CLASSIC I and Watanabe pooled data	CHARM	Conventional care failure	Adalimumab 160 80 - adalimumab 40 weekly	90	32	27
Targan 1997	ACCENT I	Conventional care failure	Placebo-placebo	24	NA	1
Targan 1997	ACCENT I	Conventional care failure	Infliximab 5	27	NA	6
Targan 1997	ACCENT I	Conventional care failure	Infliximab 5 & 10	27	NA	8
UNITI II	IM-UNITI	Conventional care failure	Placebo-placebo	209	48	38
UNITI II	IM-UNITI	Conventional care failure	Ustekinumab 6 - ustekinumab 90 q12w	209	90	77
UNITI II	IM-UNITI	Conventional care failure	Ustekinumab 6 - ustekinumab 90 q8w	209	92	84
GEMINI II and GEMINI III pooled data	GEMINI II	Conventional care failure	Placebo-placebo	127	28	18
GEMINI II and GEMINI III pooled data	GEMINI II	Conventional care failure	Vedolizumab 300 - vedolizumab 300 q8w	163	52	42

GEMINI II and GEMINI III pooled data	GEMINI II	Conventional care failure	Vedolizumab 300 - vedolizumab 300 q4w	163	46	39
GEMINI II and GEMINI III pooled data	GEMINI II	TNF failure	Placebo-placebo	227	6	23
GEMINI II and GEMINI III pooled data	GEMINI II	TNF failure	Vedolizumab 300 - vedolizumab 300 q8w	263	7	32
GEMINI II and GEMINI III pooled data	GEMINI II	TNF failure	Vedolizumab 300 - vedolizumab 300 q4w	263	45	32
UNITI I and CERTITI pooled data	IM-UNITI	TNF failure	Placebo-placebo	379	27	42
UNITI I and CERTITI pooled data	IM-UNITI	TNF failure	Ustekinumab 6 - ustekinumab 90 q12w	380	80	65
UNITI I and CERTITI pooled data	IM-UNITI	TNF failure	Ustekinumab 6 - ustekinumab 90 q8w	380	84	68
GAIN and Watanabe pooled data	CHARM	TNF failure	Placebo-placebo	179	21	20
GAIN and Watanabe pooled data	CHARM	TNF failure	Adalimumab 160 80 - adalimumab 40 eow	178	34	28
GAIN and Watanabe pooled data	CHARM	TNF failure	Adalimumab 160 80 - adalimumab 40 weekly	178	36	32
Key: CDAI, Crohn's Disease Activity Index; eow, every other week; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; TNF, tumour necrosis factor.						

Table 4: Treatment sequence analysis data for sensitivity analysis incorporating uncertainty around the placebo-placebo imputation

Uncertainty dispersion estimation around placebo-placebo arms from each study						**Uncertainty (SE)**				**Used as inputs**		
Endpoint	**P**	**N**	**LCI**	**UCI**	**Events**	**Sampling**	**Pred (LOD)**	**Pred (SE)**	**Var**	**SE**	**LOD**	**Data Source**
Anti-TNF failure Clinical response (CDAI-100) in placebo arms	0.12	379	0.09	0.15	46	0.15	0.00	0.00	0.02	0.15	-2.02	IM-UNITI
	0.12	179	0.08	0.17	22	0.21	0.23	0.02	0.10	0.31	-1.97	CHARM
	0.12	227	0.08	0.16	28	0.19	0.21	0.02	0.08	0.28	-2.01	GEMINI II
Anti-TNF failure Clinical remission (CDAI<150) in placebo arms	**P**	**N**	**LCI**	**UCI**	**Events**	**Sampling**	**Pred (LOD)**	**Pred (SE)**	**Var**	**SE**	**LOD**	**Data Source**
	0.11	379	0.08	0.14	42	0.15	0.00	0.00	0.02	0.15	-2.14	IM-UNITI
	0.11	179	0.06	0.15	20	0.22	0.25	0.03	0.11	0.33	-2.14	CHARM
	0.10	227	0.07	0.15	23	0.21	0.22	0.02	0.09	0.30	-2.17	GEMINI II
Conventional care failure Clinical response (CDAI-100) in placebo arms	**P**	**N**	**LCI**	**UCI**	**Events**	**Sampling**	**Pred (LOD)**	**Pred (SE)**	**Var**	**SE**	**LOD**	**Data Source**
	0.23	209	0.18	0.29	48	0.14	0.00	0.00	0.02	0.14	-1.20	IM-UNITI
	0.20	84	0.12	0.29	17	0.24	0.28	0.03	0.14	0.37	-1.38	CHARM
	0.22	127	0.15	0.30	28	0.19	0.22	0.02	0.08	0.29	-1.27	GEMINI II
Conventional care failure Clinical remission (CDAI<150) in placebo arms	**P**	**N**	**LCI**	**UCI**	**Events**	**Sampling**	**Pred (LOD)**	**Pred (SE)**	**Var**	**SE**	**LOD**	**Data Source**
	0.18	209	0.13	0.24	38	0.16	0.00	0.00	0.03	0.16	-1.50	IM-UNITI
	0.14	84	0.07	0.22	12	0.29	0.32	0.04	0.19	0.43	-1.82	CHARM
	0.14	127	0.08	0.20	18	0.24	0.26	0.03	0.12	0.35	-1.83	GEMINI II
	0.06	24	0.00	0.18	2	0.71	1.01	0.67	1.97	1.40	-2.74	ACCENT I

Key: Events, number of patients in response or remission; LCI, lower 95% confidence interval; LOD is the log of odds associated with P and used as input in the log odds model; N, total number of patients in placebo arm; UCI, upper 95% confidence interval; P, proportion of patients in response or remission; SE, standard error derived used as input in in the log odds model.

The calculations code for the treatment sequence analysis sensitivity analysis incorporating uncertainty around the placebo-placebo imputation is as follows:

Sampling=1/SQRT(Events); Pred(LOD)= (LN(UCI/(1-UCI))-LN(LCI/(1-LCI)))/(2*1.96); Pred(SE) =(1/SQRT(LCI*N)-1/SQRT(UCI*N))/(2*1.96); Var =Pred(LOD)^2+Sampling^2+Pred(SE)^2; SE=SQRT(Var); LOD=LN(P/(1-P))

A6. **Priority Question:** The methods section mentions that both fixed and random effects models were considered for the NMA, but it is not clear which model was used from the results presented on Page 132-141 of the main submission, and Page 77-91 of Appendix 5. Please clarify whether these results were each generated from a fixed or random effects model, and please provide the results of both models in each case.

Results were generated for both the fixed- and random-effects models, but results from the fixed-effects model were presented in the base case analysis reported in the main submission dossier, based on the DIC (Table 5 for induction and Table 6 for maintenance).

Table 5: Induction DIC

	Fixed effects model	**Random effects model**
Conventional care failure		
CDAI-70	91	93
CDAI-100	79	81
CDAI<150	84	86
TNF failure		
CDAI-70	80	82
CDAI-100	80	80
CDAI<150	70	71
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.		

Table 6: Maintenance DIC:

	Fixed effects model	**Random effects model**
Conventional care failure		
CDAI-100	64	64
CDAI<150	79	79
TNF failure		
CDAI-100	66	66
CDAI<150	65	65
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.		

Results of both the fixed effects and random effects model can be found in Table 7 to

Table 10 for each endpoint in the induction and treatment sequence network meta-analyses by subpopulation.

Table 7: Induction phase NMA results: Conventional care failure population

	CDAI-70		**CDAI-100**		**CDAI<150**	
	OR	**CrI** **Pr**	**OR**	**CrI** **Pr**	**OR**	**CrI** **Pr**
Fixed effects model						
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	1.58	[0.85 ; 2.94] Pr=93%	1.85	[0.96 ; 3.51] Pr=97%	0.93	[0.39 ; 2.08] Pr=43%
Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.92	[0.43 ; 1.91] Pr=41%	1.03	[0.47 ; 2.20] Pr=53%	0.64	[0.25 ; 1.53] Pr=16%
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	0.92	[0.46 ; 2.05] Pr=48%	1.39	[0.64 ; 2.97] Pr=80%	1.14	[0.44 ; 2.82] Pr=60%
Ustekinumab 6 mg/kg vs. Infliximab 5 mg/kg	0.11	[0.02 ; 0.48] Pr=0%	NA	NA	0.08	[0.01 ; 0.59] Pr=0%
Ustekinumab 6 mg/kg vs. Placebo	2.89	[1.95 ; 4.32] Pr=100%	3.12	[2.08 ; 4.68] Pr=100%	2.5	[1.60 ; 3.98] Pr=100%
Vedolizumab 300 mg vs. Placebo	1.83	[1.14 ; 2.95] Pr=99%	1.69	[1.02 ; 2.84] Pr=98%	2.69	[1.38 ; 5.59] Pr=100%
Adalimumab 160/80 mg vs. Placebo	3.15	[1.70 ; 5.94] Pr=100%	3.03	[1.60 ; 5.89] Pr=100%	3.92	[1.86 ; 8.95] Pr=100%
Adalimumab 80/40 mg vs Placebo	2.94	[1.59 ; 5.55] Pr=100%	2.25	[1.18 ; 4.34] Pr=99%	2.2	[1.00 ; 5.17] Pr=98%
Infliximab 5 mg/kg vs. Placebo	25.8	[6.50 ; 136.10] Pr=100%	NA	NA	31.34	[4.50 ; 963.60] Pr=100%
	CDAI-70		**CDAI-100**		**CDAI<150**	
	OR	**CrI, Pr**	**OR**	**CrI, Pr**	**OR**	**CrI, Pr**
Random model						
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	1.6	[0.17 ; 15.48] Pr=75%	1.81	[0.26 ; 12.01] Pr=82%	0.92	[0.13 ; 6.00] Pr=0.45%

Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.78	[0.05 ; 5.62]	0.99	[0.12 ; 6.63]	0.64	[0.09 ; 4.69]
		Pr=36%		Pr=49%		Pr=0.26%
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	0.86	[0.06 ; 6.62]	1.26	[0.14 ; 7.47]	1.15	[0.16 ; 8.68]
		Pr=42%		Pr=64%		Pr=0.58%
Ustekinumab 6 mg/kg vs. Infliximab 5 mg/kg	0.11	[0.01 ; 1.91]	NA	NA	0.07	[0.00 ; 1.23]
		Pr=5%				Pr=0.03%
Ustekinumab 6 mg/kg vs. Placebo	2.89	[0.47 ; 17.84]	3.1	[0.67 ; 14.26]	2.5	[0.56 ; 11.11]
		Pr=93%		Pr=95%		Pr=93%
Vedolizumab 300 mg vs. Placebo	1.82	[0.47 ; 6.81]	1.71	[0.55 ; 5.54]	2.72	[0.86 ; 9.30]
		Pr=88%		Pr=89%		Pr=96%
Adalimumab 160/80 mg vs. Placebo	3.81	[1.18 ; 23.89]	3.14	[0.93 ; 12.37]	3.92	[1.06 ; 14.48]
		Pr=98%		Pr=97%		Pr=98%
Adalimumab 80/40 mg vs Placebo	3.4	[1.02 ; 19.62]	2.48	[0.81 ; 10.87]	2.17	[0.56 ; 8.03]
		Pr=98%		Pr=96%		Pr=90%
Infliximab 5 mg/kg vs. Placebo	25.94	[2.94 ; 270.20]	NA	NA	33.19	[2.99 ; 1,190.00]
		Pr=99%				Pr=100%

Key: CDAI, Crohn's Disease Activity Index; CrI, credible interval; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; Pr, probability; vs. versus.

Table 8: Induction phase NMA results: TNF failure population

	CDAI-70		CDAI-100		CDAI<150	
	OR	**CrI Pr**	**OR**	**CrI Pr**	**OR**	**CrI Pr**
Fixed effects model						
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	0.96	[0.57 ; 1.62] Pr=45%	1.05	[0.59 ; 1.85] Pr=56%	1.53	[0.69 ; 3.39] Pr=85%
Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.83	[0.47 ; 1.46] Pr=26%	0.93	[0.51 ; 1.70] Pr=40%	0.64	[0.26 ; 1.51] Pr=16%
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	1.29	[0.38 ; 4.40] Pr=66%	0.66	[0.18 ; 2.34] Pr=26%	2.24	[0.36 ; 20.32] Pr=80%
Ustekinumab 6 mg/kg vs. Placebo	1.79	[1.24 ; 2.60] Pr=100%	1.87	[1.26 ; 2.80] Pr=100%	2.34	[1.37 ; 4.08] Pr=100%
Vedolizumab 300 mg vs. Placebo	1.86	[1.29 ; 2.72] Pr=100%	1.79	[1.20 ; 2.70] Pr=100%	1.53	[0.87 ; 2.76] Pr=93%
Adalimumab 160/80 mg vs. Placebo	2.16	[1.41 ; 3.32] Pr=100%	2.02	[1.28 ; 3.20] Pr=100%	3.65	[1.90 ; 7.38] Pr=100%
Adalimumab 80/40 mg vs Placebo	1.38	[0.43 ; 4.49] Pr=71%	2.84	[0.85 ; 9.90] Pr=96%	1.05	[0.12 ; 6.16] Pr=52%
	CDAI-70		**CDAI-100**		**CDAI<150**	
	OR	**CrI Pr**	**OR**	**OR**	**CrI Pr**	**OR**
Random effects model						
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	0.99	[0.13 ; 8.10] Pr=50%	1.12	[0.10 ; 14.21] Pr=57%	1.42	[0.10 ; 14.94] Pr=67%
Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.8	[0.09 ; 6.22] Pr=35%	0.82	[0.05 ; 8.93] Pr=39%	0.62	[0.04 ; 7.18] Pr=28%
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	1.25	[0.10 ; 14.47] Pr=60%	0.58	[0.02 ; 9.76] Pr=31%	2.14	[0.07 ; 57.80] Pr=71%
Ustekinumab 6 mg/kg vs. Placebo	1.79	[0.33 ; 9.52]	1.86	[0.25 ; 14.09]	2.35	[0.32 ; 17.09]

		Pr=86%		Pr=82%		Pr=88%
Vedolizumab 300 mg vs. Placebo	1.8	[0.51 ; 5.79]	1.66	[0.37 ; 6.76]	1.65	[0.42 ; 8.42]
		Pr=90%		Pr=82%		Pr=83%
Adalimumab 160/80 mg vs. Placebo	2.23	[0.66 ; 8.71]	2.28	[0.57 ; 13.31]	3.82	[0.84 ; 22.07]
		Pr=94%		Pr=92%		Pr=97%
Adalimumab 80/40 mg vs Placebo	1.43	[0.23 ; 9.82]	3.26	[0.41 ; 37.17]	1.1	[0.07 ; 16.33]
		Pr=68%		Pr=89%		Pr=53%
Key: CDAI, Crohn's Disease Activity Index; CrI, credible interval; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; Pr, probability; TNF, tumour necrosis factor; vs. versus.						

Table 9: Treatment sequence NMA results: Conventional care failure population

	CDAI-100			CDAI<150		
	OR	**CrI**	**Pr**	**OR**	**CrI**	**Pr**
Fixed effects model						
Ustekinumab q12w mg/kg vs. Vedolizumab q8w	1.54	[0.77 ; 3.05]	89%	1.24	[0.58 ; 2.61]	71%
Ustekinumab q12w mg/kg vs. Vedolizumab q4w	1.84	[0.92 ; 3.65]	96%	1.37	[0.64 ; 2.91]	79%
Ustekinumab q12w mg/kg vs. Adalimumab eow	1.58	[0.68 ; 3.62]	86%	1.26	[0.50 ; 3.07]	69%
Ustekinumab q12w mg/kg vs. Adalimumab weekly	1.16	[0.51 ; 2.60]	64%	1.01	[0.40 ; 2.40]	51%
Ustekinumab q12w mg/kg vs. Infliximab 5 mg/kg	NA	NA	NA	0.6	[0.07 ; 3.24]	29%
Ustekinumab q12w mg/kg vs. Infliximab 5 & 10 mg/kg	NA	NA	NA	0.41	[0.05 ; 2.13]	16%
Ustekinumab q12w mg/kg vs. Placebo-Placebo	2.55	[1.68 ; 3.90]	100%	2.64	[1.69 ; 4.17]	100%
Ustekinumab q8w mg/kg vs. Vedolizumab q8w	1.6	[0.81 ; 3.15]	91%	1.43	[0.66 ; 2.99]	82%
Ustekinumab q8w mg/kg vs. Vedolizumab q4w	1.91	[0.96 ; 3.78]	97%	1.58	[0.73 ; 3.35]	88%
Ustekinumab q8w mg/kg vs. Adalimumab eow	1.64	[0.71 ; 3.73]	88%	1.45	[0.58 ; 3.53]	79%
Ustekinumab q8w mg/kg vs. Adalimumab weekly	1.2	[0.53 ; 2.69]	67%	1.16	[0.47 ; 2.77]	63%
Ustekinumab q8w mg/kg vs. Infliximab 5 mg/kg	NA	NA	NA	0.69	[0.08 ; 3.73]	34%
Ustekinumab q8w mg/kg vs. Infliximab 5 & 10 mg/kg	NA	NA	NA	0.48	[0.06 ; 2.46]	20%
Ustekinumab q8w mg/kg vs. Placebo-Placebo	2.64	[1.74 ; 4.05]	100%	3.04	[1.96 ; 4.80]	100%
Vedolizumab q8w vs. Placebo-Placebo	1.66	[0.98 ; 2.86]	97%	2.13	[1.17 ; 4.00]	99%
Vedolizumab q4w vs. Placebo-Placebo	1.39	[0.81 ; 2.41]	88%	1.92	[1.05 ; 3.63]	98%
Adalimumab eow vs. Placebo-Placebo	1.61	[0.80 ; 3.31]	91%	2.09	[0.97 ; 4.64]	97%
Adalimumab weekly vs. Placebo-Placebo	2.2	[1.12 ; 4.47]	99%	2.61	[1.25 ; 5.77]	99%

Infliximab 5 mg/kg vs. Placebo-Placebo	NA	NA	NA	4.38	[0.87 ; 35.18]	96%
Infliximab 5 & 10 mg/kg vs. Placebo-Placebo	NA	NA	NA	6.37	[1.33 ; 50.25]	99%
	CDAI-100			**CDAI<150**		
	OR	**CrI**	**Pr**	**OR**	**CrI**	**Pr**
Random effects model						
Ustekinumab q12w mg/kg vs. Vedolizumab q8w	1.53	[0.04 ; 54.49]	66%	1.25	[0.03 ; 46.33]	58%
Ustekinumab q12w mg/kg vs. Vedolizumab q4w	1.82	[0.05 ; 66.65]	71%	1.37	[0.04 ; 51.14]	61%
Ustekinumab q12w mg/kg vs. Adalimumab eow	1.57	[0.04 ; 58.05]	66%	1.26	[0.03 ; 48.25]	58%
Ustekinumab q12w mg/kg vs. Adalimumab weekly	1.16	[0.03 ; 41.79]	55%	1	[0.03 ; 38.37]	50%
Ustekinumab q12w mg/kg vs. Infliximab 5 mg/kg	NA	NA	NA	0.58	[0.01 ; 28.41]	36%
Ustekinumab q12w mg/kg vs. Infliximab 5 & 10 mg/kg	NA	NA	NA	0.4	[0.01 ; 19.10]	28%
Ustekinumab q12w mg/kg vs. Placebo-Placebo	2.55	[0.20 ; 32.02]	84%	2.64	[0.20 ; 33.60]	84%
Ustekinumab q8w mg/kg vs. Vedolizumab q8w	1.59	[0.04 ; 56.79]	67%	1.44	[0.04 ; 52.96]	63%
Ustekinumab q8w mg/kg vs. Vedolizumab q4w	1.90	[0.05 ; 68.84]	71%	1.59	[0.04 ; 60.07]	66%
Ustekinumab q8w mg/kg vs. Adalimumab eow	1.64	[0.05 ; 59.57]	67%	1.46	[0.04 ; 55.41]	63%
Ustekinumab q8w mg/kg vs. Adalimumab weekly	1.20	[0.03 ; 44.39]	57%	1.16	[0.03 ; 44.52]	55%
Ustekinumab q8w mg/kg vs. Infliximab 5 mg/kg	NA	NA	NA	0.67	[0.01 ; 32.93]	40%
Ustekinumab q8w mg/kg vs. Infliximab 5 & 10 mg/kg	NA	NA	NA	0.46	[0.01 ; 22.11]	31%
Ustekinumab q8w mg/kg vs. Placebo-Placebo	2.65	[0.21 ; 33.38]	85%	3.05	[0.24 ; 38.77]	87%
Vedolizumab q8w vs. Placebo-Placebo	1.67	[0.13 ; 21.50]	73%	2.12	[0.16 ; 27.95]	79%
Vedolizumab q4w vs. Placebo-Placebo	1.4	[0.11 ; 17.98]	67%	1.93	[0.15 ; 25.21]	77%

Adalimumab eow vs. Placebo-Placebo	1.62	[0.12 ; 21.29]	71%	2.09	[0.15 ; 28.66]	78%
Adalimumab weekly vs. Placebo-Placebo	2.21	[0.17 ; 28.45]	80%	2.63	[0.20 ; 35.48]	83%
Infliximab 5 mg/kg vs. Placebo-Placebo	NA	NA	NA	4.52	[0.24 ; 107.70]	87%
Infliximab 5 & 10 mg/kg vs. Placebo-Placebo	NA	NA	NA	6.55	[0.35 ; 153.20]	92%
Key: CDAI, Crohn's Disease Activity Index; CrI, credible interval; eow, every other week; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; Pr , probability; vs. versus; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks.						

Table 10: Treatment sequence NMA results: TNF failure population

	CDAI-100			CDAI<150		
	OR	**CrI**	**Pr**	**OR**	**CrI**	**Pr**
Fixed effects model						
Ustekinumab q12w mg/kg vs. Vedolizumab q8w	1.77	[0.91 ; 3.45]	95%	1.35	[0.66 ; 2.73]	80%
Ustekinumab q12w mg/kg vs. Vedolizumab q4w	1.31	[0.68 ; 2.50]	80%	1.35	[0.66 ; 2.70]	80%
Ustekinumab q12w mg/kg vs. Adalimumab eow	1.15	[0.56;2.32]	65%	1.11	[0.52 ; 2.35]	61%
Ustekinumab q12w mg/kg vs. Adalimumab weekly	1.07	[0.53 ; 2.14]	57%	0.94	[0.45 ; 1.97]	44%
Ustekinumab q12w mg/kg vs. Placebo-Placebo	1.94	[1.31 ; 2.90]	100%	1.66	[1.10 ; 2.54]	99%
Ustekinumab q8w mg/kg vs. Vedolizumab q8w	1.89	[0.97 ; 3.67]	97%	1.43	[0.70 ; 2.88]	84%
Ustekinumab q8w mg/kg vs. Vedolizumab q4w	1.4	[0.73 ; 2.66]	85%	1.43	[0.70 ; 2.87]	84%
Ustekinumab q8w mg/kg vs. Adalimumab eow	1.22	[0.60 ; 2.46]	71%	1.17	[0.56 ; 2.49]	66%
Ustekinumab q8w mg/kg vs. Adalimumab weekly	1.14	[0.56 ; 2.28]	64%	1	[0.48 ; 2.09]	50%
Ustekinumab q8w mg/kg vs. Placebo-Placebo	2.06	[1.40 ; 3.08]	100%	1.75	[1.17 ; 2.68]	100%
Vedolizumab q8w vs. Placebo-Placebo	1.1	[0.64 ; 1.88]	63%	1.23	[0.70 ; 2.20]	77%
Vedolizumab q4w vs. Placebo-Placebo	1.48	[0.89 ; 2.48]	93%	1.23	[0.70 ; 2.21]	76%
Adalimumab eow vs. Placebo-Placebo	1.69	[0.95 ; 3.07]	96%	1.5	[0.81 ; 2.80]	90%
Adalimumab weekly vs. Placebo-Placebo	1.82	[1.03 ; 3.27]	98%	1.76	[0.96 ; 3.24]	97%
	CDAI-100			**CDAI<150**		
	OR	**CrI**	**Pr**	**OR**	**CrI**	**Pr**
Random effects model						
Ustekinumab q12w mg/kg vs. Vedolizumab q8w	1.78	[0.05 ; 64.03]	70%	1.35	[0.04 ; 49.69]	61%
Ustekinumab q12w mg/kg vs. Vedolizumab q4w	1.31	[0.04 ; 48.90]	60%	1.35	[0.04 ; 49.33]	61%
Ustekinumab q12w mg/kg vs. Adalimumab eow	1.14	[0.03 ; 41.06]	55%	1.11	[0.03 ; 41.13]	54%

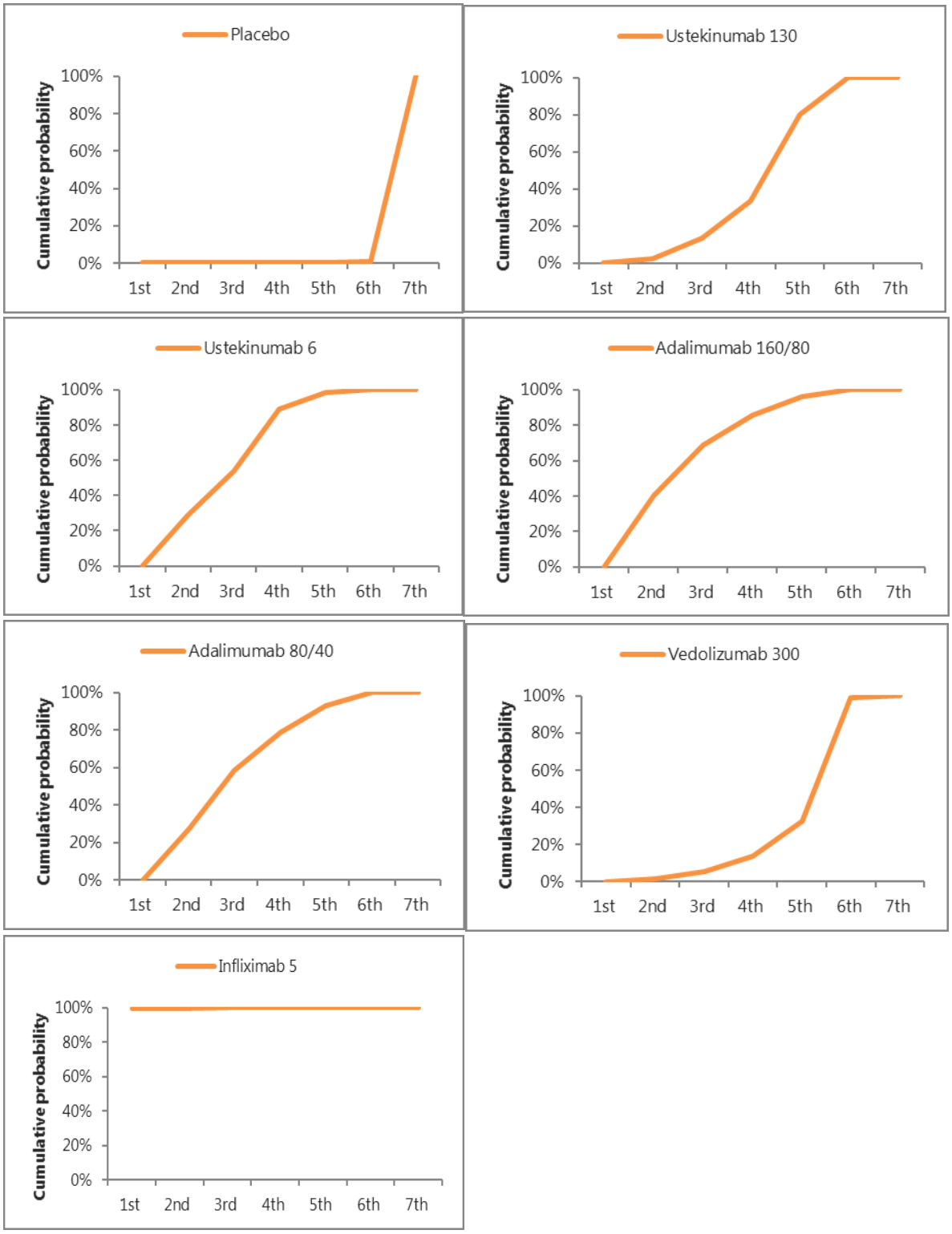
Ustekinumab q12w mg/kg vs. Adalimumab weekly	1.07	[0.03 ; 38.47]	52%	0.95	[0.03 ; 34.82]	48%
Ustekinumab q12w mg/kg vs. Placebo-Placebo	1.95	[0.15 ; 24.17]	78%	1.67	[0.13 ; 21.14]	74%
Ustekinumab q8w mg/kg vs. Vedolizumab q8w	1.89	[0.05 ; 69.54]	71%	1.42	[0.04 ; 51.95]	63%
Ustekinumab q8w mg/kg vs. Vedolizumab q4w	1.39	[0.04 ; 51.24]	63%	1.42	[0.04 ; 53.30]	63%
Ustekinumab q8w mg/kg vs. Adalimumab eow	1.21	[0.03 ; 44.32]	57%	1.18	[0.03 ; 42.48]	56%
Ustekinumab q8w mg/kg vs. Adalimumab weekly	1.13	[0.03 ; 41.51]	55%	1	[0.03 ; 35.69]	50%
Ustekinumab q8w mg/kg vs. Placebo-Placebo	2.07	[0.16 ; 25.77]	80%	1.76	[0.14 ; 21.90]	75%
Vedolizumab q8w vs. Placebo-Placebo	1.09	[0.09 ; 13.87]	55%	1.23	[0.09 ; 15.79]	61%
Vedolizumab q4w vs. Placebo-Placebo	1.48	[0.11 ; 18.61]	69%	1.24	[0.10 ; 15.64]	61%
Adalimumab eow vs. Placebo-Placebo	1.71	[0.13 ; 22.19]	73%	1.49	[0.12 ; 19.30]	69%
Adalimumab weekly vs. Placebo-Placebo	1.82	[0.14 ; 23.59]	76%	1.76	[0.14 ; 23.21]	74%

Key: CDAI, Crohn's Disease Activity Index; CrI, credible interval; eow, every other week; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; Pr, probability; vs. versus; q4w, every 4 weeks; q8w, every 8 weeks; q12w, every 12 weeks; TNF, tumour necrosis factor.

A7. Please provide the SUCRA plots for the treatments included in the NMA, as these have not been presented in the results on pages 132-141.

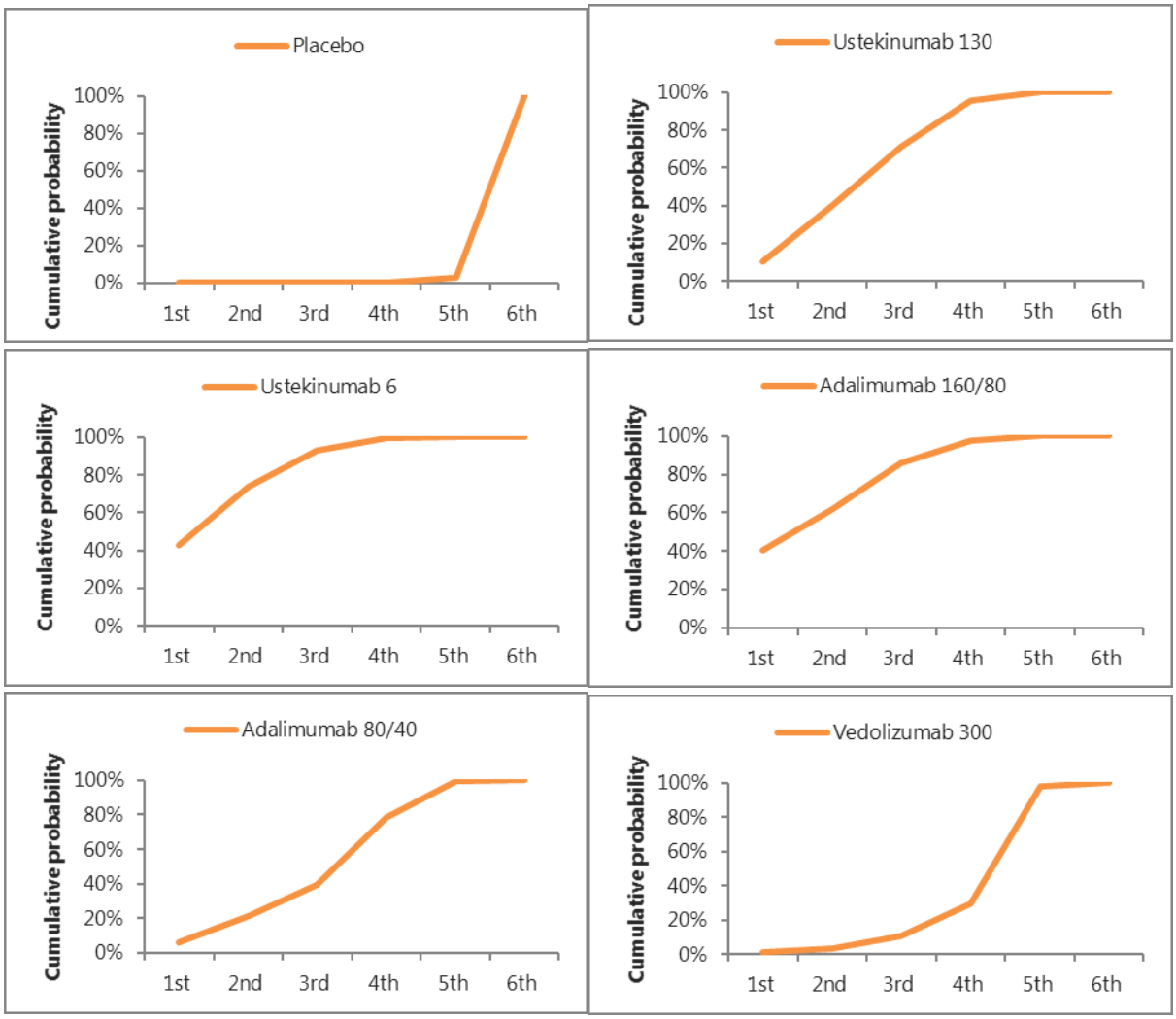
The SUCRA plots are provided in Figure 4 to Figure 6 for all outcomes of the induction NMA for the conventional care failure population; in Figure 7 to Figure 9 for all outcomes of the induction NMA for the TNF failure population, in Figure 10 and Figure 11 for all outcomes of the treatment sequence NMA for the conventional care failure population and in Figure 12 and Figure 13 for all outcomes of the treatment sequence NMA for the TNF failure population.

Figure 4: SUCRA plots: Induction – Conventional care failure: CDAI-70



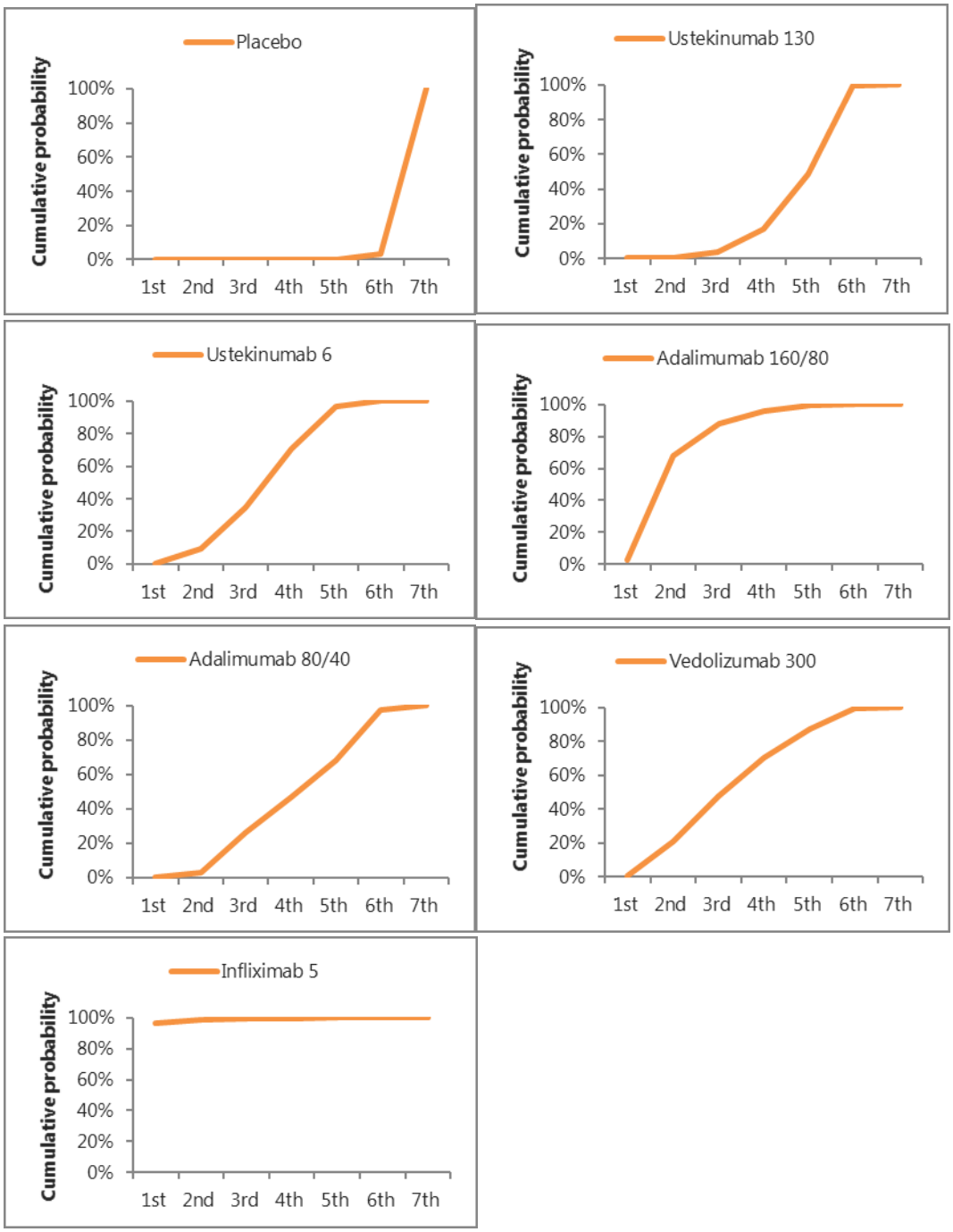
Key: CDAI, Crohn's Disease Activity Index.

Figure 5: SUCRA plots: Induction – Conventional care failure: CDAI-100



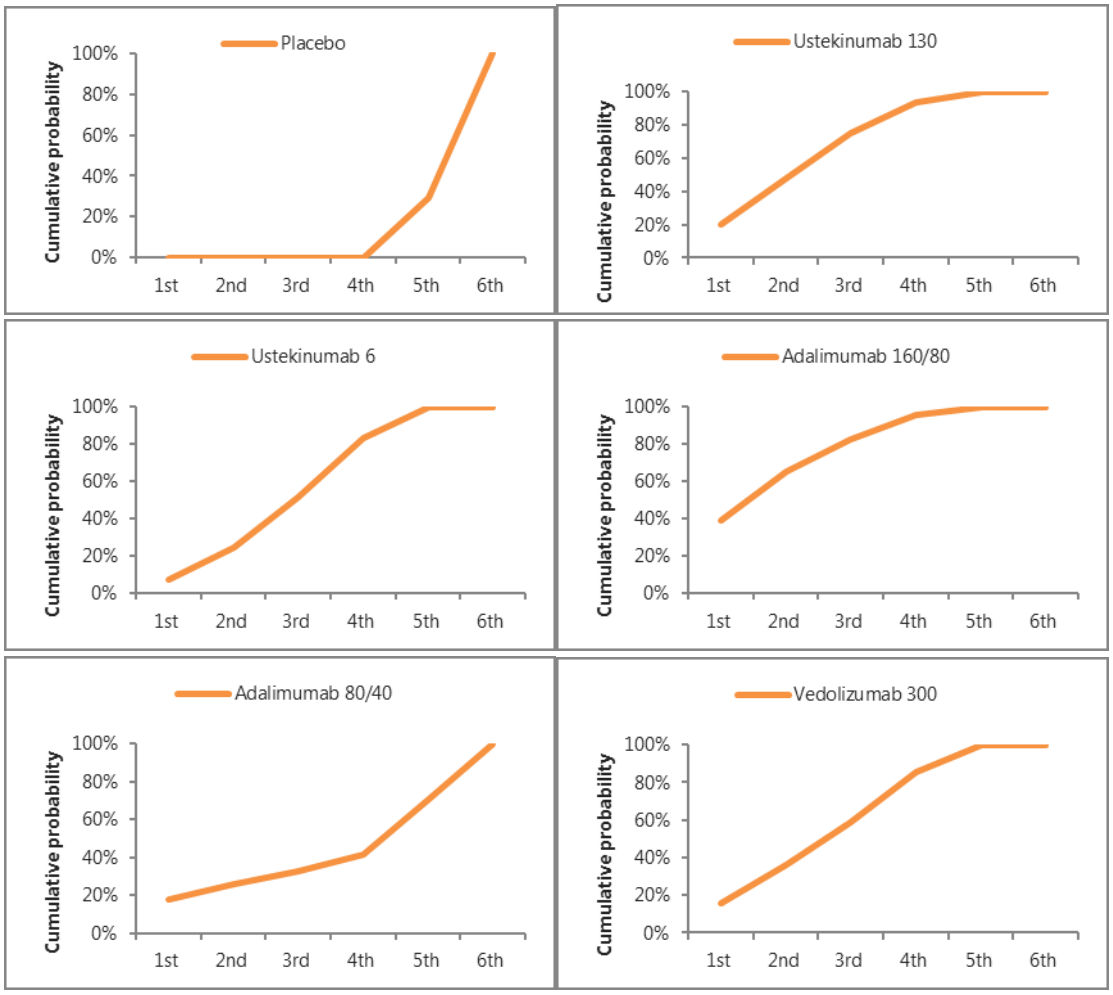
Key: CDAI, Crohn's Disease Activity Index.

Figure 6: SUCRA plots: Induction – Conventional care failure: CDAI<150



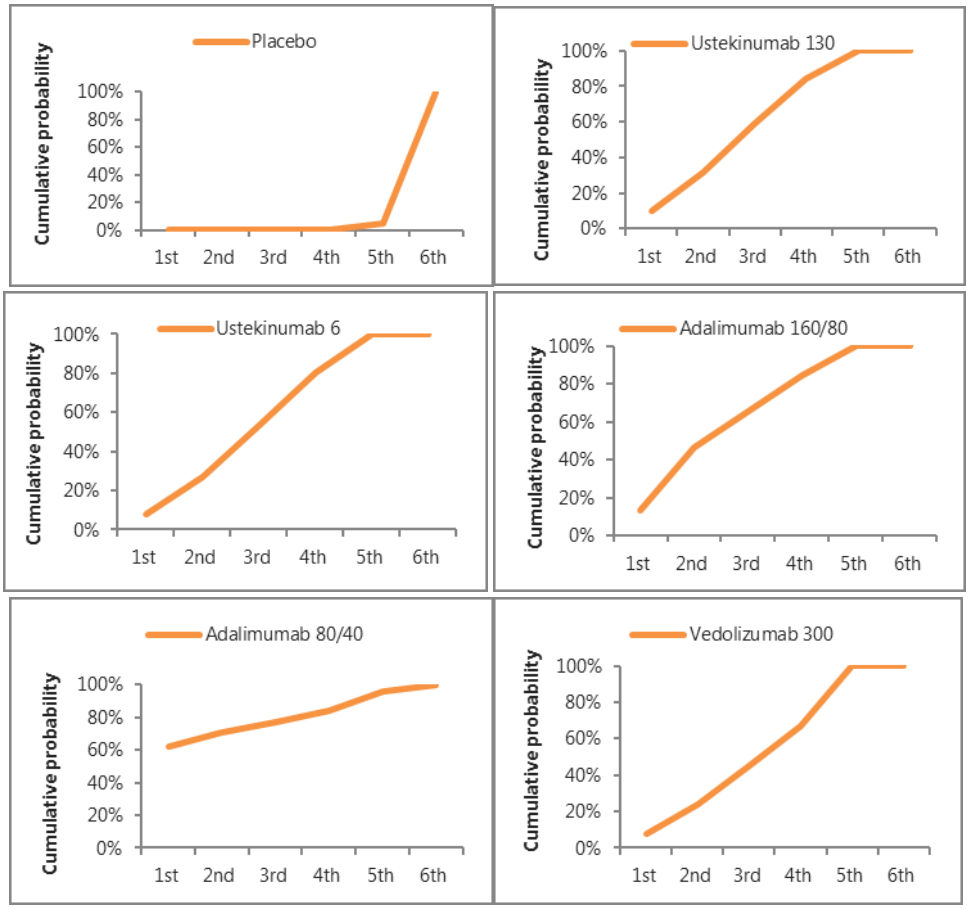
Key: CDAI, Crohn's Disease Activity Index.

Figure 7: SUCRA plots: Induction – TNF failure: CDAI-70



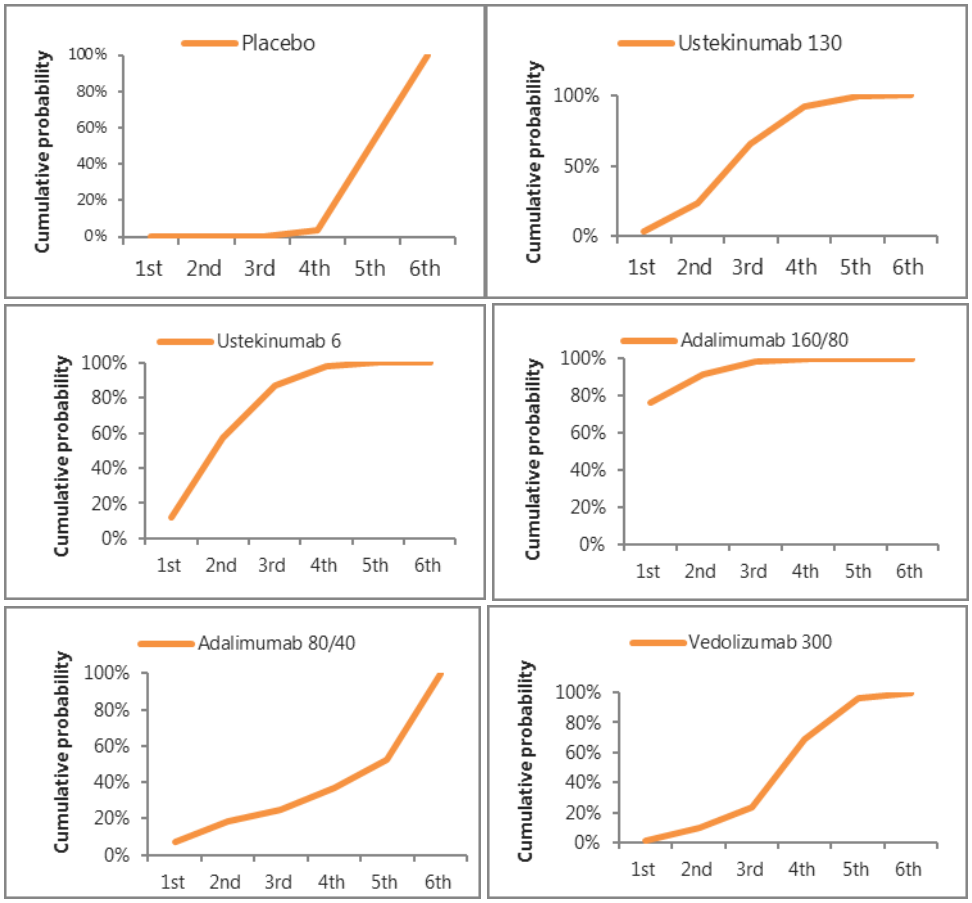
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.

Figure 8: SUCRA plots: Induction – TNF failure: CDAI-100



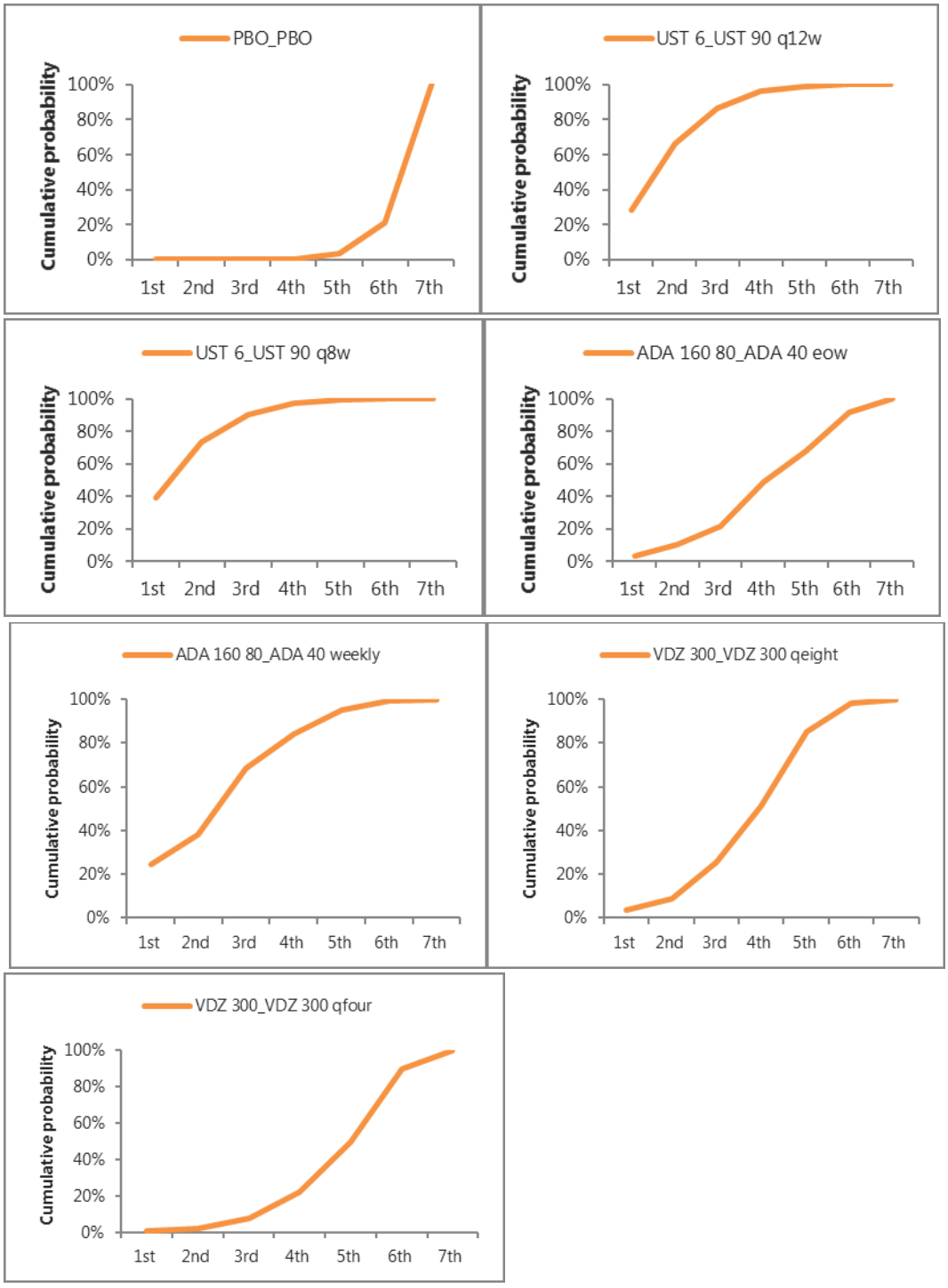
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.

Figure 9: SUCRA plots: Induction – TNF failure: CDAI<150



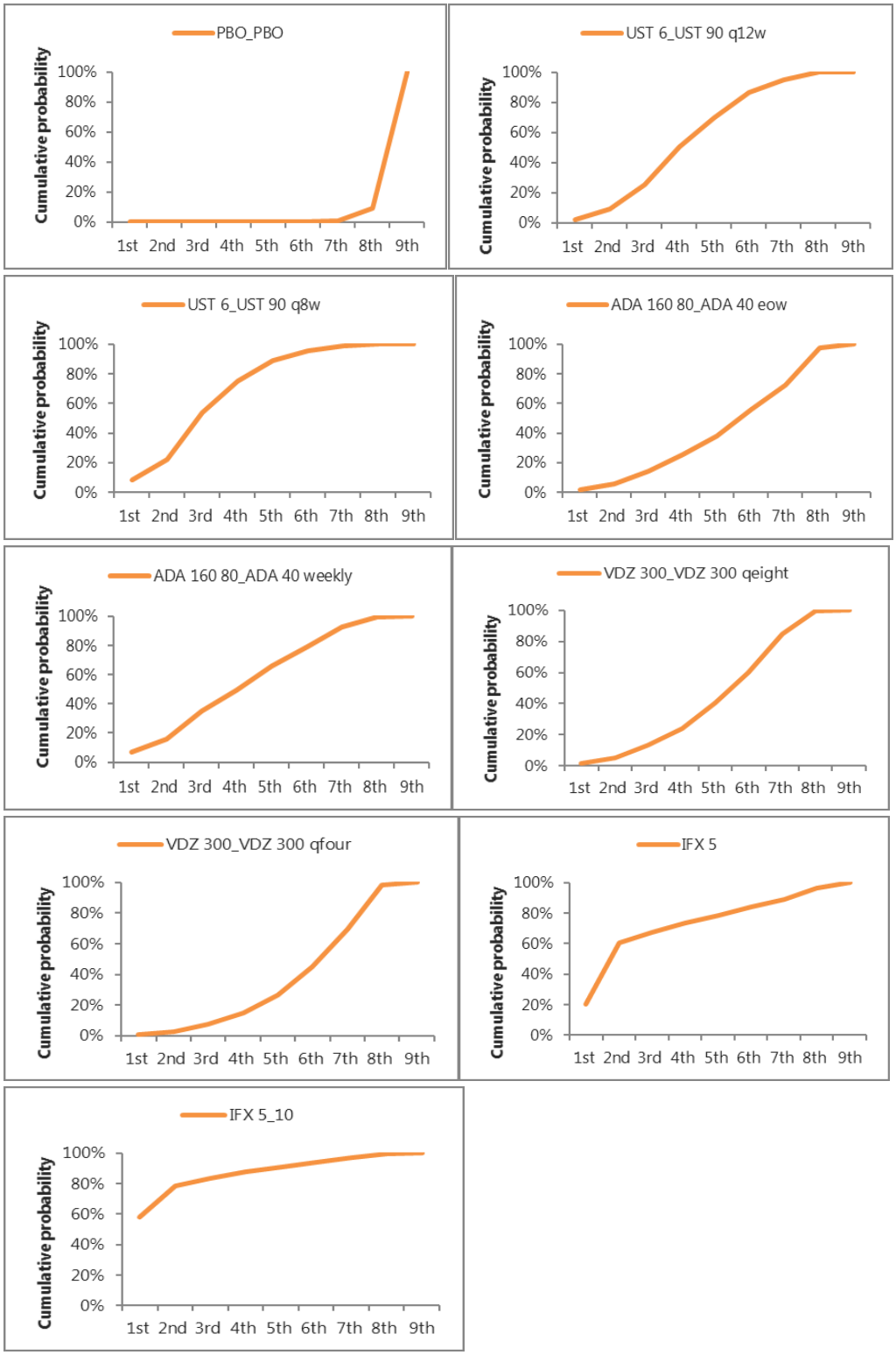
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.

Figure 10: SUCRA plots: Treatment sequence – Conventional care failure: CDAI-100



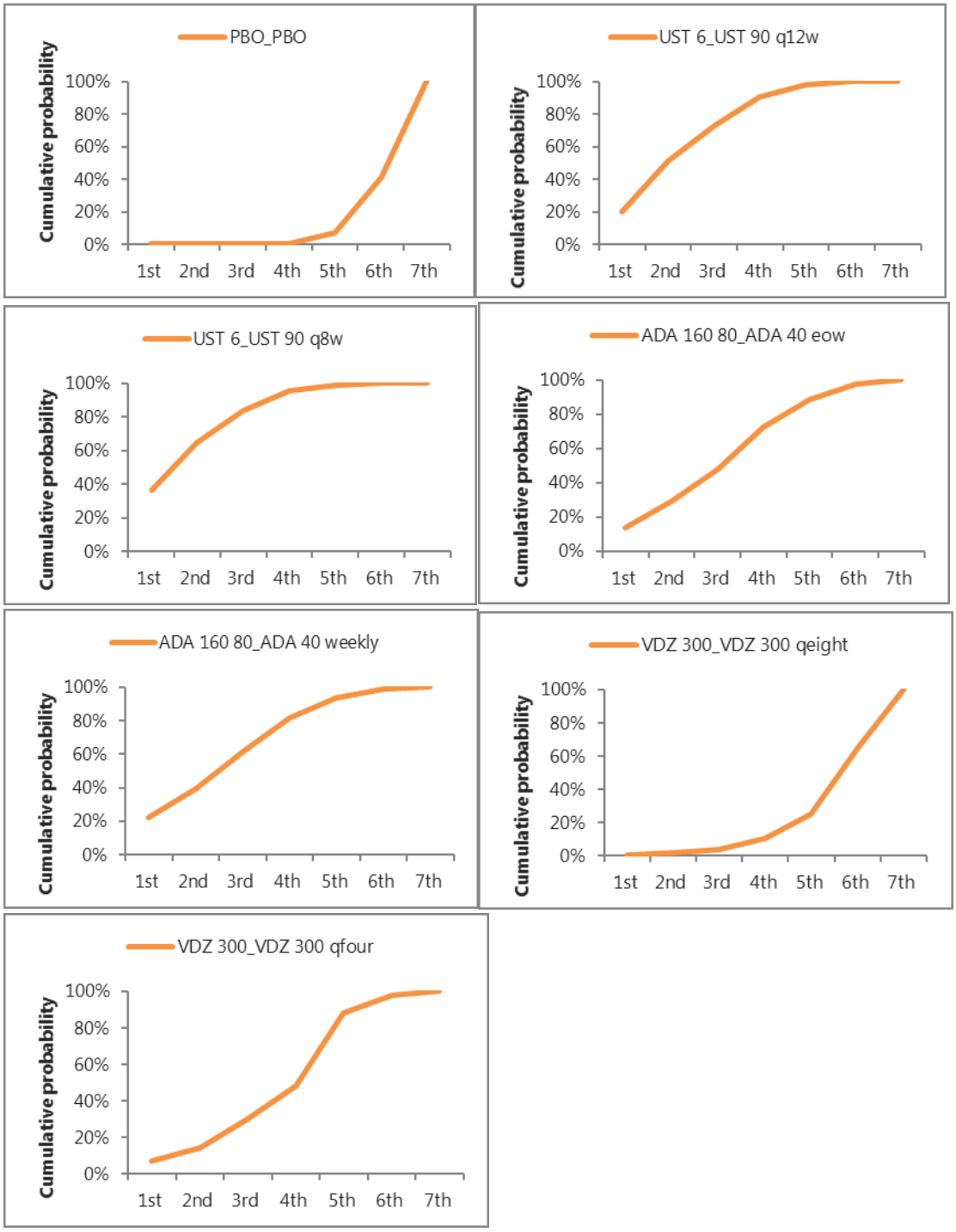
Key: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; eow, every other week; PBO, placebo;q8w, every 8 weeks; q12w, every 12 weeks; qeight, every 8 weeks; qfour, every four weeks UST, ustekinumab; VDZ, vedolizumab.

Figure 11: SUCRA plots: Treatment sequence – Conventional care failure: CDAI<150



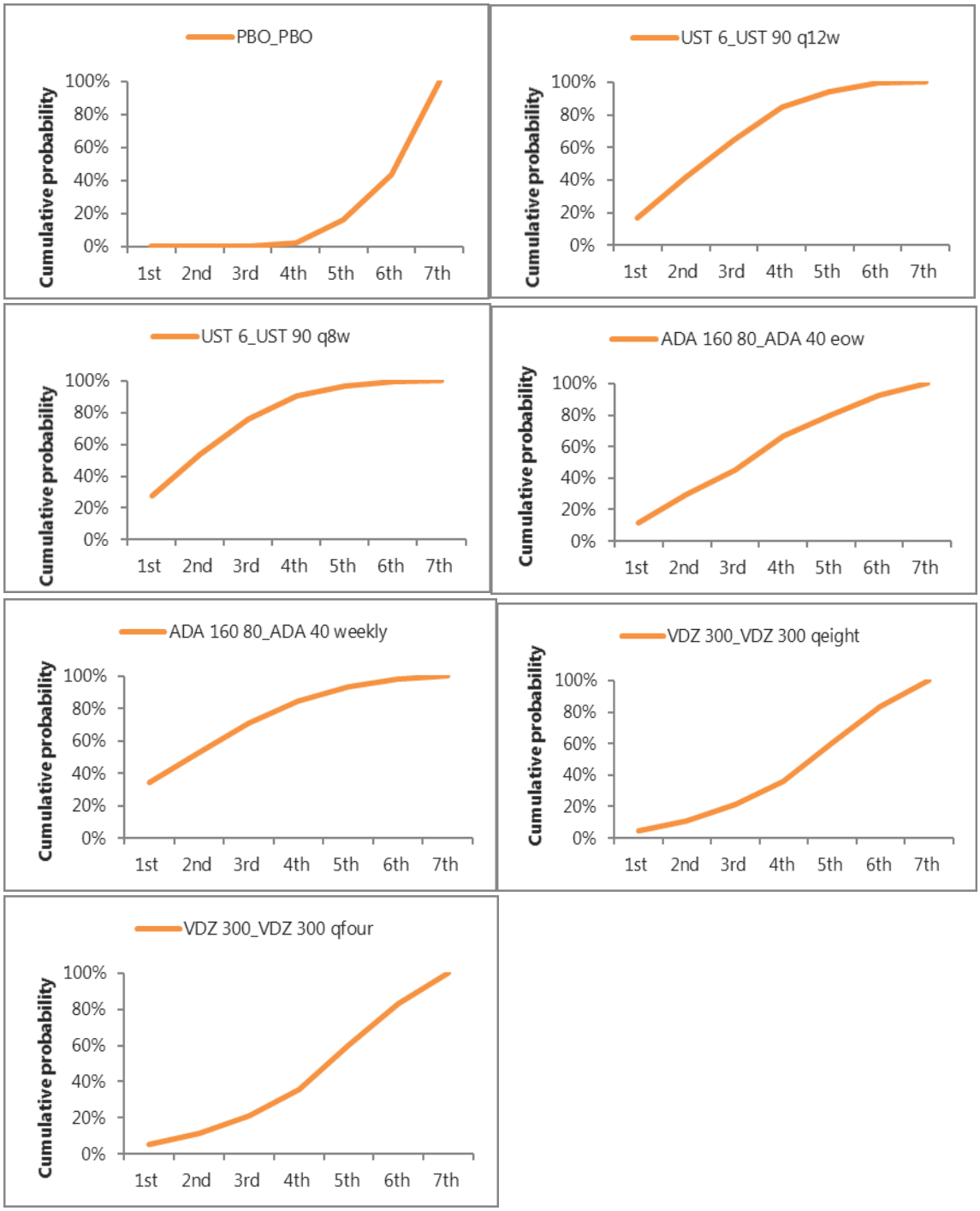
Key: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; eow, every other week; IFX, infliximab; PBO, placebo;q8w, every 8 weeks; q12w, every 12 weeks; qeight, every 8 weeks; qfour, every four weeks UST, ustekinumab; VDZ, vedolizumab.

Figure 12: SUCRA plots: Treatment sequence – TNF failure: CDAI-100



Key: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; eow, every other week; PBO, placebo;q8w, every 8 weeks; q12w, every 12 weeks; qeight, every 8 weeks; qfour, every four weeks UST, ustekinumab; VDZ, vedolizumab.

Figure 13: SUCRA plots: Treatment sequence – TNF failure: CDAI<150



Key: ADA, adalimumab; CDAI, Crohn's Disease Activity Index; eow, every other week; PBO, placebo;q8w, every 8 weeks; q12w, every 12 weeks; qeight, every 8 weeks; qfour, every four weeks UST, ustekinumab; VDZ, vedolizumab.

Clinical trial evidence

A8. **Priority Question**: From reading the submission and checking the CSR we understand that the population in UNITI-2 whilst being (almost) 100% patients who have not demonstrated failure/intolerance to TNF antagonist therapy, includes around 30% patients who have previously received (and presumably responded to anti-TNFs) and 70% who are anti-TNF naïve. Data for this 'truly naïve' population have been included in sensitivity analyses of the NMA (sequence analysis). As the decision problem includes this conventional care- only failure population please can you provide (in a table) the results for the primary outcome and main secondary outcomes (including endoscopic results) for this sub-group?

The decision problem for this appraisal includes the population of people "*with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-alpha inhibitor, or who are intolerant to either of them*". This can be considered as two separate populations of people:

- Those in whom the disease has responded inadequately to, is no longer responding to, or are intolerant to conventional therapy (described as the conventional care failure population)
- Those in whom the disease has responded inadequately to, is no longer responding to, or are intolerant to a TNFα inhibitor (described as the TNF failure population)

In clinical practice, there may be patients who have received and were tolerant of TNFα inhibitor therapy, but who are not considered to have responded inadequately or stopped responding to the treatment (for instance a patient with high levels of inflammation at diagnosis may receive a dose of infliximab to reduce the inflammation before starting treatment on conventional therapy, i.e. it was discontinued for a reason other than lack or loss of efficacy or intolerance). These patients cannot be considered part of the TNF failure population and would likely be considered eligible for further TNFα inhibitor therapy; and, therefore, should be considered as part of the conventional care failure population. The UNITI-2 trial population includes both patients who are "truly naïve" (~70%) and patients who have been exposed to treatment with TNFα inhibitor therapy but are not considered part of the TNF failure population (~30%).The primary outcome and secondary outcomes of truly naïve patients are included in Table 11 (induction Week 6) and Table 12 (maintenance Week 44). We consider that the full UNITI-2 trial population represents the conventional care failure population and that considering the "truly naïve" population to be representative of the conventional care failure population may lead to the exclusion of patients who are eligible for ustekinumab treatment under its licensed indication from the decision problem. Furthermore, the UNITI-2 population is randomised, whereas considering the "truly naïve" subgroup of patients breaks randomisation and results in a smaller sample size which increases uncertainty.

Table 11: Summary of primary and secondary endpoints at Week 6 of induction: Truly naïve population

	Ustekinumab 6mg/kg[a]
Total N	144
Subjects in clinical response (CDAI-100)[b,c], n (%)	81 (56.3%)
Subjects in clinical remission[b,c], n (%)	56 (38.9%)
Subjects in 70-point response	94 (65.3%)
Notes: [a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg). [b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response/remission. [c] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response/remission. **Source:** Data on file.[3]	

Table 12: Summary of primary and secondary endpoints at Week 44 of maintenance: Truly naïve population

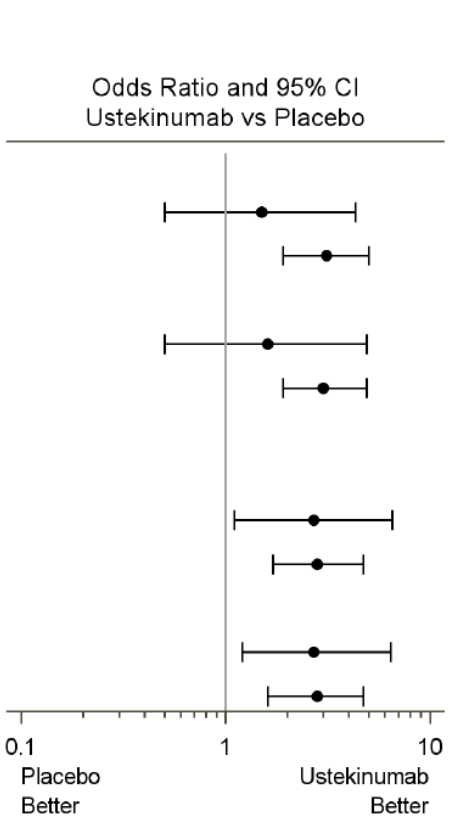
	Ustekinumab 90mg SC q12w	**Ustekinumab 90mg SC q8w**
Total N	53	52
Subjects in clinical response (CDAI-100)[a,b], n (%)	36 (67.9%)	37 (73.1%)
Subjects in clinical remission[a,b], n (%)	30 (56.6%)	34 (65.4%)
Key: q8w, every 8 weeks; q12w, every 12 weeks. **Notes:** [a] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score. [b] Subjects who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission. **Source:** Data on file.[4, 5]		

As reported in Section 4.8 of the main submission (Page 109):

"In subgroup analysis of UNITI-2, patients who had not previously received a TNFα inhibitor demonstrated similar efficacy (clinical response and clinical remission rates at Week 6) to those patients who had previously been exposed to a TNFα inhibitor (but who did not meet the failure criteria specified for UNITI-1)."

Forest plots of results specific to the population of patients in UNITI-2 who had not previously received a TNFα inhibitor were presented within Appendix 4.4 of the main submission, and the relevant data are presented again here for your convenience.

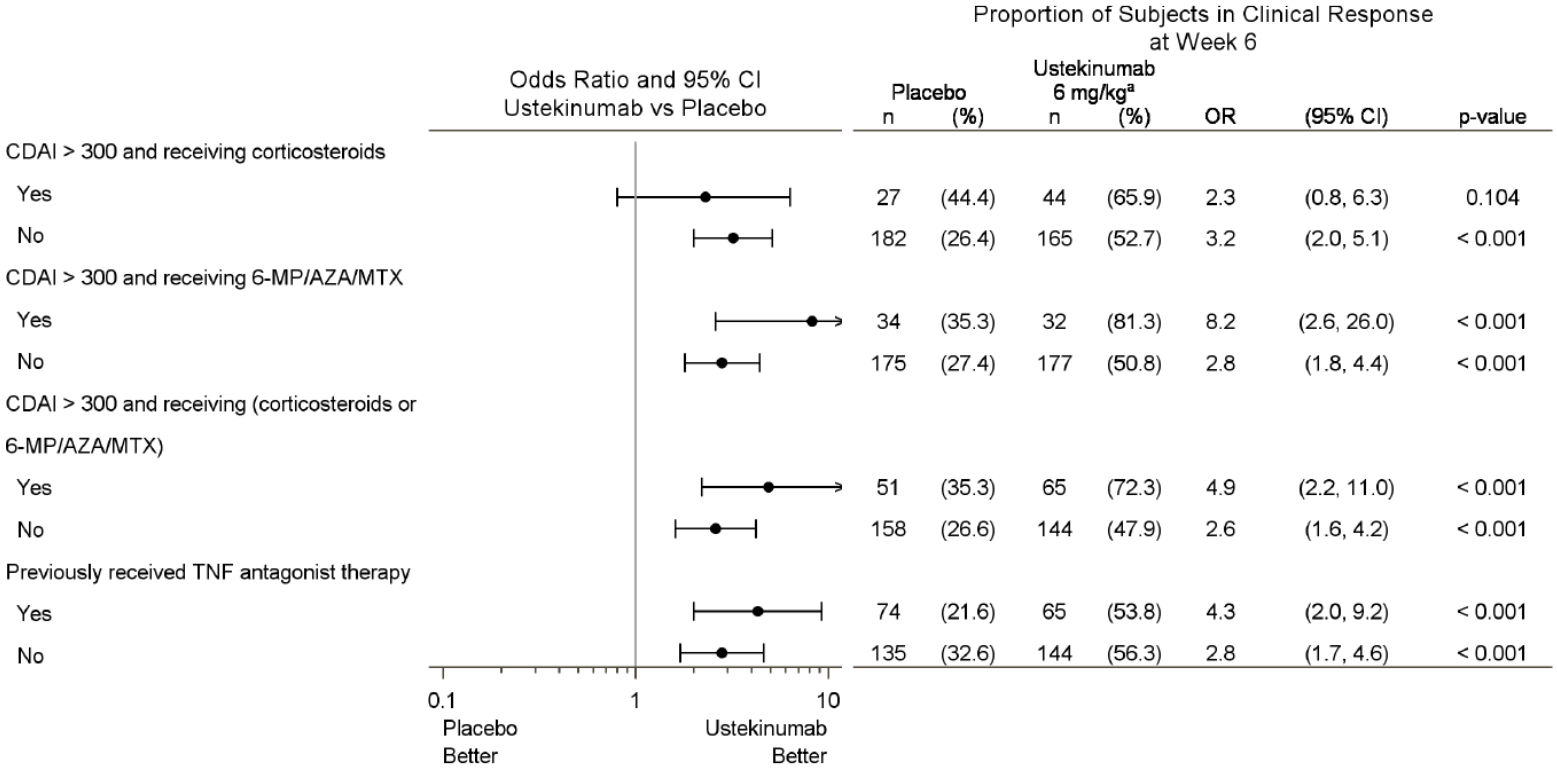
Figure 14: Subgroup analysis for clinical remission at Week 8 by CD-related drug history in the ustekinumab ~6mg/kg group versus the placebo group (ITT population)



	Proportion of Subjects in Clinical Remission at Week 8						
	Placebo		Ustekinumab 6 mg/kg[a]				
	n	(%)	n	(%)	OR	(95% CI)	p-value
CDAI > 300 and receiving corticosteroids							
Yes	27	(25.9)	44	(36.4)	1.5	(0.5, 4.3)	0.501
No	182	(18.7)	165	(41.2)	3.1	(1.9, 5.0)	< 0.001
CDAI > 300 and receiving 6-MP/AZA/MTX							
Yes	34	(20.6)	32	(28.1)	1.6	(0.5, 4.9)	0.458
No	175	(19.4)	177	(42.4)	3.0	(1.9, 4.9)	< 0.001
CDAI > 300 and receiving (corticosteroids or 6-MP/AZA/MTX)							
Yes	51	(17.6)	65	(36.9)	2.7	(1.1, 6.5)	0.028
No	158	(20.3)	144	(41.7)	2.8	(1.7, 4.7)	< 0.001
Previously received TNF antagonist therapy							
Yes	74	(14.9)	65	(30.8)	2.7	(1.2, 6.4)	0.022
No	135	(22.2)	144	(44.4)	2.8	(1.6, 4.7)	< 0.001

Key: 5-ASA, 5-aminosalicylic acid (mesalazine); 6-MP, 6-Mercaptopurine; AZA, azathioprine; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; ITT, intention-to-treat; MTX, methotrexate; OR, odds ratio; TNF, tumour necrosis factor.
Note: [a]Weight-range based ustekinumab doses approximating 6mg/kg: 260 mg (weight ≤55kg), 390mg (weight >55kg and ≤85kg) and 520 mg (weight >85kg).
Source: UNITI-2 CSR.[6]

Figure 15: Subgroup analysis for clinical response at Week 6 by CD-related drug history in the ustekinumab ~6mg/kg group versus the placebo group (ITT population)



Key: 5-ASA, 5-aminosalicylic acid (mesalazine); 6-MP, 6-Mercaptopurine; AZA, azathioprine; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; ITT, intention-to-treat; MTX, methotrexate; OR, odds ratio; TNF, tumour necrosis factor.
Note: [a]Weight-range based ustekinumab doses approximating 6mg/kg: 260 mg (weight ≤55kg), 390mg (weight >55kg and ≤85kg) and 520 mg (weight >85kg).
Source: UNITI-2 CSR.[6]

The endoscopic sub-study included only small patient numbers (Table 13). In particular only 29 patients in the placebo arm were naïve to TNFα inhibitors; therefore, the results were not analysed separately for subgroups of these data.

Table 13: Randomised patients in the endoscopic sub-study (UNITI-1 and UNITI-2)

	Randomised patients in endoscopic sub-study	
	Ustekinumab[a]	**Placebo**
Total population	155	97
UNITI-1	66	41
UNITI-2	89	56
TNFα inhibitor naïve	65	29
TNFα inhibitor failure	66	41
TNFα inhibitor experienced (not failed)	24	27
Note: [a]Ustekinumab 130 mg and tiered ustekinumab doses approximating 6 mg/kg combined **Source:** Endoscopic sub-study report.[7]		

A9. In table 19 (page 107) of the company submission, the endoscopic results are presented at week 8, but baseline measures are not reported. Please provide baseline scores for SES-CD, and numbers of patients in the different response states for UNITI-1 and UNITI-2 separately. On page 110 of the company submission, pre-planned and post-hoc analyses of endoscopic data from the maintenance trial are referred to. Please provide the details of these analyses and the results.

A summary of the endoscopic outcomes (SES-CD score, endoscopic remission and endoscopic response) for the UNITI-1 and UNITI-2 trials is presented in Table 14. A summary of the endoscopic outcomes (SES-CD score, endoscopic remission and endoscopic response) that formed the pre-planned and *post hoc* analyses of endoscopic data from the IM-UNITI maintenance trial is presented in Table 15.

Table 14: Summary of endoscopic outcomes in the UNITI-1 and UNITI-2 trials

	UNITI-1		**UNITI-2**	
	Ustekinumab[a]	**Placebo**	**Ustekinumab[a]**	**Placebo**
Randomised patients	66	41	89	56
Baseline				
SES-CD score, mean (SD)	14.6 (8.3)	12.3 (6.7)	13.9 (8.0)	12.4 (8.3)
Week 8				
SES-CD CFB, mean (SD)	-2.3 (5.2)	0.2 (3.2)	-3.1 (6.0)	-1.4 (5.9)

≥3-point reduction from baseline in SES-CD score, n (%)	29 (43.9)	7 (17.1)	45 (50.6)	22 (39.3)
Patients in endoscopic remission, n (%)	2 (3.0)	0	10 (11.2)	4 (7.1)
Patients in endoscopic response, n (%)	9 (13.6)	0	23 (25.8)	13 (23.2)

Key: CFB, change from baseline; CRP, C-reactive protein; SD, standard deviation.
Note: [a]Due to small patient numbers the ustekinumab 130mg and tiered ustekinumab doses approximating 6 mg/kg were combined for this analysis.
Source: Endoscopic sub-study report.[7]

Table 15: Summary of endoscopic outcomes in the IM-UNITI trial

	IM-UNITI			
	Ustekinumab			**Placebo**
	q12w	**q8w**	**Combined**	
Randomised patients	17	29	46	24
Baseline of induction				
SES-CD score, mean (SD)	14.1 (8.9)	15.8 (7.8)	15.2 (8.2)	15.7 (8.3)
Week 0 of maintenance				
SES-CD CFB, mean (SD)	-2.8 (4.0)	-4.1 (5.2)	-3.6 (4.8)	-3.4 (7.9)
Week 44 of maintenance				
SES-CD CFB, mean (SD)	-1.6 (2.8)	-3.1 (4.1)	-2.5 (3.7)	-1.9 (4.1)
≥3-point reduction from baseline in SES-CD score, n (%)	5 (29.4)	12 (41.4)	17 (37.0)	6 (25.0)
Patients in mucosal healing, n (%)	1 (5.9)	5 (17.2)	6 (13.0)	1 (4.2)
Patients in endoscopic remission, n (%)	NR	NR	5 (10.9)	1 (4.2)
Patients in endoscopic response, n (%)	1 (5.9)	7 (24.1)	8 (17.4)	1 (4.2)

Key: CFB, change from baseline; CRP, C-reactive protein; q8w, every 8 weeks; q12w, every 12 weeks; SD, standard deviation.
Note: [a]Due to small patient numbers the ustekinumab q12w and q8w schedules were combined for this analysis.
Source: Endoscopic sub-study report.[7]

A10. For Inflammatory biomarkers, please tabulate more detailed results for CRP/Faecal calprotein/ Faecal lactoferrin including:
- the mean at baseline in the two trials; the number of patients in UNITI-1 and UNITI-2 with abnormal biomarkers at baseline;

- the actual proportions of patients in both trials with normalised biomarkers at week 8 for each trial;

- the mean biomarkers at week 8 for each trial

The requested data are provided in Table 16. In the UNITI-1 and UNITI-2 trials CRP was collected at Week 8; however, faecal calprotectin and faecal lactoferrin were collected at Week 6. Data have therefore been presented at these time-points for the respective outcomes. Furthermore, mean biomarker levels at Week 8 (CRP) or Week 6 (faecal calprotectin and faecal lactoferrin) are not available, only the mean change from baseline in these biomarkers were planned analyses in the UNITI trial programme. Hence, data are presented for the mean change from baseline in these biomarkers at Week 8 or Week 6 and not for the mean biomarker levels at Week 8 or Week 6.

Table 16: Summary of inflammatory biomarkers (CRP, faecal calprotectin and faecal lactoferrin) in the UNITI-1 and UNITI-2 trials

	UNITI-1			**UNITI-2**		
	Ustekinumab		**Placebo**	**Ustekinumab**		**Placebo**
	130mg	~6mg/kg		130mg	~6mg/kg	
Patients randomised	245	249	247	209	209	209
CRP						
Baseline, mean (SD), mg/L	20.0 (24.8)	19.5 (25.3)	16.6 (21.1)	15.3 (21.4)	17.5 (24.1)	15.1 (16.8)
Baseline, CRP>3mg/L, n	191	197	192	157	165	160
Week 8, mean (SD), mg/L	14.8 (22.9)	14.0 (23.7)	19.9 (27.5)	11.3 (20.8)	9.0 (12.8)	15.0 (17.6)
Week 8, CFB, mean (SD), mg/L	-5.2 (21.2)	-5.6 (21.2)	3.3 (18.6)	-4.0 (22.0)	-8.6 (20.0)	-0.1 (14.7)
Week 8, normalised CRP, n (%)	32 (16.8)	42 (21.3)	16 (8.3)	33 (21.0)	43 (26.1)	15 (9.4)
Faecal calprotectin						
Baseline, mean (SD), mg/kg	808.0 (1,344.2)	963.0 (1,364.3)	1133.6 (2,109.0)	784.7 (1,025.1)	784.2 (1,080.7)	665.2 (923.7)
Baseline, faecal calprotectin >250mg/kg, n	150	158	162	133	135	127

Week 6, mean (SD), mg/kg	633.5 (1004.7)	723.9 (1378.2)	1082.7 (1974.1)	597.0 (1201.1)	471.5 (765.3)	684.6 (948.2)
Week 6, CFB, mean (SD), mg/kg	-174.5 (1,180.1)	-239.1 (1,242.7)	-50.9 (2,242.9)	-187.7 (1,211.1)	-312.7 (1,110.0)	19.43 (894.0)
Week 6, faecal calprotectin ≤250mg/kg, n (%)	35 (23.3)	44 (27.8)	17 (10.5)	35 (26.3)	41 (30.4)	20 (15.7)
Week 6, faecal calprotectin ≤100mg/kg, n (%)	16 (10.7)	17 (10.8)	6 (3.7)	18 (13.5)	24 (17.8)	5 (3.9)
Faecal lactoferrin						
Baseline, mean (SD), µg/g	211.5 (268.0)	246.9 (298.3)	263.3 (314.3)	210.0 (288.5)	228.1 (290.4)	174.8 (251.6)
Baseline, lactoferrin>7.24µg/g, n	213	222	209	174	175	176
Week 6, mean (SD), µg/g	187.1 (269.9)	189.7 (272.3)	263.5 (307.6)	147.4 (256.2)	121.6 (213.0)	178.5 (257.1)
Week 6, CFB, mean (SD), µg/g	-24.4 (217.3)	-57.3 (237.8)	0.17 (293.1)	-62.7 (249.8)	-106.5 (250.1)	3.6 (191.8)
Week 6, normalised faecal lactoferrin, n (%)	24 (11.3)	31 (14.0)	5 (2.4)	24 (13.8)	26 (14.9)	13 (7.4)

Key: CFB, change from baseline; CRP, C-reactive protein; SD, standard deviation.
Note: [a]p<0.001; [b]p<0.05; [c]p<0.01 (all p-values are versus placebo).
Source: UNITI-1 CSR[8]; UNITI-2 CSR[6]; data on file.[9-14]

A11. Figure 20 page 106 of the company submission provides the proportion of patients in clinical remission throughout the IM-UNITI study extension. Please provide absolute numbers of patients in clinical remission over time. Please clarify whether these data are available by previous anti-TNF status (failed, intolerant, experienced but not failed, or truly naïve).

Table 17 presents the proportion of patients in clinical remission throughout the IM-UNITI extension study, from Week 44 through to Week 92.

These data are not available by previous anti-TNF status. Extension data from week 44 through week 92 are relatively new data and the CSR is not yet finalised. In addition, due to the small patient numbers (~80 patients per ustekinumab group) it is unlikely that these data will provide additional insights if split by previous anti-TNF status.

Table 17: Patients in clinical remission over time from Week 44 through to Week 92 in the IM-UNITI trial

	Ustekinumab 90mg SC q12w[a]	Ustekinumab 90mg SC q8w				Placebo[a]
		q8w[a]	Prior dose adjustment[b]	Combined	All ustekinumab	
Randomised patients who were in clinical response at Week 44[c] and entered a long-term extension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: IV, intravenous; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous.
Notes: [a], Subjects who were in clinical response to ustekinumab IV induction dosing, were randomised to receive study drugs on entry into the maintenance study, and did not meet loss of response criteria from Week 8 through to Week 32;
[b], Subjects who were in clinical response to ustekinumab induction dosing, were randomised, met loss of clinical response criteria from Week 8 through Week 32, and initiated ustekinumab 90 mg SC q8w (for subjects randomised to receive placebo SC or ustekinumab 90 mg SC q12w on entry into the maintenance study) or continue ustekinumab 90 mg SC q8w (for subjects randomised to receive ustekinumab 90 mg SC q8w on entry into the maintenance study) in this maintenance study;
[c], Based on calculated CDAI without treatment failure rules applied.
Source: IM-UNITI CSR Addendum.[15]

A12. The term used to define responders is not consistent in pages 124-148 in the main submission. Two terms were used: “responders” and “responders non remitters”. Please clarify whether these are the same term used to define the participants who achieved CDAI <100 or <70 (in respect to criteria used for achieving response) but did not achieve CDAI under 150.

The two terms discussed were used within the submission to define two different populations of patients, as follows:

The term “responders” is used to describe patients who achieved reduction in CDAI of at least 100 or 70 points (irrespective of whether they achieved CDAI<150 or not). Response (CDAI-100) is the primary endpoint of the UNITI-1 and UNITI-2 trials and a secondary endpoint in IM-UNITI.

The term “responders non remitters” is used to describe patients who achieved a reduction in CDAI of at least 100 or 70 points but did not achieve CDAI<150. The population of “responders non remitters” is used specifically in the economic model to refer to the patients that achieve response but not remission. This is relevant to calculate as accurately as possible the number of patients that enter the Markov phase in the mild and in the moderate to severe health states and reflects that a patient with a baseline CDAI score>320 may achieve a 100-point reduction in their CDAI score but still have CDAI score>220 (the lower threshold for moderate to severe Crohn’s disease). This population was additionally used in the treatment sequence NMA to weight the placebo-to-placebo arm.

A13. Please clarify which results for ‘conventional care failure’ in Appendix 5 refer to the full UNITI-2 trial or the ‘truly anti-TNF-naïve’ population.

Table 18 presents a summary of which populations are referred to in each table/figure of results in Appendix 5 that refer to the conventional care failure population.

As discussed in the response to Question A8, we consider that the full UNITI-2 trial population represents the conventional care failure population and that considering the “truly naïve” population to represent the conventional care failure population may lead to the exclusion of patients who are eligible for treatment with ustekinumab under its licensed indication from the decision problem. Furthermore, the UNITI-2 population is randomised, whereas considering the “truly naïve” subgroup of patients breaks randomisation and results in a smaller sample size, which increases uncertainty.

Table 18: Summary of populations referred to in each table/figure of results in Appendix 5

Table/figure reference	Table/figure title	Population represented in table/figure
Tables		
Table 12	Baseline characteristics for induction studies	Full UNITI-2 trial population
Table 13	Conventional care failure sub-population inputs for the treatment sequence analysis	IM-UNITI inputs are from all UNITI-2 patients who entered the IM-UNITI arms in this graph[a]
Table 16	Induction phase results: conventional care failure	Full UNITI-2 trial population receiving ustekinumab 6mg/kg (based on inputs in Figure 18)
Table 19	Results of the treatment sequence analysis: conventional care failure	Results are for the full UNITI-2 trial population patients except for the rows of the table representing 'Sensitivity analysis (Truly naïve subgroup)', which refer to the comparison against the truly anti-TNF naïve subset of the UNITI-2 trial population
Table 21	Uncertainty dispersion estimation around imputed placebo-placebo rates from each study	Full UNITI-2 trial population
Table 22	Treatment sequence sensitivity analysis to account for the uncertainty associated with the imputed placebo-to-placebo rates: CDAI-100	Full UNITI-2 trial population
Table 23	Treatment sequence sensitivity analysis to account for the uncertainty associated with the imputed placebo-to-placebo rates: CDAI<150	Full UNITI-2 trial population
Figures		
Figure 18	Individual trial results for CDAI-70 clinical response in the conventional care failure subpopulation	Full UNITI-2 trial population

Figure 19	Individual trial results for CDAI-100 clinical response in the conventional care failure subpopulation	Full UNITI-2 trial population
Figure 20	Individual trial results for CDAI<150 clinical remission in the conventional care failure subpopulation	Full UNITI-2 trial population
Figure 24	Individual trial maintenance results for clinical response (CDAI-100) in the conventional care failure subpopulation	IM-UNITI inputs are from all UNITI-2 patients who entered the IM-UNITI arms in this graph[a]
Figure 25	Individual trial maintenance results for clinical remission (CDAI<150) in the conventional care failure subpopulation	IM-UNITI inputs are from all UNITI-2 patients who entered the IM-UNITI arms in this graph[a]
Figure 28	Forest plot for the analysis of CDAI-70 at the end of induction – conventional care failure (median OR and 95% CrI)	Full UNITI-2 trial population receiving ustekinumab 6mg/kg (based on inputs in Figure 18)
Figure 30	Maintenance of response (CDAI-100) after 1 year in treatment sequence analysis – conventional care failure, ustekinumab q8w (median OR and 95% CrI)	Orange and blue bars refer to comparison against the full UNITI-2 trial population receiving 6mg/kg induction and ustekinumab q8w in maintenance and the purple bar refers to comparison with truly anti-TNF naïve subset of UNITI-2 trial population
Figure 31	Maintenance of remission after 1 year in treatment sequence analysis – conventional care failure, ustekinumab q8w (median OR and 95% CrI)	Orange and blue bars refer to comparison against the full UNITI-2 trial population receiving 6mg/kg induction and ustekinumab q8w in maintenance and the purple bar refers to comparison with truly anti-TNF naïve subset of UNITI-2 trial population

Key: CDAI, Crohn's Disease Activity Index; CrI, credible interval, OR, odds ratio; q8w, every 8 weeks; q12w, every 12 weeks.
Note: [a]Randomised ustekinumab-placebo, randomised ustekinumab q8w, randomised ustekinumab q12w.

Sensitivity analysis

A14. The sensitivity analysis and results across subgroups analysis by induction study and by induction dose used different approaches to handling missing data, but it is unclear which approaches were used in the presented results within Tables 16 and 17 in the appendix. Please confirm if there were any differences generated by the two methods?

Janssen is unsure in which specific section it was mentioned that sensitivity analysis and results across subgroups analysis by induction study and by induction dose used different approaches to handling missing data.

In the submission, a number of closely related definitions were used, which will be further explained below in order to clarify any potential misunderstanding:

1) Sensitivity analysis of the primary endpoint in the clinical studies
2) Subgroup analysis in the clinical studies
3) Sensitivity analysis of the NMA

Specifically, table 16 and 17 in appendix refer to the sensitivity analysis that were conducted for the NMA.

1) Sensitivity analysis of the primary endpoint in the clinical studies

To assess the robustness of the primary endpoint in the UNITI-1, UNITI-2 and IM-UNITI studies, a number of sensitivity analysis were conducted using different approaches to handling missing data. These were

- Observed case
- Last observation carried forward
- Multiple imputation
- Worst case
- Excluding subjects who were randomised but never treated

2) Subgroup analysis in the clinical studies

Subgroup analysis in the clinical studies were conducted to assess the consistency of effect of the primary endpoint. A summary of these subgroups can be found in Table 11 (Page 64–71) of the main submission document.

3) Sensitivity analysis of the NMA

Sensitivity analysis of the NMA were conducted to test the robustness of the results obtained in the base case analysis. These additional analyses were as follows

<u>Induction</u>

- The base case analysis was also conducted under a frequentist framework. The Bucher method for adjusted indirect comparisons was used to generate relative treatment effect estimates
- Different times of assessments: UNITI Week 8 results and Targan 1997 Week 2 results
- Exclusion of Targan 1997 from the failed conventional subpopulation network
    - Rationale: older study reporting unusual placebo rates

- Exclusion of vedolizumab trials from the failed conventional subpopulation network
    - Rationale: To adapt to NICE scope for the UK HTA submission
    - Inclusion of CERTIFI in the failed anti-TNF subpopulation
        - Rationale: 6 mg/kg dose not comparable to UNITI-1 "~6mg/kg" dose
- Exclusion of adalimumab trials from the failed anti-TNF subpopulation network
    - Rationale: restricted (not completely comparable) patient population used in the trials with adalimumab
- Analyses of endpoints selecting time points based on times of re-randomisation
- Exclusion of Watanabe 2012 from both subpopulation networks (study in Japanese patients only)

<u>Maintenance (Treatment sequence analysis)</u>

- Frequentist framework based on the approach by Bucher et al.
- Individual patient data were used to generate inputs for patients from the UNITI program who were "truly naïve" to biologics.[1] These inputs replaced those used in the conventional care failure subpopulation analysis
- Pooling of maintenance dosing
    - Rationale: To assess if an increase in statistical power of direct comparisons to placebo affected the uncertainty around the indirect treatment effect estimates obtained through the treatment sequence analysis when different maintenance doses of the same biologic were compared to each other
- An '*a posteriori*' sensitivity analysis to account for prediction uncertainty around the imputed placebo-to-placebo arms
    - Rationale: While sampling uncertainty was considered in the base case analysis, prediction uncertainty around the imputed placebo-to-placebo arms generated based on weights obtained via the IM-UNITI population was not accounted for in the base case analysis

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** A number of resource items listed in Appendix 13 appear to have a frequency of zero. Is this correct?

The reported frequencies were taken from the Delphi panel conducted with UK gastroenterologists. Some resources were not used for all health states, as per the consensus of the attendees. Therefore, the zero-frequency resources were included in the model as they have a non-zero frequency for another health state. Some examples of this are provided in Table 19 for illustration. For example, the attendees agreed that only patients in the moderate to severe health state, or patients requiring surgery longer than a day case, may need access to a clinical psychologist and that patients in remission would not require a CT scan of the abdomen/pelvis but those

[1] "Truly naïve" patients are defined as a subpopulation of failed patients having failed conventional care and having never received any anti-TNFs.

with mild or worse disease may need this resource. Furthermore, the attendees agreed that if a patient was in remission without needing biologic treatment (“remission off biologic”) they would not require an MRI scan of the abdomen/pelvis, however if they were in remission using biologic (“remission on biologic”) or had mild or worse disease, this may be required.

Table 19: Examples of resources that are not required for all health states

Resource	Average units per patient per year							
	Remission on biologic	**Remission off biologic**	**Mild on biologic**	**Mild off biologic**	**Moderate to severe**	**Surgery day case**	**Surgery <5 days**	**Surgery complex >5 days**
(Clinical) psychologist	0.00	0.00	0.00	0.00	1.00	0.00	0.20	1.00
CT scan of abdomen/pelvis	0.00	0.00	0.13	0.25	1.00	0.00	0.85	2.00
MRI scan of abdomen/pelvis	0.25	0.00	0.50	0.50	1.00	1.00	0.50	1.50

Key: CT, computerised tomography; MRI, magnetic resonance imaging.
Source: Delphi panel report.[16]

B2. **Priority Question:** There are missing monitoring costs in the submission namely for A&E attendances, iron infusion, and virtual clinic. Please confirm that the costs listed in the executable model are correct.

We confirm that the costs listed in the executable model are correct. A summary of the missing costs is provided in Table 20.

Table 20: Resource use unit costs

Resource	Unit cost	Reference
Virtual clinic	£22	PSSRU 2015.[17] 30 mins of hospital pharmacist. £44 Per hour without qualifications. Page 222.
Iron infusion	£220	£79.70 (2x vials of CosmoFer; NICE guidance ng24)[18] + £140 (outpatient appointment: NHS Reference Costs 2014/15.[19] Outpatient attendances; Service Code 301 Gastroenterology)
A&E attendances	£153	Weighted average of codes from NHS Reference Costs 2014/15[19]: Consultant Led. Currency code WF01B Non-Admitted Face to Face Attendance, First NHS Reference Costs 2014/15. Non Consultant Led. Currency code WF01B Non-Admitted Face to Face Attendance, First NHS Reference Costs 2014/15. Outpatient Procedures. Currency code FZ64A Combined Upper and Lower Gastrointestinal Tract Diagnostic Endoscopic Procedures with Biopsy, 19 years and over NHS Reference Costs 2014/15. Outpatient Procedures. Currency code FZ91M Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2
Key: A&E, accident and emergency, CC, currency code; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSRU, Personal Social Services Research Unit.		

B3. **Priority Question:** There appears to be a discrepancy between estimated total monitoring costs for each health state and the figures listed in Table 57 (pg. 209 of the company submission). This problem affects all health state costs with the exception of remission off a biologic. Please check the implementation of monitoring costs and revise as necessary.

The total monitoring costs in the executable model are correct and are corrected in Table 21.

Table 21: CDAI health state cycle costs (Table 57 in original submission)

	Remission		**Mild**		**Moderate to severe**
On/off biologic	**On**	**Off**	**On**	**Off**	
Total costs per patient per year	£1,116	£426	£5,800	£7,764	£14,096
Total costs per patient per cycle	£44.69	£16.32	£222.30	£297.60	£540.29

We also note that this correction further affects Tables 59, 60 and 61 from the submission dossier. Corrected versions of these are presented below in Table 22, Table 23 and Table 24.

Table 22: Weighted surgery category costs (Table 59 in original submission)

Surgery category	**Cost**	**Proportion**	**Weighted cost**
Surgery day case	£2,767.70	20.00%	£553.54
Surgery <5 days	£5,734.36	10.00%	£573.44
Surgery >5 days	£10,992.76	70.00%	£7,964.93
		Total cost:	£8,821.91

Table 23: Additional resource costs for surgical complications (Table 60 in original submission)

Resource type	**Costs**	**Reference**
Additional hospital days	£1,007	NHS Reference Costs 2014/15.[19] Total HRGs Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 0 (FZ24J) Elective inpatients excess bed day
Outpatient visits	£135	NHS Reference Costs 2014/15.[19] Outpatient attendances; Service Code 301 Gastroenterology

Table 24: Total surgery cost (Table 61 in original submission)

Costs	Additional hospital days	Outpatient visits	Risk per surgery	Weighted costs
Wound infection	4.0	1.0	2.10%	£338.58
Prolonged ileus/small bowel obstruction	4.5	1.0	1.15%	£211.00
Abdominal abscess	7.0	2.5	0.40%	£118.97
Anastomotic leak	9.5	2.5	1.02%	£396.31
Surgery			-	£8,821.91
	Total cost of surgery			**£9,886.76**

B4. **Priority Question:** It appears that the monitoring costs in the model include additional surgical costs. See Rows 57, 58 and 62 on the "Resource Use costs" sheet. These have non-zero frequency in the mild and moderate/severe health states. This seems to imply double counting of surgery costs as this is also modelled as a separate health state. Please comment on whether this is in fact the case and provide a justification for these costs.

These frequencies were determined as part of the same Delphi process described above in response to Question B1. Participants in the Delphi panel were aware that there was a separate health state for surgery; however, the consensus was that to include these non-zero frequencies in the mild and moderate/severe health states was appropriate.

The items in question are:

- Non-elective surgery
- Elective surgery
- Day case surgery (fistula, abscess)

The frequency for "Day case surgery (fistula, abscess)" (Row 62) is zero within the economic model for all health states except surgery day case.

There are non-zero frequencies in the mild and moderate-to-severe health states, as well as the surgery states for "non-elective surgery" (Row 57) and "Elective surgery" (Row 58) in addition to "Elective day case" (Row 64); the third of these was not listed in the question. Therefore, we agree that there may be some double-counting of the costs of surgery.

To test the impact of this, a scenario analysis is presented in Table 25 and Table 26, in which the frequencies of these surgeries are set to zero in the mild and moderate/severe health states. The results of this scenario are in line with the results of the base case analysis.

Table 25: Scenario analysis results excluding surgery costs from the mild and moderate/severe health states – conventional care failure

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£218,119	43.0941	13.0799				Dominant	
Conventional care	£227,730	43.0941	12.6796	£9,612	0.0000	-0.4003	-	Dominated
Adalimumab	£236,872	43.0941	12.9406	£18,754	0.0000	-0.1393	£35,024	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 26: Scenario analysis results excluding surgery costs from the mild and moderate/severe health states – TNF failure

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£239,447	44.9817	12.9819				Dominant	
Conventional care	£242,877	44.9817	12.7578	£3,429	0.0000	-0.2241	-	Dominated
Vedolizumab	£252,351	44.9817	12.8474	£12,903	0.0000	-0.1345	£105,782	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TNF, tumour necrosis factor.								

B5. **Priority Question**: There appears to be an error in the calculation of the proportion of patients who are moderate/severe responders in the model. This is calculated correctly in Cell P22 (Calc_Ustekinumab sheet) and is applied correctly in P34. In the subsequent transitions contained in row 35, however, this proportion is calculated as $\gamma(1-\beta+\beta\gamma)$ when in fact it should be should be $\frac{\beta\gamma}{1-\beta}$. Please confirm the error and rectify the affected calculations (note this problem may also affect other calculation sheets).

When considering the induction phase, including delayed responders, there are essentially two groups of responders:

- Responders to the first induction, β_1
- Moderate to severe responders to the first induction, γ_1
- Responders to the second induction, β_2
- Moderate to severe responders to the second induction, γ_2 (assumed for simplicity to be equal to γ_1)

Within the calculations for the second induction efficacy, the denominator for the percentage of responders (β_2) and remitters is the number of patients who did not respond to the first induction dose, i.e. (1-β_1). Therefore, the active calculation at the time of the second induction dose, P38, is the following:

$$\frac{1-\beta_2 \ + \ \beta_2\gamma_2}{1-\beta_1}$$

We therefore believe this to be the correct calculation to implement at this time point as the patients in the moderate to severe health state during this cycle should be the non-responders to second induction (1-β_2) plus the moderate to severe responders at second induction ($\beta_2\gamma_2$). In the following cycle, non-responders are moved to standard care, while the moderate to severe responders continue to receive active treatment.

B6. **Priority Question:** In a number of transitions calculations in the model, the MOD function is being used cycle through week 38 to 44 transition, see for example Q35, Calc_Ustekinumab sheet. Please explain why this is the case and justify.

The MOD function is used in the calculations as there is only 1 years' worth of data available from the IM-UNITI trial to inform the model. Therefore, within the model transition probabilities have been programmed up to 1 year.

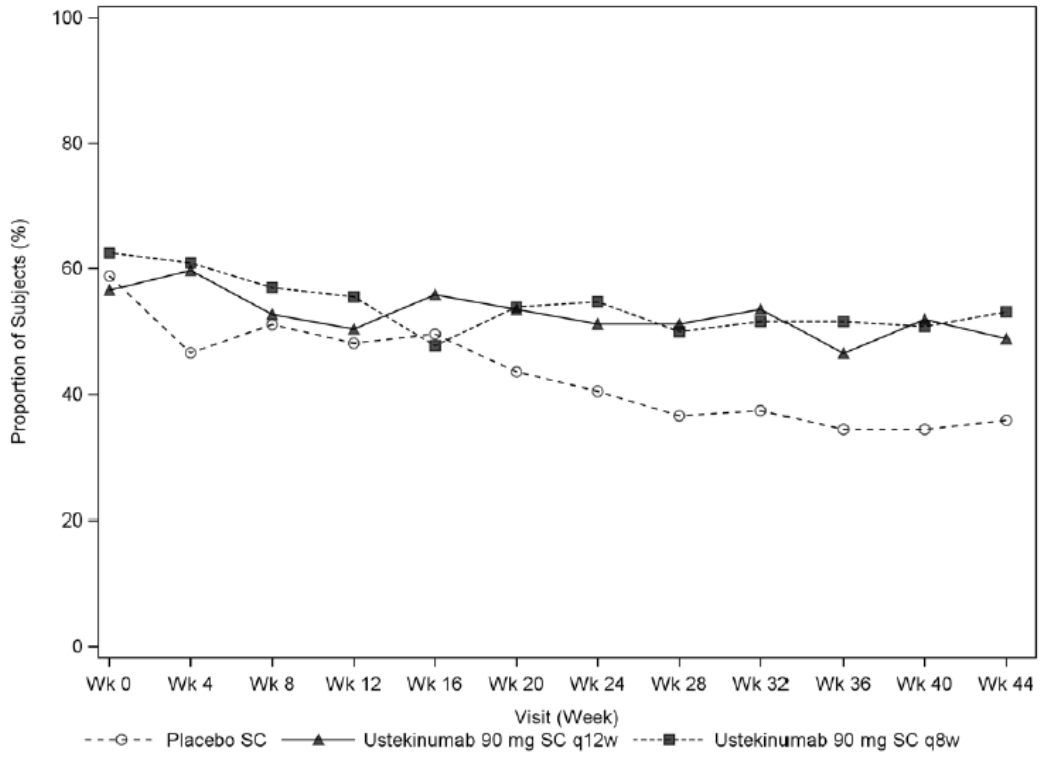
Beyond 1 year, the model extrapolates using last observation carried forward (i.e. repeating the final set of transition matrices). However, movements from surgery obtained from TA352 were only available for an 8-week period (i.e. every fourth 2-week cycle). Attempts were made to search for alternative data to support transitions from surgery, however none were identified. Therefore, due to lack of available data the 8-week rates reported in TA352 were used in our model.

Hence, to incorporate the movements relating to the surgery health state beyond 1 year, it is necessary to cycle through the final four cycles (Weeks 38 to 44), which is achieved by use of the MOD function.

B7. **Priority Question:** The maintenance transition probabilities for patients on all treatment show surprisingly little movement and appear to be inconsistent with presented clinical results. For example, there is nearly a 90% probability that a patient who achieves remission following induction with ustekinumab will maintain that remission for a further 44 weeks based on the transition probabilities used in the model (this applies to both TNF naive and TNF experienced populations). However, Table 16 on page 91 of the company submission suggests that the probability is only about 60% (56% for q12w and 67% for q8w). Please comment on this inconsistency. It would seem to suggest that the maintenance transitional probabilities are overestimating the probability of patients retaining remission in the maintenance period.

Figure 16 below demonstrates that the proportion of patients in clinical remission over time (out of the total population of patients) in the IM-UNITI trial was approximately stable. This includes patients who remained in remission and patients who achieved delayed remission through continued treatment. An example of the ustekinumab calibrated transition matrix is presented in Table 27 and demonstrates that relatively few patients are estimated to move from mild disease into remission and no patients are estimated to move from moderate to severe disease into remission. Therefore, considering the full matrix, the proportion of the total population in remission over time will remain approximately stable, which reflects what was observed in the IM-UNITI trial data (Figure 16).

Figure 16: Proportion of patients in remission over time in the IM-UNITI trial



Key: q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; Wk, week.
Source: IM-UNITI CSR.[2]

Table 27: Calibrated transition matrix: Ustekinumab q12w, conventional care failure

From \To	Remission	Mild	Moderate-severe	Surgery
Remission	0.994	0.006	0.000	0.000
Mild	0.041	0.639	0.319	0.000
Moderate-severe	0.000	0.033	0.967	0.003
Surgery	0.527	0.077	0.058	0.338

When considering the cost-effectiveness of interventions, it is important that the proportion of patients estimated to be in each health state over time is estimated as accurately as possible and given the memoryless nature of the Markov model structure, the previous health state is not important (i.e. a patient in remission is considered the same irrespective of whether they were in remission or mild disease during the previous cycle). As shown in Table 83 (Page 249) of the company submission (and described further in the response to question B11), the model predicts the outcomes of the treatment sequence NMA well for all treatment arms (when the model assumptions are set to be comparable with the data used in the NMA). At the end of 1 year the proportion of patients predicted to be in remission by the model is aligned with the proportion of patients predicted to be in remission by the NMA. These data are repeated in Table 28 for convenience. Given this validation, we believe that the modelled maintenance transition probabilities are appropriate and reflect an accurate distribution of patients across the health states over time.

Table 28: Comparison of model and treatment sequence NMA at 1 year

		NMA			Model		
Induction	**Maintenance**	**Rem**	**Mild**	**Mod-Sev**	**Rem**	**Mild**	**Mod-Sev**
Conventional care failure							
Ustekinumab 6mg/kg	Ustekinumab q12w	36.7%	[redacted]	[redacted]	34.7%	[redacted]	[redacted]
Ustekinumab 6mg/kg	Ustekinumab q8w	40.0%	[redacted]	[redacted]	37.5%	[redacted]	[redacted]
Adalimumab 160/80	Adalimumab eow	31.4%	[redacted]	[redacted]	32.7%	[redacted]	[redacted]
Adalimumab 160/80	Adalimumab weekly	36.5%	[redacted]	[redacted]	37.6%	[redacted]	[redacted]
Placebo	Placebo-placebo	18.0%	[redacted]	[redacted]	18.0%	[redacted]	[redacted]
TNF failure							
Ustekinumab 6mg/kg	Ustekinumab q12w	17.0%	[redacted]	[redacted]	17.3%	[redacted]	[redacted]
Ustekinumab 6mg/kg	Ustekinumab q8w	17.8%	[redacted]	[redacted]	17.7%	[redacted]	[redacted]

		NMA			Model		
Induction	**Maintenance**	**Rem**	**Mild**	**Mod-Sev**	**Rem**	**Mild**	**Mod-Sev**
Vedolizumab 300	Vedolizumab q8w	13.2%	[redacted]	[redacted]	13.7%	[redacted]	[redacted]
Vedolizumab 300	Vedolizumab q4w	13.2%	[redacted]	[redacted]	13.0%	[redacted]	[redacted]
Placebo	Placebo-placebo	11.0%	[redacted]	[redacted]	11.0%	[redacted]	[redacted]
Key: eow, every other week; Mod- Sev; moderate-severe; NMA, network meta-analysis; q4w, every 4 weeks, q8w, every 8 weeks; q12w, every 12 weeks; Rem, remission.							

Furthermore, the methods used to derive the maintenance transition probabilities are comparable with those used in TA352, in which the estimated probability of retaining remission over 8 weeks for all biologic treatments was estimated to be >0.95. This is crudely comparable to a 2-week probability of 0.987258[2] (ignoring all other transitions), which is similar to the estimates obtained for vedolizumab within our submission of 0.993 (conventional care failure) and 0.995 (TNF failure) for the vedolizumab q8w regimen and 0.990 (conventional care failure) and 0.995 (TNF failure) for the vedolizumab q4w regimen.

[2] 0.987258^4 = 0.949998

B8. **Priority Question:** Please provide the Excel spread sheet which was used to generate the maintenance transition probabilities (page 297 of the company submission - Appendix 12) so that the ERG can see clearly how these were generated and can generate alternative transition probabilities in a way consistent with the company approach.

The Excel® spreadsheet used to generate maintenance transition probabilities using the outcomes of the NMA is provided with these responses.

We have additionally identified a minor inconsistency in the submitted materials relating to the generation of the maintenance transition probabilities, which we would like to flag to the ERG and the NICE committee to avoid potential confusion.

On Page 298 of the appendices (Appendix 12, section 12.1) the paragraph:

"*The distribution of patients across the health states at the start of the maintenance phase is defined using the proportion of patients in remission and response at the end of the induction period. These end-of-induction proportions are calculated using ORs from the induction NMA (as described in Section 4.10.6). The proportion of patients in each health state is calculated using the formulas from Table 41, consistent with the induction phase calculations. Non-responders are then removed, and remaining patients are re-scaled to 100%, as only responders continued in the maintenance phase of the relevant clinical trials.*"

Should read as follows:

"*The distribution of patients across the health states at the start of the maintenance phase is defined using the proportion of patients in remission and response at the end of the induction period. These end-of-induction proportions are calculated using ORs from the induction NMA (as described in Section 4.10.6). The proportion of patients in each health state is calculated using the formulas from Table 41, consistent with the induction phase calculations.*"

The final sentence of this paragraph was included in error.

B9. **Priority Question:** Please provide further clarification on whether the Patient Access Scheme (PAS) will still be applied for patients for whom re-treatment is required, i.e. would a patient who achieves remission on ustekinumab and later relapses be subject to PAS pricing in a second induction phase with ustekinumab?

We would like to clarify that the pricing agreement included within the submission is not a PAS (i.e. it has not been agreed by The Patient Access Scheme Liaison Unit), but is a national confidential pricing agreement with the Commercial Medicines Unit for the 130mg solution for infusion.

The recommendation within the ustekinumab label, is that resumption of treatment after an interruption should be with 90mg subcutaneous dose every 8 weeks and this formulation is not affected by the confidential price agreement.

Re-treatment with ustekinumab after a long period of discontinuation, where a second induction phase may be required, has not been studied within the clinical trial programme and is not something we envisage will routinely occur. However, if this situation arises and the clinician considers it appropriate to reinitiate maintenance therapy then we can confirm the same pricing arrangement will be available as if they were a new patient, in that the price arrangement applies to the single infusion dose prior to ongoing SC maintenance therapy.

B10. **Priority Question:** Please provide further details of the table and page numbers in which the data on delayed responders quoted in table 40 on Page 178 of the company submission is found in the IM-UNITI CSRs. If it is not in the CSR please provide the source data.

These data are not in the IM-UNITI CSR, the source data are provided in the reference pack accompanying this response, and are as follows:

Table TEXPCRES12D[20]: Clinical response at Week 8 of IM-UNITI study; patients who were Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance; conventional care failure population

Table TEXPCREM12D[21]: Clinical remission at Week 8 of IM-UNITI study; patients who were Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance; conventional care failure population

Table TEXPCRES12C[22]: Clinical response at Week 8 of IM-UNITI study; patients who were Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance; TNF failure population

Table TEXPCREM12C[23]: Clinical remission at Week 8 of IM-UNITI study; patients who were Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance; TNF failure population

B11. **Priority Question:** Please clarify which model was compared with the NMA in Table 83 on Page 249 of the company submission.

The model used to compare against NMA results was the submitted executable model. However, several settings were changed from the base case settings to enable a fair comparison with the NMA. The settings that were changed are summarised below:

- Delayed responders were not considered as the induction and maintenance trials informing the treatment sequence NMA did not consider the impact of delayed responders to treatment
    - "Model Controls" sheet cells I55 and I57 set to 'No'[3]
- The annual rate of surgery was set to 0% as the NMA did not predict the impact of surgery on the distribution of patients across the health states
    - "Model Controls" sheet cell I71 set to 0%
- Dose-escalation was not considered for all treatments and high/low maintenance doses (e.g. ustekinumab q12w and q8w) were considered as separate treatment arms as the treatment sequence NMA considered the efficacy of individual maintenance treatment regimens as part of the treatment sequence
    - "Model Controls" sheet cell I67 set to 'No'
    - Rows 74 to 88 of the "Drug Costs" sheet were changed such that maintenance for each treatment arm was 100% of patients receiving either the upper or lower dose, in turn

[3] We note that in the executable model cell M57 on the "Model Controls" sheet states "*No data for 2nd induction dose of adalimumab; assumptions made*" in error. Data were identified for the second induction dose for adalimumab as described in the "Efficacy" sheet of the model and in the main submission dossier. This has been corrected in the updated executable model provided with these responses.

B12. Some details of the concomitant therapies used in the UNITI trials are presented in the CSRs. If any further information on the therapies used is available, please provide this information, for example dose of concomitant therapies and greater detail on drugs used.

Very limited data on concomitant therapies are available beyond those that were already presented in the CSRs, there is no further information to be provided at this time and it will take at least 2 months to generate such data. In addition, Janssen is not aware that other trials or submissions in Crohn's disease have reported these data and would therefore like to understand the rationale for this request.

Table 29 summarises the administration of concomitant therapy in induction trials included in the NMA. This demonstrates that, based on the limited summary data available, concomitant medication use was similar across trials.

Table 29: Administration of concomitant therapy in induction trials included in the NMA

Trial	Subpopulation	Intervention	Administration of concomitant therapy							
			Corticosteroids		Immunosuppresants		Antibiotics		Previous anti-TNF	
			n	%	n	%	n	%	n	%
UNITI1	Failed anti-TNF	Placebo	111	44.9	81	32.8	21	8.5	247	100
		Ustekinumab 130	121	49.4	74	30.2	19	7.8	245	100
		Ustekinumab 6	108	43.4	78	31.3	24	9.6	249	100
UNITI2	Failed conventional care	Placebo	75	35.7	73	34.8	8	3.8	75	36
		Ustekinumab 130	80	38.3	74	35.4	4	1.9	57	27
		Ustekinumab 6	92	44.0	72	34.4	9	4.3	65	31
Targan 1997	Failed conventional care	Placebo	10 (<20 mg/day) 6 (>20 mg/day)	40(<20 mg/day) 24 (>20 mg/day)	4 on MRC 7 on AZA	16 on MRC 28 on AZA	NR	NR	NR	NR
		Infliximab 5	8 (<20 mg/day) 7 (>20 mg/day)	30(<20 mg/day) 26 (>20 mg/day)	4 on MRC 5 on AZA	15 on MRC 19 on AZA	NR	NR	NR	NR
CLASSIC I	Failed conventional care	Placebo	25	34	22	30	NR	NR	0	0
		Adalimumab 160/80	24	32	22	29	NR	NR	0	0
		Adalimumab 80/40	32	43	21	28	NR	NR	0	0

Trial	Subpopulation	Intervention	Administration of concomitant therapy							
			Corticosteroids		Immunosuppresants		Antibiotics		Previous anti-TNF	
			n	%	n	%	n	%	n	%
Watanabe 2012	Overall population	Placebo	5	21.7	8	34.8	2	8.7	13	56
		Adalimumab 160/80	8	24.2	10	30.3	2	6.1	19	58
		Adalimumab 80/40	6	17.6	11	32.4	1	2.9	20	59
GAIN	Failed anti-TNF	Placebo	73	44	85	51	NR	NR	NR	100
		Adalimumab 160/80	55	35	73	46	NR	NR	NR	100
GEMINI III	Failed anti-TNF	Placebo	85	54	42	27	NR	NR	157	100
		Vedolizumab 300	86	54	43	27	NR	NR	158	100
GEMINI III	Failed conventional care	Placebo	23	46	27	54	NR	NR	0	0
		Vedolizumab 300	24	47	28	55	NR	NR	0	0
GEMINI II	Overall population	Placebo	45	30.4	25	16.9	NR	NR	72	49
		Vedolizumab 300	67	30.5	37	16.8	NR	NR	111	51
Key: AZA, azathioprine; MRC, mercaptopurine; NMA, network meta-analysis; NR, not reported.										

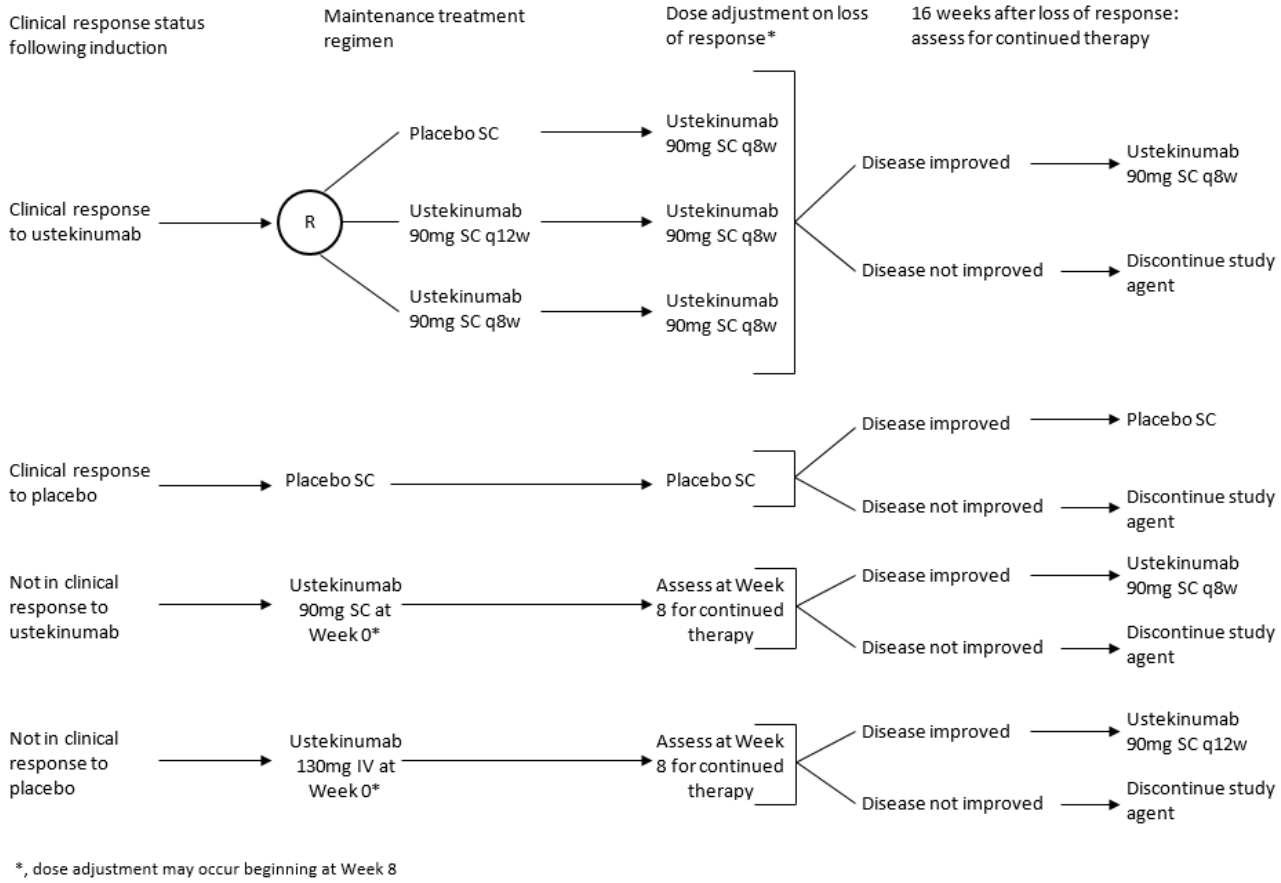
Scenario analyses

Please carry out further scenario analyses (see questions below) and where possible please ensure that it is possible to carry out all of these scenarios together as well as separately so the ERG can incorporate multiple alternative assumptions in any alternative base-case.

B13. **Priority Question:** Please provide a modified version of the IM-UNITI maintenance transitions scenario in which the transitions for the placebo arm are generated from the patients randomised to placebo at the induction phase (this should ideally include both placebo responders and non-responders). The ERG feels that this group would better represent the conventional care patients than patients re-randomised to placebo in IM-UNITI and avoid the issues highlighted on page 182 of the company submission.

As discussed in the response to Question A3, data are not available for patients receiving placebo maintenance who did not respond to placebo induction and therefore it is not possible to provide the requested comparison. Due to the structure of the trial, patients who did not respond to induction placebo were not eligible for maintenance placebo and were offered induction treatment with ustekinumab. The maintenance study populations and respective treatment groups are shown in Figure 17.

Figure 17: Study populations of IM-UNITI



Key: IV, intravenous; R, randomisation; SC, subcutaneous; q8w, every 8 weeks; q12w, every 12 weeks.
Note: To maintain the blind for the non-randomised patients, both IV and SC administrations were given to all patients not in clinical response following induction.
Source: IM-UNITI CSR.[2]

Therefore (as described in more detail in the response to Question A3) the only data available for patients who received placebo maintenance are as follows:

- Patients who responded to ustekinumab during induction and who were re-randomised to placebo during maintenance (the data used in the scenario presented within the main submission)
- Patients who responded to placebo during induction and who continued to receive placebo during maintenance

B14. **Priority Question:** Please provide a scenario analysis incorporating the actual components of conventional therapy utilised in the different arms of the UNITI trials during the induction and maintenance phases.

As discussed in the response to Question B12, very limited data on concomitant therapies are available beyond those that were already presented in the CSRs, and there is no further information to be provided at this time. Additionally, the concomitant medication use was similar across all induction studies for which these data were available. Given this, we believe that our base case analysis using the mix of treatments that compose conventional care based on those presented in the manufacturer's submission for TA352 which was based on the UK IBD audit is appropriate. In TA352 it was assumed that patients receiving biologic received only 50% of the cost of conventional care, an assumption that has been used in the base case analysis for this submission. Table 30 and Table 31 present the results of a scenario analysis where patients on biologic treatment are assumed to incur 100% of the cost of conventional care. This assumption has a negligible impact on the results of the cost-effectiveness analysis.

Table 30: Scenario analysis results assuming 100% of the cost of conventional care while receiving biologic treatment – Conventional care failure

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£263,417	43.0941	13.0799				Dominant	
Conventional care	£278,542	43.0941	12.6796	£15,125	0.0000	-0.4003	-	Dominated
Adalimumab	£284,096	43.0941	12.9406	£20,679	0.0000	-0.1393	£21,277	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 31: Scenario analysis results assuming 100% of the cost of conventional care while receiving biologic treatment – TNF failure

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£288,395	44.9817	12.9819				Dominant	
Conventional care	£294,600	44.9817	12.7578	£6,205	0.0000	-0.2241	-	Dominated
Vedolizumab	£303,068	44.9817	12.8474	£14,673	0.0000	-0.1345	£94,550	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

B15. **Priority Question:** Please provide a scenario analysis incorporating the sensitivity analysis using truly naive patients from UNITI-2 into the economic model.

As requested, a scenario analysis has been presented in Table 39 using the truly naïve population data. The analysis uses the following data specific to the truly naïve population:

- Proportion of ustekinumab patients achieving clinical response (CDAI-100) and clinical remission (CDAI < 150) at Week 6 (Table 32)
- Delayed responders to ustekinumab treatment (Table 33)
- Proportion of moderate to severe responders at the end of induction and maintenance (Table 34)
- NMA treatment sequence analysis results

Table 32: Summary of clinical response and clinical remission status at Week 6: Truly naïve population

	Ustekinumab 6mg/kg[a]
Total N	144
Subjects in clinical response[b,c], n (%)	81 (56.3%)
Subjects in clinical remission[b,c], n (%)	56 (38.9%)
Notes: [a] Weight-range based ustekinumab doses approximating 6mg/kg: 260mg (weight ≤55kg), 390mg (weight >55kg and ≤85kg) and 520mg (weight >85kg); [b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response/remission; [c] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response/remission. **Source:** Data on file.[3]	

Table 33: Summary of clinical response and clinical remission status at Week 8 of maintenance study (delayed responders): Truly naïve population

	Non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance[a]
Total N	128
Subjects in clinical response[b,c], n (%)	87 (68.0%)
Subjects in clinical remission[b,c], n (%)	59 (46.1%)
Notes: [a] Subjects who received ustekinumab 90 mg SC at Week 0. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC q8w; [b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response/remission; [c] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response/remission. **Source:** Data on file.[24]	

Table 34: Responders to treatment with moderate to severe disease

	Pooled[a]
Induction	
Total N	431
Induction Week 6: Subjects in clinical response and with CDAI score ≥220[b,c]	19 (4.4%)
Maintenance	
Total N	403
Maintenance Week 44: Subjects in clinical response and with CDAI score ≥220[b,c,d]	6 (1.5%)
Notes: [a] Includes all subjects who were randomised (induction) or all subjects who were enrolled in the maintenance study (maintenance); [b] Subjects who had a prohibited Crohn's disease-related surgery or had prohibited concomitant medication changes are considered not to be in clinical response/remission; [c] Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response/remission; [d] Subjects who had a prohibited Crohn's disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease prior to the designated analysis timepoint are considered not to be in clinical response, regardless of their CDAI score. **Source:** Data on file.[25, 26]	

Baseline characteristics were assumed to be equal to the full UNITI-2 trial population.

Induction probabilities of response and remission for comparator treatments were derived by applying the odds ratios calculated in the base case induction NMA (main submission Section 4.10.6) to ustekinumab induction results specific to the truly naïve population (Table 32), as no scenario analysis was performed for the truly naïve population in the induction NMA. The resulting probabilities of response and remission for each comparator treatment are shown in Table 35.

Table 35: Probabilities of response and remission for comparators

Comparators	**Probabilities**	
	Response (CDAI-100)	**Remission**
Truly naïve population		
Adalimumab 80/40mg	48.1%	35.8%
Adalimumab 160/80mg	55.5%	49.9%
Conventional care	29.2%	20.3%
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.		

As for the base case analysis, the proportion of moderate to severe responders is assumed to be equal for all treatments, based on the data in Table 34. Data for delayed responders were available for the truly naïve population only for ustekinumab (Table 33) hence, for

comparators, the probability of delayed response was assumed equal to the base case conventional care failure inputs (Table 40 of the main submission dossier).

In the maintenance phase, data from the truly naïve scenario analysis of the treatment sequence NMA were used to calibrate a fixed 2-week maintenance transition matrix for each treatment, as per the base case analysis, using the data in Table 36 along with the induction data described above, and the methods described in Appendix 12.

Table 36: Maintenance network meta-analysis results: truly naïve population

OR vs placebo	Response (CDAI-100)	Remission
Ustekinumab q12w	2.24 (1.36; 3.72)	2.66 (1.56; 4.63)
Ustekinumab q8w	2.64 (1.61; 4.39)	3.52 (2.08; 6.11)
Vedolizumab 8 week	1.79 (1.05; 3.11)	2.72 (1.46; 5.30)
Vedolizumab 4 week	1.46 (0.85; 2.55)	2.38 (1.27; 4.67)
Adalimumab eow	1.71 (0.85; 3.49)	2.46 (1.14; 5.61)
Adalimumab weekly	2.2 (1.11; 4.45)	2.9 (1.36; 6.60)
Placebo results	26.28%	18.98%

Key: CDAI, Crohn's Disease Activity Index; eow, every other week; OR, odds ratio; q8w, every 8 weeks; q12w, every 12 weeks.

The proportions of patients in each of the health states predicted by the NMA are given in Table 37. The proportions for the remission and mild health states are used as the basis for the transition probabilities.

Table 37: Split between health states at the end of induction and the end of maintenance

			Failed conventional care					
			Induction end			Maintenance end		
Induction	**Maintenance**	**Induction length (weeks)**	**Rem**	**Mild**	**Mod-sev**	**Rem**	**Mild**	**Mod -sev**
Ust ~6mg/kg	Ust q12w	**8**	39%	[redacted]	[redacted]	38%	[redacted]	[redacted]
Ust ~6mg/kg	Ust q8w	**8**	39%	[redacted]	[redacted]	45%	[redacted]	[redacted]
Ada 160/80	Ada eow	**4**	50%	[redacted]	[redacted]	37%	[redacted]	[redacted]
Ada 160/80	Ada weekly	**4**	50%	[redacted]	[redacted]	40%	[redacted]	[redacted]
Placebo	Placebo-placebo	**8**	20%	[redacted]	[redacted]	19%	[redacted]	[redacted]

Key: Ada, adalimumab; eow, every other week; q8w, every 8 weeks; q12w, every 12 weeks; mod, moderate; rem, remission; sev, severe; ust, ustekinumab; vedo, vedolizumab.

The resulting transition probability matrices are comparable to those obtained in the base case analysis, and they are presented in

Table 38.

Table 38: NMA transition matrices truly naïve population

Ust 6mg/kg; Ust q12w				
From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]
Ust 6mg/kg; Ust q8w				
From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]
Ada 160/80; Ada eow				
From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]
Ada 160/80; Ada weekly				
From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]
Placebo; placebo-placebo				
From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]
Key: Ada, adalimumab; Mod-sev, moderate to severe; Rem, remission; Ust, ustekinumab.				

The results of the sensitivity analysis are presented in Table 39 and demonstrate that this does not impact the decision; ustekinumab remains dominant compared with adalimumab and conventional care.

Table 39: Scenario analysis results using truly naïve population inputs – Conventional care failure

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£272,140	43.0941	12.9304				Dominant	
Adalimumab	£290,357	43.0941	12.4817	£18,217	0.0000	-0.4487	-	Dominated
Conventional care	£292,393	43.0941	12.7991	£20,252	0.0000	-0.1313	£6,413	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Section C: Textual clarifications and additional points

Literature Searching

C1: On Page 6 of Appendix 2 of the company submission, CINAHL is listed as one of the databases searched for the clinical effectiveness review, but no strategy has been provided. If this database was indeed searched, please provide the search strategy.

The CINAHL database was not searched in the clinical effectiveness review and this database was included in the list reported on Page 6 of the submission appendices in error. The list should read as follows:

Searches were performed in the following electronic databases:

- MEDLINE and MEDLINE-In-Process
- Embase
- The Cochrane Library, including:
- Cochrane Central Register of Controlled Trials (CENTRAL)
- The Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Database of Health Technology Assessments (HTA)

C2: Please provide the search strategy used for clinicaltrials.gov and the WHO meta registry.

The search strategies for clinicaltrials.gov and the WHO meta-registry are provided below:

Clinicaltrials.gov
(infliximab [TREATMENT] OR adalimumab [TREATMENT] OR vedolizumab [TREATMENT] OR certolizumab [TREATMENT] OR natalizumab [TREATMENT] OR ustekinumab [TREATMENT]) AND Crohn's disease [DISEASE] AND EXACT Adult [AGE-GROUP] AND EXACT (Phase 2 OR Phase 3 OR Phase 4) [PHASE]

WHO meta-registry
Using the advanced search function:

Condition: Crohn's disease
Intervention: infliximab OR adalimumab OR certolizumab OR natalizumab OR vedolizumab OR ustekinumab
Phases: 2, 3, 4

C3: In the original set of searches conducted in July 2015 (Pages 7-10 of Appendix 2 of the company submission), please clarify why terms for ustekinumab or Stelara are not included in the search strategies.

The original set of searches conducted in July 2015 did not contain terms for ustekinumab or Stelara®. The submitting company was the sole holder for all ustekinumab clinical data in Crohn's disease at time of the submission and these data were directly included in the evidence base through hand searching. While this can be considered a methodological limitation, the overall impact is expected to be low given that the submitting company owned and provided all available evidence for ustekinumab in Crohn's disease. Furthermore, in the update to the SLR conducted in October 2016, included terms for ustekinumab and Stelara and the date restriction of studies published since July 2015 were not applied to these terms to ensure that all relevant publications for ustekinumab in Crohn's disease were identified and included.

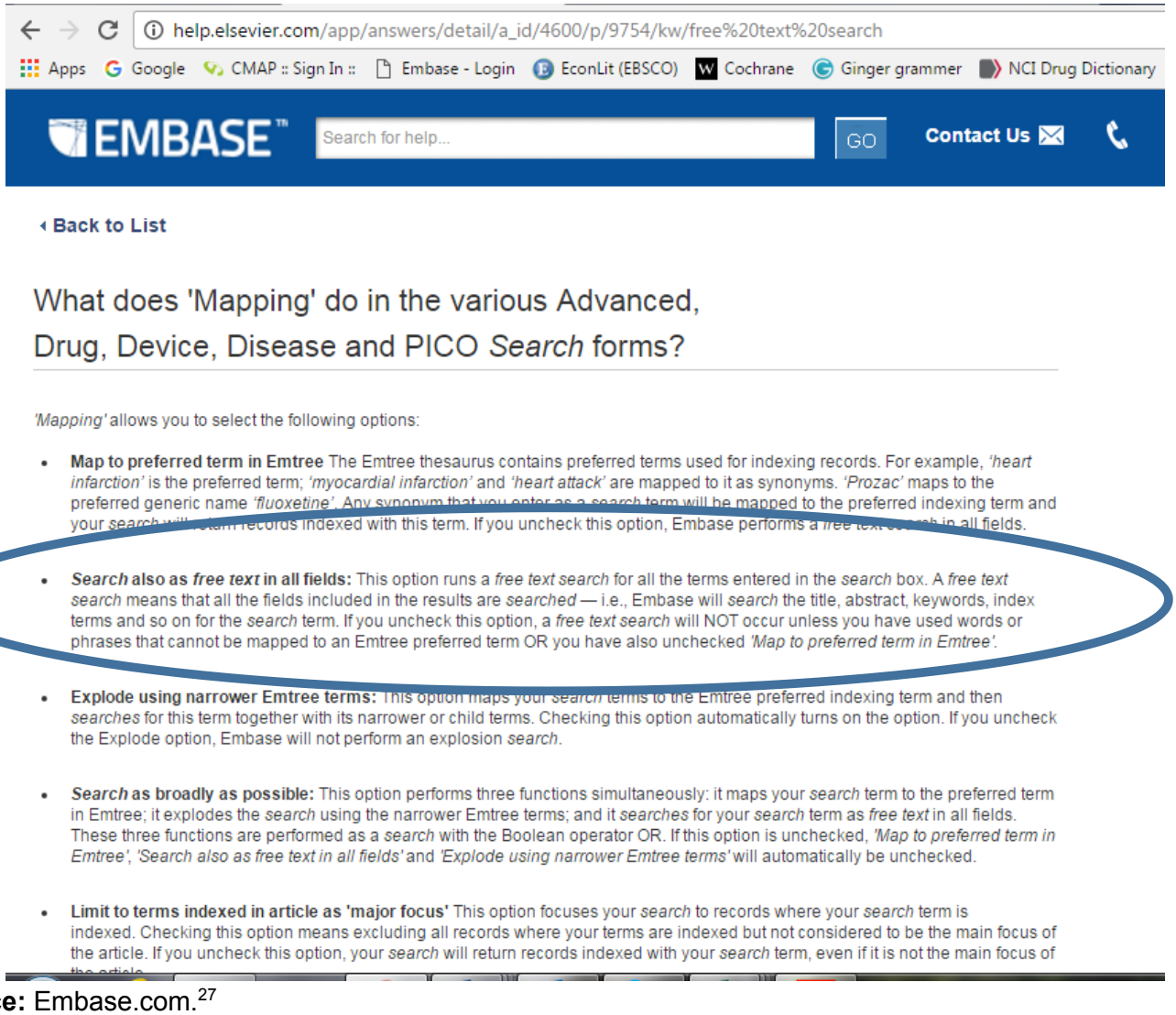
C4: Please clarify whether line 30 of the MEDLINE search strategy (Table 1, page 9 of Appendix 2 of the company submission) should read "#29 NOT #28", rather than "#28 NOT #28" as is written.

The ERG is correct and line 30 of the MEDLINE search strategy should read "#29 NOT #28", rather than "#28 NOT #28" as is written. This is a typographical error in reporting the search strategy, and we can confirm that the original search string as was run in the database read correctly as "#29 NOT #28". We can further confirm that the error was not carried forward into the updated searches, and these correctly used the string "#29 NOT #28".

C5: In the EMBASE.com search strategy (Table 4 of Appendix 2 of the company submission), please clarify which fields were searched for line 2, line 4, and line 31.

In the original SLR, Medline was searched using Pubmed.com interface whereas Embase was searched using the Ovid platform with .mp. as a field. In contrast for the SLR update, the Embase.com interface was used to retrieve relevant articles from both the MEDLINE and Embase databases. No field codes were applied for the search terms in Line 2, Line 4, and Line 31. The search terms were searched as free text implying that the term will be searched in titles, abstracts, keywords, and/or in index terms as shown in Figure 18.

Figure 18: Embase.com interface



Source: Embase.com.[27]

C6: Please clarify how many records were retrieved from the searches of CDSR, DARE, and HTA. Results were only presented from CENTRAL in Tables 3 and 5 in Appendix 2 of the company submission.

For the original SLR (Table 3) through the Cochrane Library the observed number of hits was:
Cochrane reviews (CDSR) – n=19
Technology Assessments (HTA) – n=34
Other reviews (DARE) – n=41

For the updated SLR (Table 5) the observed number of hits was:
Cochrane reviews (CDSR) – n=6
Technology Assessments (HTA) – n=6
Other reviews (DARE) – n=0

C7: In the PRISMA flow diagram for the update to the review conducted in October 2016, papers identified through database searching are reported as n=1324 in Figure 1 of Appendix 2. This does not correspond with the search results in Tables 4 & 5, showing 1075 found from MEDLINE and EMBASE, and 135 from CENTRAL, totalling 1210.Please clarify.

The search results from Medline-in process (search via Pubmed.com interface) have not been included in the total calculated from Tables 4 and 5 of Appendix 2 (1210). A total of 114 citations for screening were retrieved from MEDLINE In-Process (Table 40).

Table 40: MEDLINE In-Process search for efficacy and safety data in updated systematic literature review

	#	Search terms	Hits
Crohn's disease	1	"Crohn disease"[MeSH] OR "Inflammatory Bowel Diseases"[MeSH]	66,649
	2	"Crohn disease"[TW] OR "Crohns Dosease"[TW] OR "Crohn's Disease"[TW] OR "Inflammatory Bowel Diseases"[TW] OR "Inflammatory Bowel Disease[TW] OR IBD[TW]	70,059
	3	#1 OR #2	87,385
Interventions	4	"Biological Therapy"[MeSH] OR "Antibodies, Monoclonal"[MeSH] OR infliximab[TW] OR remicade[TW] OR adalimumab[TW] OR humira[TW] OR vedolizumab[TW] OR entyvio[TW] OR certolizumab[TW] OR cimzia[TW] OR natalizumab[TW] OR ustekinumab[TW] OR Stelara[TW]	569,749
	5	#3 AND #4	7,975
Citation status	6	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	432,289
Final results	7	#5 AND #6	114

C8: In the EMBASE search strategy found in Table 34 of Appendix 7 on Page 155, please clarify whether lines 50-52 are relevant to the search, or have these been included by mistake.

The numbering in Table 34 of Appendix 7 is incorrectly reported as after Line 25 it goes directly to Line 44. The search terms in these lines are relevant to the search as they combine Disease with Outcomes strings and introduce “non-animal” and “English language” limits. The full, corrected search string has been provided in Table 41.

Table 41: Embase (Ovid) search terms – corrected

		Date of the search:	**21/07/2015**	
	#	**Search terms**	**Hits**	**References**
Crohns	1	Crohn Disease'/ OR 'Inflammatory Bowel Disease'/	68,307	Cochrane
	2	'Crohn Disease'.mp. OR 'Crohns Disease'.mp. OR 'Inflammatory Bowel Diseases'.mp. OR 'Inflammatory Bowel Disease'.mp. OR IBD.mp.	100,404	
	3	1 OR 2	100,404	
Study type: Economic studies	4	Socioeconomics/	117,324	
	5	Cost benefit analysis/	68,817	SIGN
	6	Cost effectiveness analysis/	107,143	
	7	Cost of illness/	15,617	
	8	Cost control/	52,580	
	9	Economic aspect/	105,430	
	10	Financial management/	104,220	
	11	Health care cost/	140,641	
	12	Health care financing/	11,769	
	13	Health economics/	34,638	
	14	Hospital cost/	15,146	
	15	(fiscal or financial or finance or funding).tw.	118,872	
	16	Cost minimization analysis/	2,671	
	17	(cost adj estimate$).mp.	2,260	
	18	(cost adj variable$).mp.	170	
	19	(unit adj cost$).mp.	2,832	
	20	or/4-19	714,556	

	21	(burden AND (illness* OR disease*)).TI,AB.	73,935	
	22	(((work OR productivity) AND (loss OR lost)) OR absenteeism).TI,AB.	47,740	
	23	((resource OR health?care) AND (use* OR utilisation OR utilization OR allocation OR consumption*)).TI,AB.	145,932	
Exclusion	24	or/21-23	260,021	
	25	20 OR 24	927,676	
	26	Case Report'.tw. OR 'Case study'/ OR Abstract report/ OR Letter/ OR Randomized controlled trial/ OR Clinical trial/ OR review/ OR Randomi?ed controlled trial$.mp. OR Placebo.mp. OR review/ OR meta analysis/ OR major clinical study/ OR review.ti. OR practice guideline/ or clinical practice/ OR controlled clinical trial/	6,712,469	
	27	animal/ NOT human/	1,263,360	Cochrane
	28	26 OR 27	7,891,898	
Economic evaluation studies	29	3 AND 25	3,555	
	30	29 NOT 28	1,856	
	31	Limit to: English	1,772	
	26	Case Report'.tw. OR 'Case study'/ OR Abstract report/ OR Letter/ OR Randomized controlled trial/ OR Clinical trial/ OR review/ OR Randomi?ed controlled trial$.mp. OR Placebo.mp. OR review/ OR meta analysis/ OR major clinical study/ OR review.ti. OR practice guideline/ or clinical practice/ OR controlled clinical trial/	3,822	
	27	animal/ NOT human/	1,776	
	28	26 OR 27	1,658	

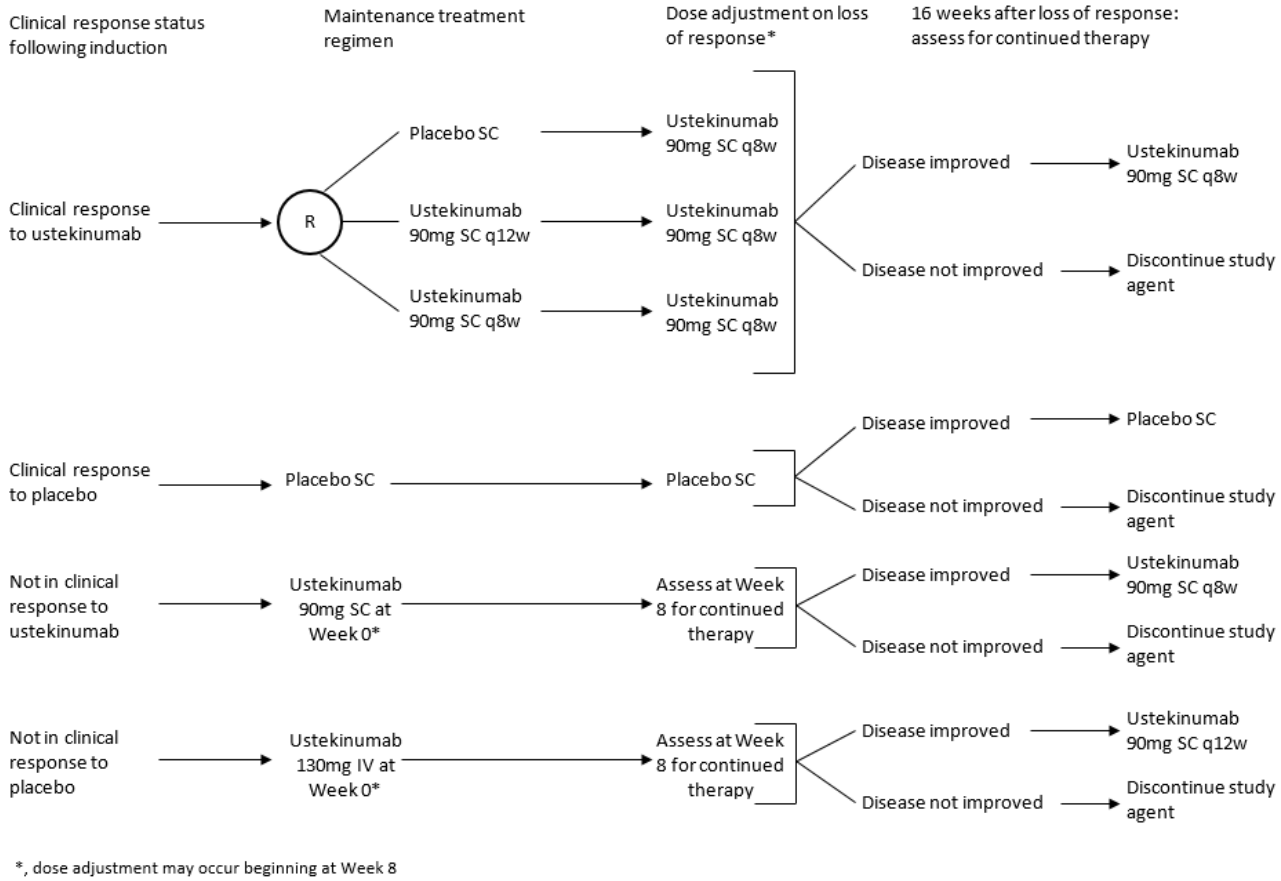
Section D: Erratum to submitted material

In addition to the questions posed by the ERG and the inconsistencies/corrections arising from these, we have identified some additional minor inconsistencies in the submitted materials that we would like to flag to the ERG and the NICE committee to avoid potential confusion.

Figure 7, main submission dossier

As noted in the response to Questions A3 and B13, the breakdown of the different treatment pathways into the IM-UNITI trial were incorrectly presented in Figure 7 on Page 62 of the main submission dossier. This figure incorrectly stated in the final pathway that patients "not in clinical response to ustekinumab" went on to receive ustekinumab 130mg at Week 0 of the IM-UNITI study. This should have stated patients not in clinical response to placebo would follow this pathway. A corrected version of this figure has been re-presented in Figure 19.

Figure 19: Study populations of the IM-UNITI trial



Key: IV, intravenous; R, randomisation; SC, subcutaneous; q8w, every 8 weeks; q12w, every 12 weeks.
Note: To maintain the blind for the non-randomised patients, both IV and SC administrations were given to all patients not in clinical response following induction.
Source: IM-UNITI CSR.[2]

Table 37, main submission dossier

Table 37 presented on Page 176 of the main submission dossier included two incorrect values. The corrected table is presented below (Table 42) with the updated values in italics. These updated values are consistent with the values in the executable model.

Table 42: Probabilities of response and remission for comparators (Table 37 in main submission dossier)

Comparators	Probabilities		
	Response (CDAI-70)	Response (CDAI-100)	Remission
Conventional care failure population			
Adalimumab 80/40mg	65.1%	47.3%	32.0%
Adalimumab 160/80mg	66.5%	54.8%	45.6%
Conventional care	38.7%	28.6%	17.7%
Infliximab 5mg/kg[a]	94.3%	N/A	87.0%
TNF failure population			
Vedolizumab 300mg	44.8%	*32.7%*	12.90%
Conventional care	30.3%	*21.4%*	8.83%

Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.
Notes: [a] Infliximab included as scenario analysis only.

Table 40, main submission dossier

Table 40 presented on Page 178 of the main submission dossier included six incorrect values. The corrected table is presented below (Table 43) with the updated values in italics. These updated values are consistent with the values in the executable model.

Table 43: Delayed responder's efficacy inputs (Table 40 in main submission dossier)

	N	Events	%	Source
Ustekinumab (conventional care failure)				
Response (CDAI-70)		N/A: Assumed equal to CDAI-100	*64.9%*	IM-UNITI data
Response (CDAI-100)	185	120	*64.9%*	
Remission	185	83	*44.9%*	
Ustekinumab (TNF failure)				
Response (CDAI-70)		N/A: Assumed equal to CDAI-100	*41.1%*	IM-UNITI data
Response (CDAI-100)	282	116	*41.1%*	
Remission	282	52	*18.4%*	
Vedolizumab (failure)				

Response (CDAI-70)	86	N/A: Assumed equal to CDAI-100	*18.6%*	Sandborn *et al*.[1]
Response (CDAI-100)	86	16	16.0%	
Remission	86	9	6.8%	
Adalimumab (conventional care failure)				
Response (CDAI-70)	-	N/A: Assumed equal to CDAI-100	43.0%	Adalimumab SPC[28]
Response (CDAI-100)	-	-	43.0%	
Remission	-	-	28.0%	Panaccione *et al*.[29]
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor.				

Table 41, main submission dossier

Table 41 presented on Page 184 of the main submission dossier included one incorrect value. The corrected table is presented below (Table 44) with the updated value in italics. This updated value is consistent with the value in the executable model.

Table 44: Discontinuation due to lack of efficacy (Table 41 in main submission dossier)

	Number of patients	**Number discontinued**	**% discontinued**	**Instantaneous rate**	**Cycle probability**	**Reference**
Ustekinumab q12w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IM-UNITI CSR
Ustekinumab q8w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IM-UNITI CSR
Ustekinumab combined					[redacted]	Calculated
Infliximab combined[a]	385	31	8.05%	0.16%	0.32%	ACCENT I
Adalimumab	385	31	8.05%	0.16%	0.32%	Assumed equal to Infliximab
Vedolizumab 8 week	154	58	37.66%	1.03%	2.03%	GEMINI II
Vedolizumab 4 week	154	48	31.17%	0.81%	1.61%	GEMINI II
Vedolizumab combined					2.03%	Calculated

Key: CSR; clinical study report; q8w, every 8 weeks; q12w, every 12 weeks.
Note: [a] Infliximab included as scenario analysis only.

Table 44, main submission dossier

Table 44 presented on Page 191 of the main submission dossier included one incorrect value. The corrected table is presented below (Table 45) with the updated value in italics. The updated value is consistent with the value in the executable model.

Table 45: Cycle rates of AEs (Table 44 in main submission dossier)

Treatment	Serious infection	Tuberculosis	Lymphoma	Hypersensitivity	Skin reactions	Source
Ustekinumab	0.34%	0.00%	0.00%	0.01%	0.75%	UNITI-1, UNITI-2 and IM-UNITI[6, 8, 30]
Vedolizumab	0.32%	0.00%	0.00%	0.00%	*0.59%*	GEMINI I & GEMINI II[31]
Adalimumab	0.32%	0.00 %	0.00%	0.00%	10.37%	Colombel *et al.*[32], Hanauer *et al.*[33], Rutgeerts *et al.*[34], Sandborn *et al.*[35], and Watanabe *et al.*[36]
Conventional care	0.37%	0.00%	0.00%	0.00%	1.45%	Pooled placebo data from above trials
Infliximab[a]	0.20%	0.00%	0.00%	0.00%	0.72%	Hanauer *et al.*[37] and Colombel *et al.*[38]

Key: AEs, adverse events.
Note: [a] Infliximab included as scenario analysis only.

Table 48 and 50, main submission dossier and executable economic model

Table 48 presented on Page 198 of the main submission dossier included correct values for utility decrements; however, in the executable model some of the values had been assigned to the wrong adverse events. The same is true for the adverse event decrements presented in Table 50 of the main submission dossier (results of disutility study, used in scenario analysis only). In the updated version of the executable model we have corrected for these errors. The revised base case results are presented in Table 46 and Table 47 and show that this has minimal impact on the total and incremental QALYs. A fully updated results section incorporating this correction is provided as an appendix to this document.

Table 46: Updated base case results correcting for utility decrements due to adverse events: conventional care failure population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£263,053	43.0941	13.0799				Dominant	
Conventional care	£278,542	43.0941	12.6796	£15,489	0.0000	-0.4003	-	Dominated
Adalimumab	£283,762	43.0941	12.9406	£20,709	0.0000	-0.1393	£19,999	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 47: Updated base case results correcting for utility decrements due to adverse events: TNF failure population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£288,088	44.9817	12.9819				Dominant	
Conventional care	£294,600	44.9817	12.7578	£6,512	0.0000	-0.2241	-	Dominated
Vedolizumab	£302,820	44.9817	12.8474	£14,732	0.0000	-0.1345	£91,779	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TNF, tumour necrosis factor.								

Table 49, main submission dossier

Table 49 on Page 198 of the submission incorrectly reports QALY weighting factors for both induction and maintenance periods. The single table of QALY weights in the executable model is correct and as such the corrected table is provided in Table 48 (including the correction to the adverse event disutilities within the executable model noted above)

Table 48: Weighting factors

Treatment	Weighting factor
Ustekinumab	99.60%
Vedolizumab	99.04%
Adalimumab	99.75%
Conventional care	99.63%
Infliximab[a]	99.53%
Note: [a] Infliximab included as scenario analysis only.	

Tables 57, 59, 60 and 61, main submission dossier

In Question B3 the ERG identified a discrepancy between the monitoring costs reported in the executable model and those in the main submission dossier (Table 57). We have confirmed that the total monitoring costs in the executable model are correct, and these are corrected in Table 49.

Table 49: CDAI health state cycle costs (Table 57 in original submission)

	Remission		Mild		Moderate to severe
On/off biologic	**On**	**Off**	**On**	**Off**	
Total costs per patient per year	£1,116	£426	£5,800	£7,764	£14,096
Total costs per patient per cycle	£44.69	£16.32	£222.30	£297.60	£540.29

We also note that this correction further affects Tables 59, 60 and 61 from the submission dossier. Corrected versions of these are presented below in Table 50, Table 51 and Table 52.

Table 50: Weighted surgery category costs (Table 59 in original submission)

Surgery category	Cost	Proportion	Weighted cost
Surgery day case	£2,767.70	20.00%	£553.54
Surgery <5 days	£5,734.36	10.00%	£573.44
Surgery >5 days	£10,992.76	70.00%	£7,964.93
		Total cost:	£8,821.91

Table 51: Additional resource costs for surgical complications (Table 60 in original submission)

Resource type	Costs	Reference
Additional hospital days	£1,007	NHS Reference Costs 2014/15.[19] Total HRGs Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over, with CC Score 0 (FZ24J) Elective inpatients excess bed day
Outpatient visits	£135	NHS Reference Costs 2014/15[19] Outpatient attendances; Service Code 301 Gastroenterology

Table 52: Total surgery cost (Table 61 in original submission)

Costs	Additional hospital days	Outpatient visits	Risk per surgery	Weighted costs
Wound infection	4.0	1.0	2.10%	£338.58
Prolonged ileus/small bowel obstruction	4.5	1.0	1.15%	£211.00
Abdominal abscess	7.0	2.5	0.40%	£118.97
Anastomotic leak	9.5	2.5	1.02%	£396.31
Surgery			-	£8,821.91
	Total cost of surgery			**£9,886.76**

Appendix 1, Page 6 appendices

As discussed in the response to question C1, the CINAHL database was not searched in the clinical effectiveness review and this database was included in the list reported on Page 6 of the submission appendices in error. The list should read as follows:

Searches were performed in the following electronic databases:

- MEDLINE and MEDLINE-In-Process
- Embase
- The Cochrane Library, including:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- The Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Database of Health Technology Assessments (HTA)

Appendix 2, Table 1, Page 9 appendices

As discussed in the response to Question C4, Line 30 of the MEDLINE search strategy should read "#29 NOT #28", rather than "#28 NOT #28" as is written. This is a typographical error in reporting of the search strategy, and we can confirm that the original search string as was run in the database read correctly as "#29 NOT #28". We can further confirm that the error was not carried forward into the updated searches, and these correctly used the string "#29 NOT #28".

Appendix 2, appendices

As discussed in the response to Question C7, the search results from MEDLINE In-Process (search via Pubmed.com interface) have not been included in the total calculated from Tables 4 and 5 of Appendix 2 (1210). A total of 114 citations for screening were retrieved from Medline In-Process (Table 53).

Table 53: MEDLINE In-Process search for efficacy and safety data in updated systematic literature review

	#	Search terms	Hits
Crohn's disease	1	"Crohn disease"[MeSH] OR "Inflammatory Bowel Diseases"[MeSH]	66,649
	2	"Crohn disease"[TW] OR "Crohns Dosease"[TW] OR "Crohn's Disease"[TW] OR "Inflammatory Bowel Diseases"[TW] OR "Inflammatory Bowel Disease[TW] OR IBD[TW]	70,059
	3	#1 OR #2	87,385
Interventions	4	"Biological Therapy"[MeSH] OR "Antibodies, Monoclonal"[MeSH] OR infliximab[TW] OR remicade[TW] OR adalimumab[TW] OR humira[TW] OR vedolizumab[TW] OR entyvio[TW] OR certolizumab[TW] OR cimzia[TW] OR natalizumab[TW] OR ustekinumab[TW] OR Stelara[TW]	569,749
	5	#3 AND #4	7,975
Citation status	6	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)	432,289
Final results	7	#5 AND #6	114

Appendix 7, appendices

As discussed in the response to Question C8, the numbering in the Table 34 of Appendix 7 is incorrectly reported as from Line 25 as it goes directly to Line 44. The search terms in these lines are relevant to the search as they combine Disease with Outcomes strings and introduce “non-animal” and “English language” limits. The full, corrected search string has been provided in Table 54.

Table 54: Embase (Ovid) search terms – corrected

		Date of the search:	**21/07/2015**	
	#	**Search terms**	**Hits**	**References**
Crohns	1	Crohn Disease'/ OR 'Inflammatory Bowel Disease'/	68,307	Cochrane
	2	'Crohn Disease'.mp. OR 'Crohns Disease'.mp. OR 'Inflammatory Bowel Diseases'.mp. OR 'Inflammatory Bowel Disease'.mp. OR IBD.mp.	100,404	
	3	1 OR 2	100,404	
Study type: Economic studies	4	Socioeconomics/	117,324	
	5	Cost benefit analysis/	68,817	SIGN
	6	Cost effectiveness analysis/	107,143	
	7	Cost of illness/	15,617	
	8	Cost control/	52,580	
	9	Economic aspect/	105,430	
	10	Financial management/	104,220	
	11	Health care cost/	140,641	
	12	Health care financing/	11,769	
	13	Health economics/	34,638	
	14	Hospital cost/	15,146	
	15	(fiscal or financial or finance or funding).tw.	118,872	
	16	Cost minimization analysis/	2,671	
	17	(cost adj estimate$).mp.	2,260	
	18	(cost adj variable$).mp.	170	
	19	(unit adj cost$).mp.	2,832	
	20	or/4-19	714,556	

	21	(burden AND (illness* OR disease*)).TI,AB.	73,935	
	22	(((work OR productivity) AND (loss OR lost)) OR absenteeism).TI,AB.	47,740	
	23	((resource OR health?care) AND (use* OR utilisation OR utilization OR allocation OR consumption*)).TI,AB.	145,932	
Exclusion	24	or/21-23	260,021	
	25	20 OR 24	927,676	
	26	Case Report'.tw. OR 'Case study'/ OR Abstract report/ OR Letter/ OR Randomized controlled trial/ OR Clinical trial/ OR review/ OR Randomi?ed controlled trial$.mp. OR Placebo.mp. OR review/ OR meta analysis/ OR major clinical study/ OR review.ti. OR practice guideline/ or clinical practice/ OR controlled clinical trial/	6,712,469	
	27	animal/ NOT human/	1,263,360	Cochrane
	28	26 OR 27	7,891,898	
Economic evaluation studies	29	3 AND 25	3,555	
	30	29 NOT 28	1,856	
	31	Limit to: English	1,772	
	26	Case Report'.tw. OR 'Case study'/ OR Abstract report/ OR Letter/ OR Randomized controlled trial/ OR Clinical trial/ OR review/ OR Randomi?ed controlled trial$.mp. OR Placebo.mp. OR review/ OR meta analysis/ OR major clinical study/ OR review.ti. OR practice guideline/ or clinical practice/ OR controlled clinical trial/	3,822	
	27	animal/ NOT human/	1,776	
	28	26 OR 27	1,658	

Appendix 12, Page 298 appendices

As discussed in the response to Question B8, on Page 298 of the appendices (Appendix 12, section 12.1) the paragraph:

"*The distribution of patients across the health states at the start of the maintenance phase is defined using the proportion of patients in remission and response at the end of the induction period. These end-of-induction proportions are calculated using ORs from the induction NMA (as described in Section 4.10.6). The proportion of patients in each health state is calculated using the formulas from Table 41, consistent with the induction phase*

calculations. Non-responders are then removed, and remaining patients are re-scaled to 100%, as only responders continued in the maintenance phase of the relevant clinical trials."

Should read as follows:

"*The distribution of patients across the health states at the start of the maintenance phase is defined using the proportion of patients in remission and response at the end of the induction period. These end-of-induction proportions are calculated using ORs from the induction NMA (as described in Section 4.10.6). The proportion of patients in each health state is calculated using the formulas from Table 41, consistent with the induction phase calculations.*"

The final sentence of this paragraph was included in error.

References

1. Sandborn WJ, Feagan B, Reinisch W, et al. Efficacy of continued vedolizumab therapy in patients with Crohn's disease who did not respond to vedolizumab induction therapy at Week 6. 9th Congress of ECCO. Copenhagen, Denmark. 20-22 February 2014. P497.

2. Janssen Research and Development. A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab maintenance therapy in subjects with moderately to severely active Crohn's disease (44-week clinical study report). (EDMS-ERI-97847519, 1.0) 9 November 2015. Data on file.

3. Janssen Research and Development. TEUEFCORE05A: Summary of clinical response, clinical remission and 70-point response status at Week 6; subjects in CNTO1275CRD3002 who were anti-TNF naïve and were randomized to receive ustekinumab 6mg/kg IV, excluding those enrolled prior to study re-start and excluding site 1127. 28 December 2016. Data on file.

4. Janssen Research and Development. TEFCREM13A: Number of subjects in clinical remission at each visit through Week 44; randomized subjects who were TNF naïve, excluding those enrolled prior to study re-start. 07 October 2015. Data on file.

5. Janssen Research and Development. TEFCRES13A: Number of subjects in clinical response at each visit through Week 44; randomized subjects who were TNF naïve, excluding those enrolled prior to study re-start. 07 October 2015. Data on file.

6. Janssen Research and Development. A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease (Uniti 2). (EDMS-ERI-86643187, 1.0) 13 October 2015. Data on file.

7. Janssen Research and Development. Ustekinumab endoscopy substudy for Phase 3 Crohn's disease studies substudy report. (EDMS-ERI-103534224, 1.0) 29 October 2015. Data on file.

8. Janssen Research and Development. A Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapy (Uniti 1). (EDMS-ERI-65460596) 17 September 2015. Data on file.

9. Janssen Research and Development. TEUEFCRP02A: Summary of CRP concentration (mg/L) at each visit through Week 8; Randomized subjects in CNTO1275CRD3001 excluding those enrolled prior to study re-start. 11 January 2017 2017. Data on file.

10. Janssen Research and Development. TEUEFCRP02B: Summary of CRP concentration (mg/L) at each visit through Week 8; Randomized subjects in CNTO1275CRD3002 excluding those enrolled prior to study re-start and excluding site 1127. 11 January 2017 2017. Data on file.

11. Janssen Research and Development. TEUEFFECL01A: Summary of fecal calprotectin concentration (micrograms/kg) at baseline and Week 6; Randomized subjects in CNTO1275CRD3001 excluding those enrolled prior to study re-start. 11 January 2017 2017. Data on file.

12. Janssen Research and Development. TEUEFFECL01B: Summary of fecal calprotectin concentration (micrograms/kg) at baseline and Week 6; Randomized subjects in CNTO1275CRD3002 excluding those enrolled prior to study re-start and excluding site 1127. 11 January 2017 2017. Data on file.

13. Janssen Research and Development. TEUEFFECL02A: Summary of fecal lactoferrin concentration (micrograms/g) at baseline and Week 6; Randomized subjects in CNTO1275CRD3001 excluding those enrolled prior to study re-start. 11 January 2017 2017. Data on file.

14. Janssen Research and Development. TEUEFFECL02B: Summary of fecal lactoferrin concentration (micrograms/g) at baseline and Week 6; Randomized subjects in CNTO1275CRD3002 excluding those enrolled prior to study re-start and excluding site 1127. 11 January 2017 2017. Data on file.

15. Janssen Research and Development. Abbreviated health technology assessment report of ustekinumab maintenance of efficacy in Crohn's disease through 2 years (IM-UNITI). (EDMS-ERI-132762380, 1.0) 25 October 2016. Data on file.

16. Janssen Research and Development. Ustekinumab for Crohn's disease: Medical resource use Delphi panel. 11 October 2016. Data on file.

17. Curtis L. Unit costs of health and social care. 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php. Accessed: 16 April 2016.

18. National Institute for Health and Care Excellence. NICE guideline NG24: Blood transfusion. 2015. Available at: https://www.nice.org.uk/guidance/ng24. Accessed: 5 January 2016.

19. National Health Service. Department of Health reference costs 2014-15. 2015. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed: 27 March 2016.

20. Janssen Research and Development. TEXPCRES12D: Number of subjects in clinical response at each visit from Week 8 to Week 44; non-randomized subjects enrolled from CNTO1275CRD3002 excluding those enrolled prior to study re-start and excluding site 1127. 6 July 2016. Data on file.

21. Janssen Research and Development. TEXPCREM12D: Number of subjects in clinical remission at each visit from Week 8 to Week 44; non-randomized subjects enrolled from CNTO1275CRD3002 excluding those enrolled prior to study re-start and excluding site 1127. 6 July 2016. Data on file.

22. Janssen Research and Development. TEXPCRES12C: Number of subjects in clinical response at each visit from Week 8 to Week 44; non-randomized subjects enrolled from CNTO1275CRD3001 excluding those enrolled prior to study re-start. 6 July 2016. Data on file.

23. Janssen Research and Development. TEXPCREM12C: Number of subjects in clinical remission at each visit from Week 8 to Week 44; non-randomized subjects enrolled from CNTO1275CRD3001 excluding those enrolled prior to study re-start. 6 July 2016. Data on file.

24. Janssen Research and Development. TEUEFCORE06A: Summary of clinical response and clinical remission status at Week 8 of maintenance study; subjects in CNTO1275CRD3003 who were anti-TNF naïve and were non-responders to ustekinumab IV induction dosing and received ustekinumab in maintenance, excluding those enrolled prior to study re-start and site 1127. 28 December 2016. Data on file.

25. Janssen Research and Development. TEUEFCORE07A: Summary of clinical response status at induction Week 6; randomized subjects in CNTO1275CRD3002 who were anti-TNF naïve, excluding those enrolled prior to study re-start and site 1127. 28 December 2016. Data on file.

26. Janssen Research and Development. TEUEFCORE07B: Summary of clinical response status at induction Week 6 and at maintenance Week 44; subjects who were anti-TNF naïve and were enrolled in CNTO1275CRD3003, excluding those enrolled prior to study re-start and site 1127. 28 December 2016. Data on file.

27. Elsevier. EMBASE.com. 2016. Available at: help.elsevier.com/app/answers/detail/a_id/4600/p/9754/kw/free%20text%20search. Accessed: 22 December 2016.

28. European Medicines Agency (EMA). Summary of Product Characteristics. Adalimumab. 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf. Accessed: 10 October 2016.

29. Panaccione R, Sandborn W, Colombel J, et al. Impact of Adalimumab therapy after 12 Weeks In patients with Crohn's Disease who were non res ponders at week4: P-0059. *Inflamm Bowel Dis*. 2008; 14:S28.

30. Sandborn W, Gasink C, Blank M, et al. O-001 A Multicenter, Double-Blind, Placebo-Controlled Phase3 Study of Ustekinumab, a Human IL-12/23P40 mAB, in Moderate-Service Crohn's Disease Refractory to Anti-TFNalpha: UNITI-1. *Inflamm Bowel Dis*. 2016; 22 Suppl 1:S1.

31. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013; 369(8):711-21.

32. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. *Gastroenterology*. 2007; 132(1):52-65.

33. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. *Gastroenterology*. 2006; 130(2):323-33; quiz 591.

34. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012; 142(5):1102-11 e2.

35. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007; 56(9):1232-9.

36. Watanabe M, Hibi T, Lomax KG, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. *J Crohns Colitis*. 2012; 6(2):160-73.

37. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002; 359(9317):1541-9.

38. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010; 362(15):1383-95.

Appendix 1: Updated results section

5.7 Base-case results

Base-case results are presented for both the conventional care failure and TNF failure populations. Results are shown for the CDAI-100 response criteria and using list prices for all treatments.

Vedolizumab has a confidential patient access scheme (PAS), and biosimilar prices are variable; however, we are not privy to confidential simple patient access schemes and thus results are presented using list prices for all comparators.

5.7.1 Base-case incremental cost-effectiveness analysis results

Incremental analyses are shown for the conventional care failure population and the TNF failure population in Table 65 and Table 66, respectively.

An incremental analysis compares multiple mutually exclusive treatments against each other to find the most cost-effective treatment option out of all the available interventions. This is done in three steps:

1. Treatments are ordered from least to most expensive.
2. Check for strong dominance. Treatments are dominated if they are both costlier and less effective than another treatment included in the analysis.
3. Check for extended dominance. Treatments are extendedly dominated if an alternative treatment can provide more QALYs for a lower cost per QALY. This is because decision makers prefer a more effective treatment with a lower incremental cost-effectiveness ratio (ICER).

The results from the incremental analysis indicate that ustekinumab dominates both conventional care and adalimumab in the conventional care failure population, and that ustekinumab dominates both conventional care and vedolizumab in the TNF failure population. In addition, despite the fact that only 1 year of biologic treatment is modelled, significant QALY gains are accrued for ustekinumab compared to conventional care, with important relative gains over biologic comparators, thus strengthening the model findings. This is further confirmed in scenario analyses (Section 5.8.3).

Table 65: Base-case results: conventional care failure population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£263,053	43.0941	13.0799				Dominant	
Conventional care	£278,542	43.0941	12.6796	£15,489	0.0000	-0.4003	-	Dominated
Adalimumab	£283,762	43.0941	12.9406	£20,709	0.0000	-0.1393	£19,999	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 66: Base-case results: TNF failure population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£288,088	44.9817	12.9819				Dominant	
Conventional care	£294,600	44.9817	12.7578	£6,512	0.0000	-0.2241	-	Dominated
Vedolizumab	£302,820	44.9817	12.8474	£14,732	0.0000	-0.1345	£91,779	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TNF, tumour necrosis factor.

5.7.1.1 Base-case incremental cost-effectiveness analysis including infliximab

Infliximab is not included in the base case due to lack of CDAI-100 induction efficacy data. However, it is included as a scenario analysis in Table 67, using the CDAI-100 outcome and assuming equal efficacy for adalimumab and infliximab, and in Table 68 using the CDAI-70 outcome. In the CDAI-100 scenario ustekinumab remains the cost-effective treatment option. In the CDAI-70 scenario ustekinumab is no longer cost-effective, and Inflectra is the cost-effective treatment option; however these results should be interpreted with caution given the limitations of the NMA outcomes for infliximab noted previously in Section 4.10.4.

Table 67: Base-case results: conventional care failure population including infliximab (CDAI-100)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£263,053	43.0941	13.0799				Dominant	
Conventional care	£278,542	43.0941	12.6796	£15,489	0.0000	-0.4003	-	Dominated
Infliximab - Inflectra	£278,693	43.0941	12.8503	£15,640	0.0000	-0.2296	£883	Dominated
Infliximab - Remsima	£278,693	43.0941	12.8503	£15,640	0.0000	-0.2296	£883	Dominated
Infliximab - Remicade	£279,698	43.0941	12.8503	£16,645	0.0000	-0.2296	£6,772	Dominated
Adalimumab	£283,762	43.0941	12.9406	£20,709	0.0000	-0.1393	£19,999	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 68: Base-case results: conventional care failure population including infliximab (CDAI-70)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)
Ustekinumab	£264,420	43.0941	13.0583				Dominant	
Infliximab - Inflectra	£264,476	43.0941	13.1688	£56	0.0000	0.1104	Dominant	£504
Infliximab - Remsima	£264,476	43.0941	13.1688	£0	0.0000	0.0000	Dominant	Dominated
Infliximab - Remicade	£265,930	43.0941	13.1688	£1,454	0.0000	0.0000	Dominant	Dominated
Conventional care	£278,219	43.0941	12.6851	£13,743	0.0000	-0.4836	-	Dominated
Adalimumab	£286,251	43.0941	12.9153	£21,776	0.0000	-0.2535	£34,897	Dominated

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

5.7.2 Clinical outcomes from the model

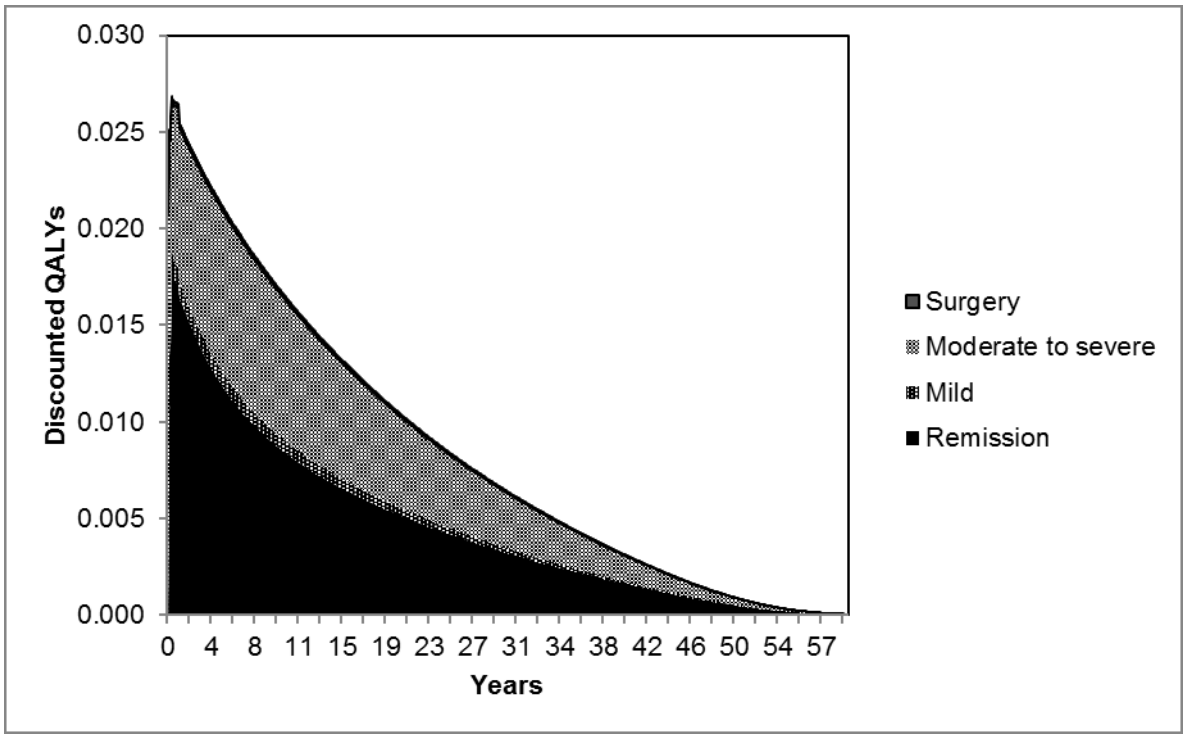
5.7.2.1 Markov trace – life years

The proportion of patients in each health state over time (Markov Trace) for all treatments are shown in Appendix 15.

5.7.2.2 Markov trace – QALYs

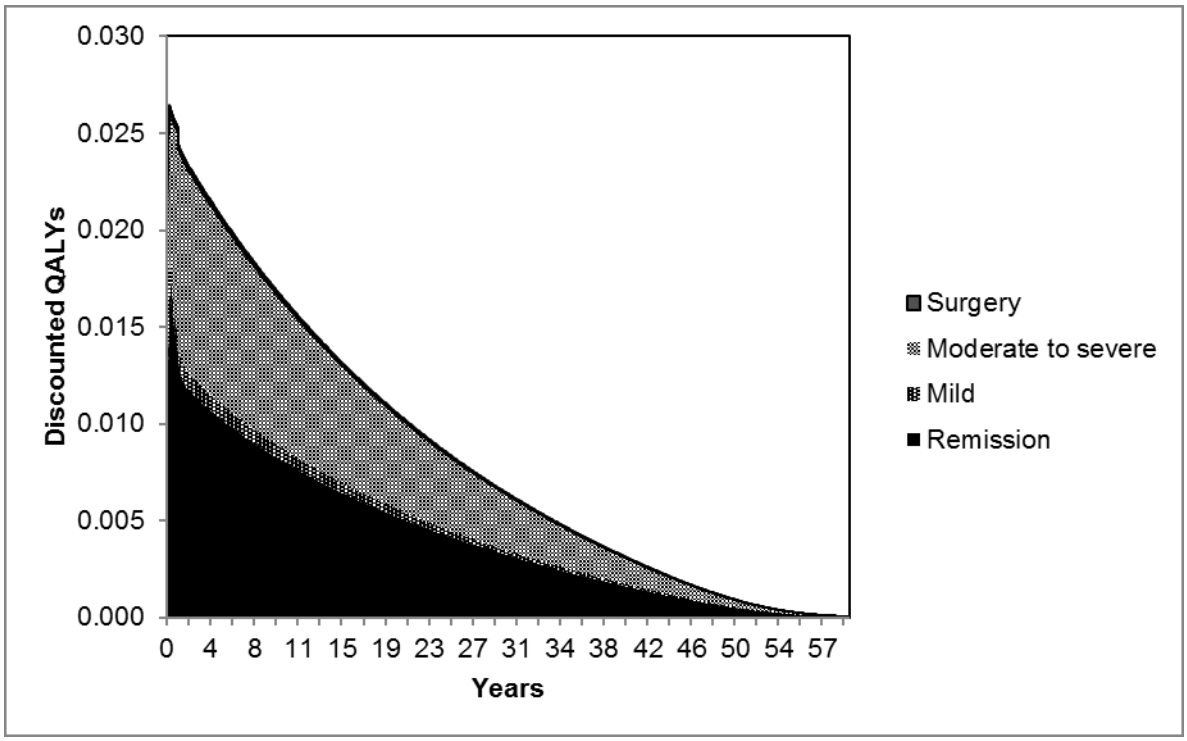
Figure 48 to Figure 53 show the split of discounted QALYs in each health state over time for the conventional care failure and TNF failure populations, respectively.

Figure 48: Markov trace QALYs: ustekinumab conventional care failure



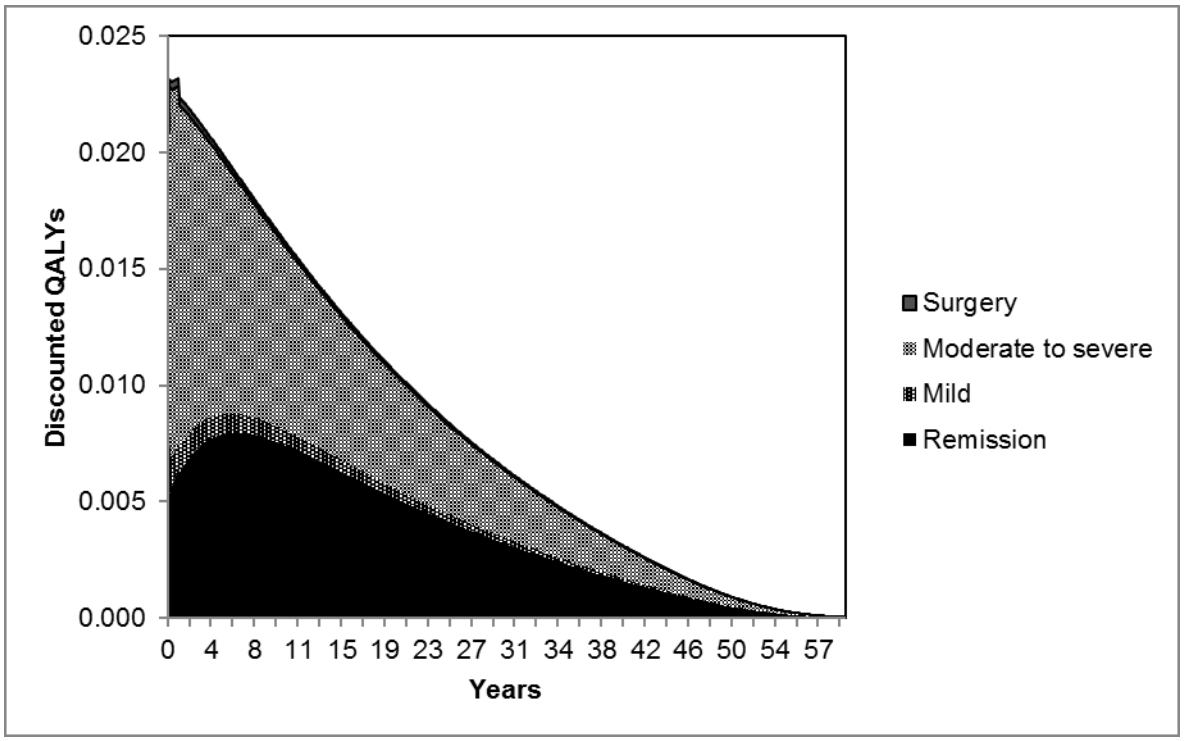
Key: QALY, quality-adjusted life year.

Figure 49: Markov trace QALYs: adalimumab conventional care failure



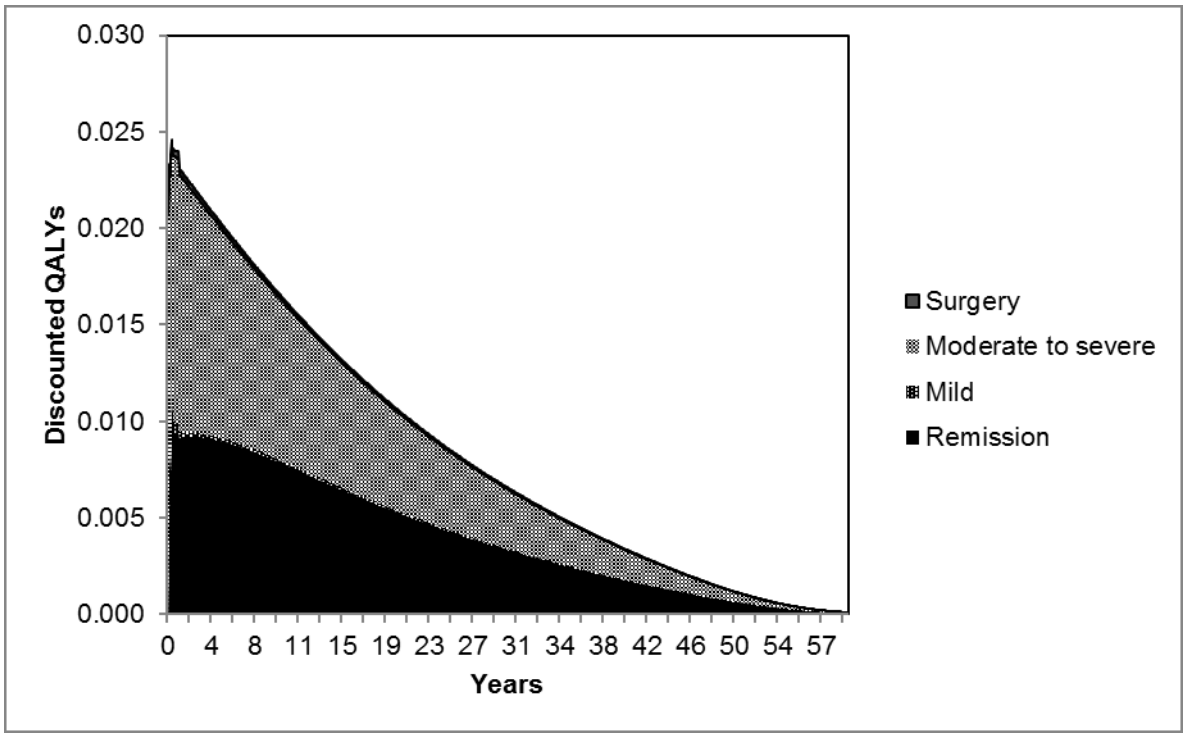
Key: QALY, quality-adjusted life year.

Figure 50: Markov trace QALYs: conventional care conventional care failure



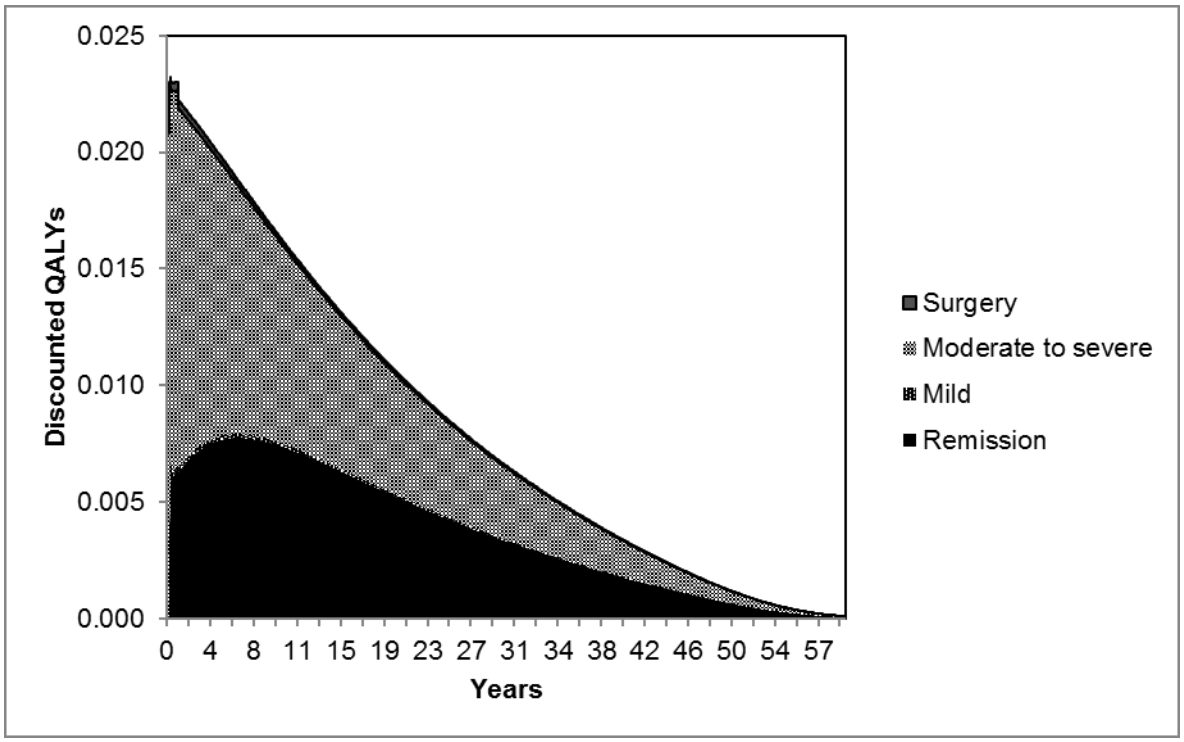
Key: QALY, quality-adjusted life year.

Figure 51: Markov trace QALYs: ustekinumab TNF failure



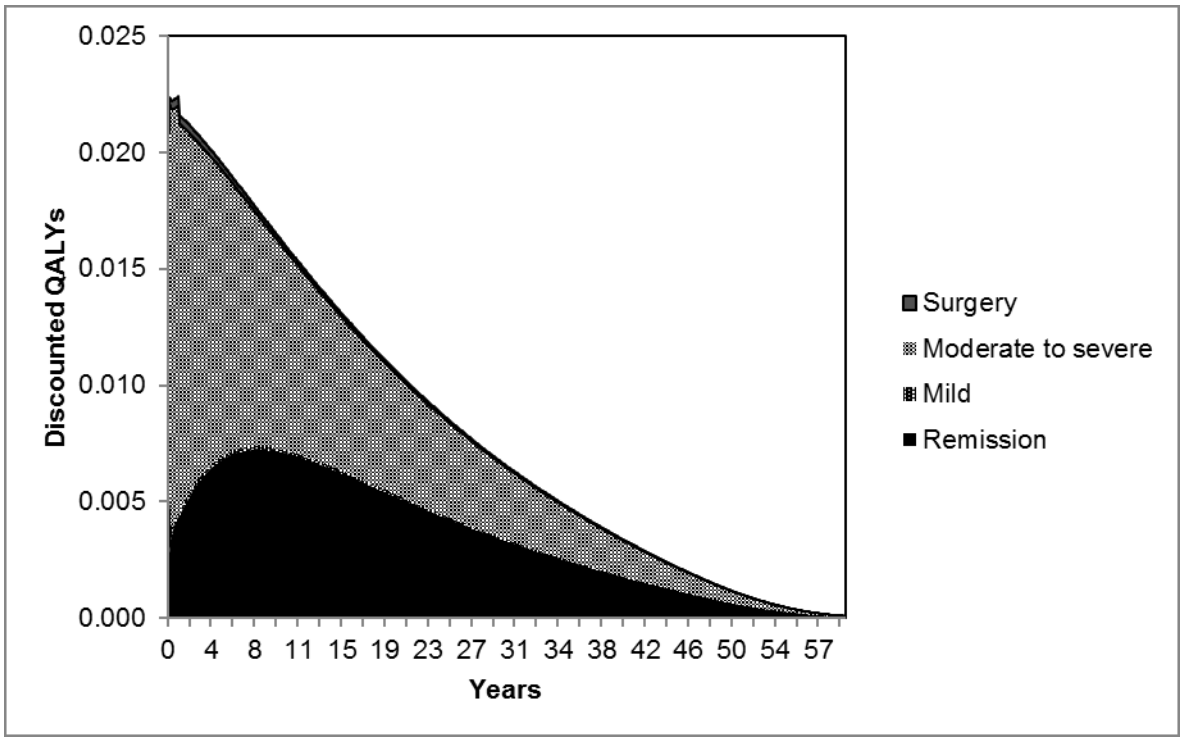
Key: QALY, quality-adjusted life year; TNF, tumour necrosis factor.

Figure 52: Markov trace QALYs: vedolizumab TNF failure



Key: QALY, quality-adjusted life year; TNF, tumour necrosis factor.

Figure 53: Markov trace QALYs: conventional care TNF failure



Key: QALY, quality-adjusted life year; TNF, tumour necrosis factor.

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 69: Ustekinumab versus conventional care – QALY gain by health state: conventional care failure population

Health state	QALY ustekinumab	QALY conventional care	Increment	Absolute increment	% absolute increment	
Remission	6.8710	5.5763	1.2947	1.2947	59.14%	
Mild	0.5012	0.5344	-0.0332	0.0332	1.52%	
Moderate to severe	5.5791	6.4213	-0.8422	0.8422	38.47%	
Surgery	0.1286	0.1476	-0.0190	0.0190	0.87%	
Total	13.0799	12.6796	0.4003	2.1890	100.00%	
Key: QALY, quality-adjusted life year.						

Table 70: Ustekinumab versus adalimumab – QALY gain by health state: conventional care failure population

Health state	QALY ustekinumab	QALY adalimumab	Increment	Absolute increment	% absolute increment
Remission	6.8710	6.4356	0.4353	0.4353	59.52%
Mild	0.5012	0.5032	-0.0020	0.0020	0.27%
Moderate to severe	5.5791	5.8667	-0.2876	0.2876	39.32%
Surgery	0.1286	0.1351	-0.0065	0.0065	0.89%
Total	13.0799	12.9406	0.1393	0.7314	100.00%

Key: QALY, quality-adjusted life year.

Table 71: Ustekinumab versus conventional care – QALY gain by health state: TNF failure population

Health state	QALYs ustekinumab	QALYs conventional care	Increment	Absolute increment	% absolute increment
Remission	6.0886	5.3896	0.6991	0.6991	57.55%
Mild	0.1397	0.1194	0.0204	0.0204	1.68%
Moderate to severe	6.6024	7.0869	-0.4845	0.4845	39.88%
Surgery	0.1511	0.1620	-0.0109	0.0109	0.89%
Total	12.9819	12.7578	0.2241	1.2148	100.00%

Key: QALY, quality-adjusted life year.

Table 72: Ustekinumab versus vedolizumab – QALY gain by health state: TNF failure population

Health state	QALYs ustekinumab	QALYs vedolizumab	Increment	Absolute increment	% absolute increment
Remission	6.0886	5.6701	0.4185	0.4185	57.08%
Mild	0.1397	0.1244	0.0154	0.0154	2.10%
Moderate to severe	6.6024	6.8952	-0.2928	0.2928	39.93%
Surgery	0.1511	0.1577	-0.0066	0.0066	0.89%
Total	12.9819	12.8474	0.1345	0.7333	100.00%

Key: QALY, quality-adjusted life year.

Table 73: Ustekinumab versus conventional care – cost by category: conventional care failure population

Health state	Cost ustekinumab	Cost conventional care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£17,390	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£209,316	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£51,836	[redacted]	[redacted]	[redacted]
Total	£263,053	£278,542	-£15,489	£33,053	100.00%

Table 74: Ustekinumab versus adalimumab – cost by category: conventional care failure population

Health state	Cost ustekinumab	Cost adalimumab	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£27,716	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£194,020	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£62,025	[redacted]	[redacted]	[redacted]
Total	£263,053	£283,762	-£20,709	£21,443	100.00%

Table 75: Ustekinumab versus conventional care – cost by category: TNF failure population

Health state	Cost ustekinumab	Cost conventional care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£17,744	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£223,965	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£52,891	[redacted]	[redacted]	[redacted]
Total	[redacted]	£17,744	[redacted]	[redacted]	[redacted]

Table 76: Ustekinumab versus vedolizumab – cost by category: TNF failure population

Health state	Cost ustekinumab	Cost conventional care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	£29,727	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	£2,190	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	£218,778	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	£52,124	[redacted]	[redacted]	[redacted]
Total	£288,088	£302,820	-£14,732	£14,743	100.00%

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was run on the model for both populations, using 5,000 simulations.

5.8.1.1 Tabulated results

The mean results over all the iterations were tabulated into incremental analyses for both populations. Results are given in Table 77 and Table 78 for the conventional care failure and TNF failure populations, respectively. The conclusions of the probabilistic results are similar to the deterministic results with both analyses indicating that ustekinumab is dominant against conventional care in both populations. Additionally, ustekinumab is against adalimumab in the conventional care population, and against vedolizumab in the TNF failure population.

Table 77: Probabilistic incremental analysis – conventional care failure population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Ustekinumab	£313,612	15.5219			
Adalimumab	£338,497	15.3670	£24,885	-0.1549	Dominated
Conventional care	£338,505	15.0933	£24,893	-0.4285	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Table 78: Probabilistic incremental analysis – TNF failure population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Ustekinumab	£347,103	15.5672			
Conventional care	£360,982	15.3017	£13,880	-0.2656	Dominated
Vedolizumab	£365,790	15.4153	£18,688	-0.1519	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TNF, tumour necrosis factor.					

5.8.1.2 Cost-effectiveness scatterplot (submission section 5.8.1.2)

Costs and QALYs from each iteration of the PSA were plotted for all treatments. Figure 54 and Figure 55 show the results for the conventional care failure and TNF failure populations, respectively. These shown the similarities in spread of costs and QALYs for all treatment arms in the analyses.

Figure 54: Cost-effectiveness scatter plot: conventional care failure

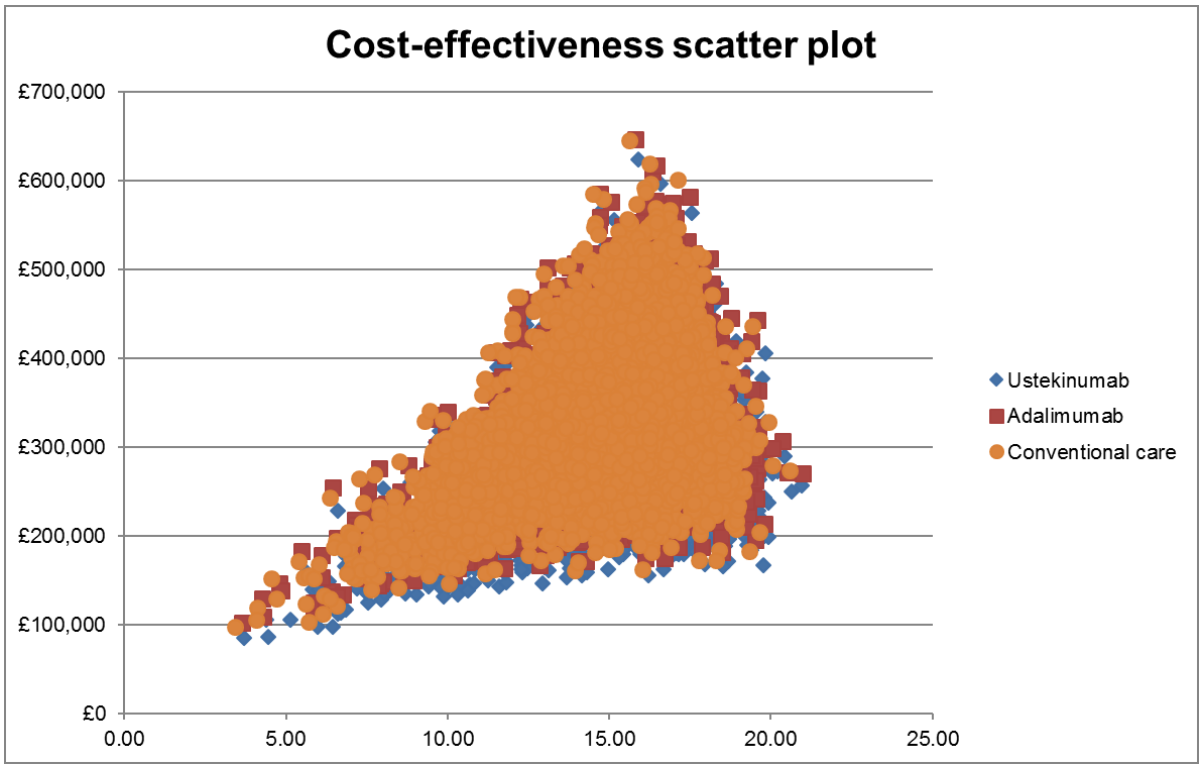
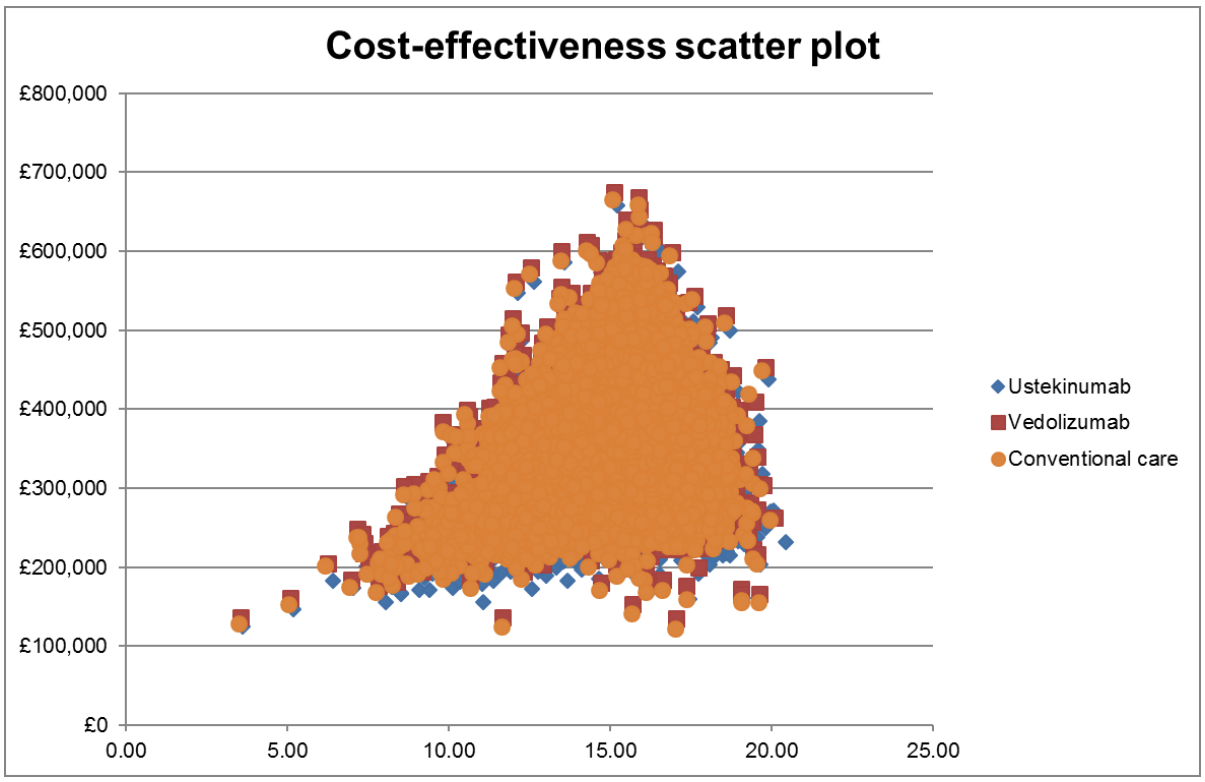


Figure 55: Cost-effectiveness scatter plot: TNF failure

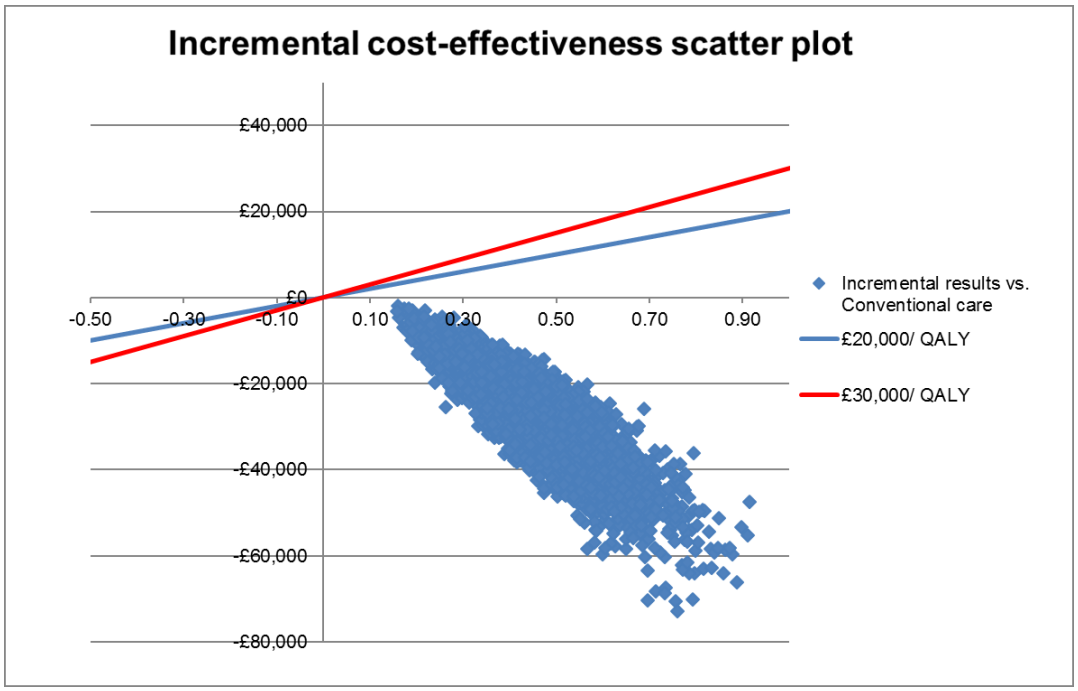


Key: TNF, tumour necrosis factor.

5.8.1.3 Pairwise cost-effectiveness scatterplot

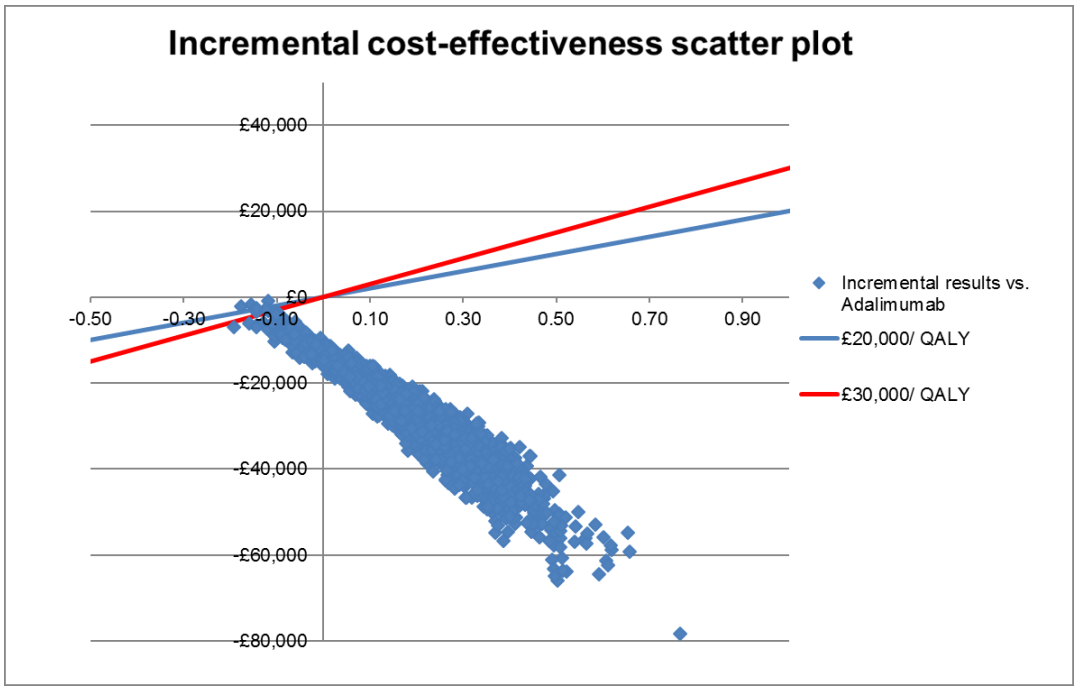
The results of each iteration were plotted on pair-wise scatter plots, showing incremental results. Figure 56 and Figure 57 show the results versus conventional care and adalimumab in the conventional care failure population, respectively. Figure 58 and Figure 59 show results in the TNF failure population versus conventional care and vedolizumab, respectively. Results indicate that for all treatments, the majority of PSA iterations result in positive incremental QALYs and negative incremental costs versus all treatments, i.e. that ustekinumab remains dominant in the majority of iterations.

Figure 56: PSA incremental scatter plot: conventional care failure population, ustekinumab versus conventional care



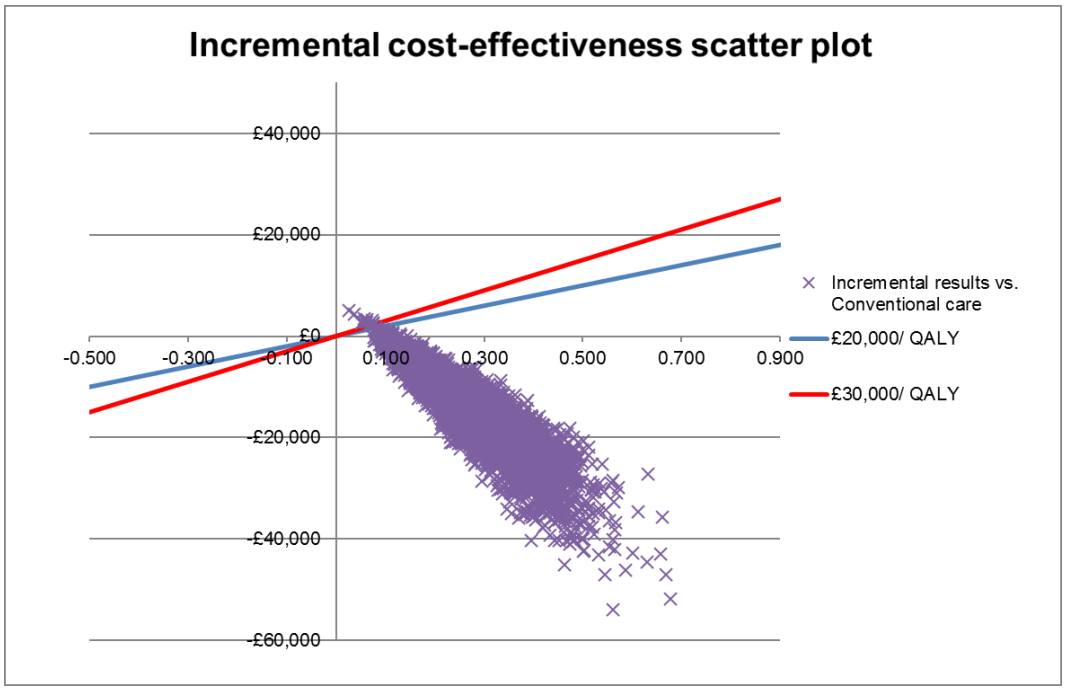
Key: PSA, probabilistic sensitivity analysis.

Figure 57: PSA incremental scatter plot: conventional care failure population, ustekinumab versus adalimumab



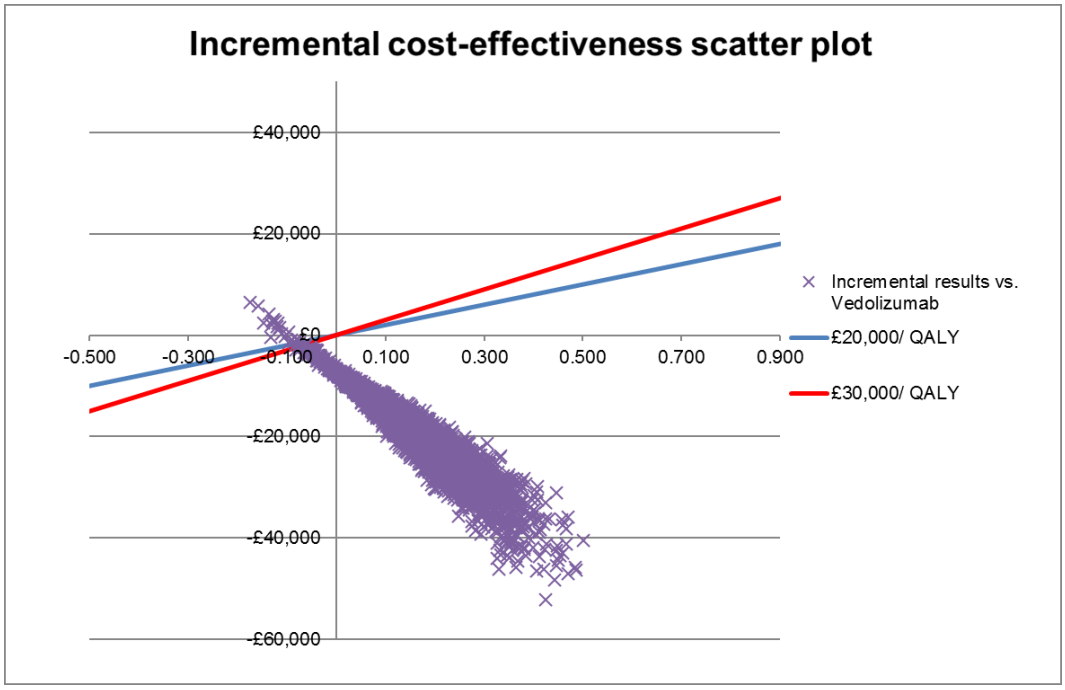
Key: PSA, probabilistic sensitivity analysis.

Figure 58: PSA incremental scatter plot: TNF failure population, ustekinumab versus conventional care



Key: PSA, probabilistic sensitivity analysis; TNF, tumour necrosis factor.

Figure 59: PSA incremental scatter plot: TNF failure population, ustekinumab versus vedolizumab



Key: PSA, probabilistic sensitivity analysis; TNF, tumour necrosis factor.

5.8.1.4 Cost-effectiveness acceptability curve

Cost-effectiveness acceptability curves (CEACs) are present in Figure 60 and Figure 61 for the conventional care failure and TNF failure populations, respectively. The results indicate that, in both populations, ustekinumab has a 100% chance of being the most cost-effective treatment available at the £30,000 WTP threshold.

Figure 60: Cost-effectiveness acceptability curve: conventional care failure

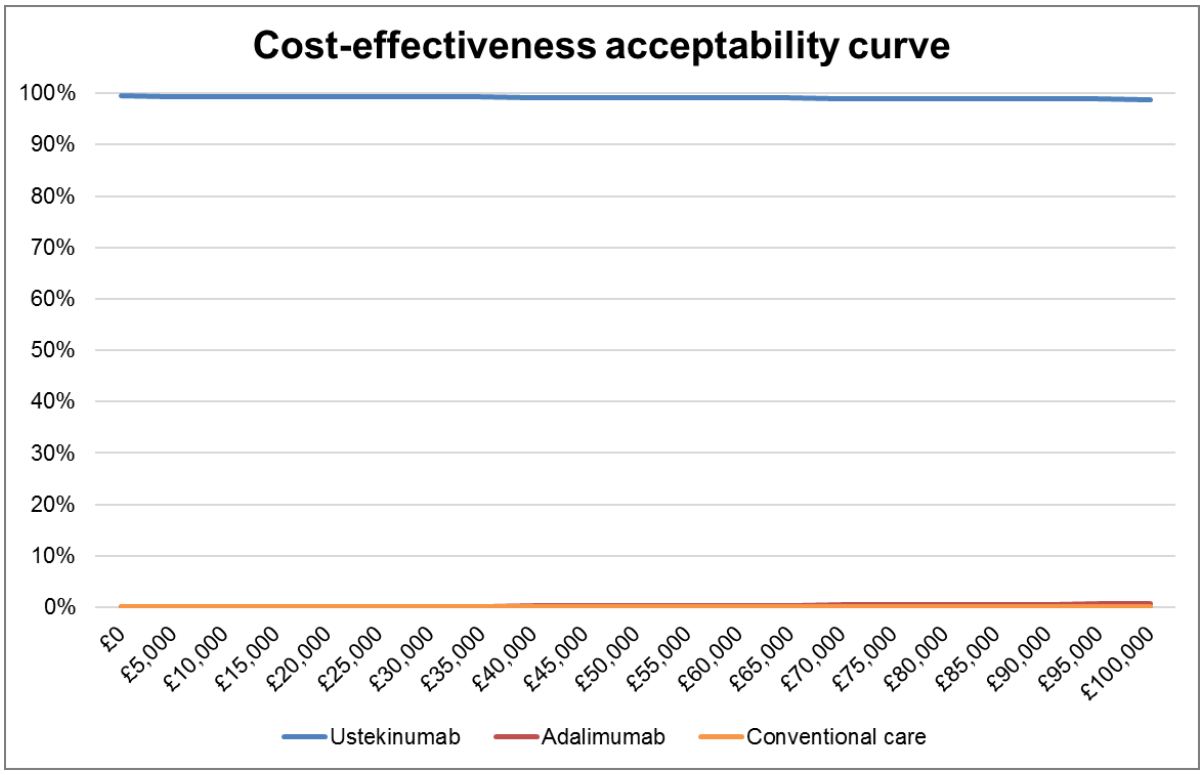
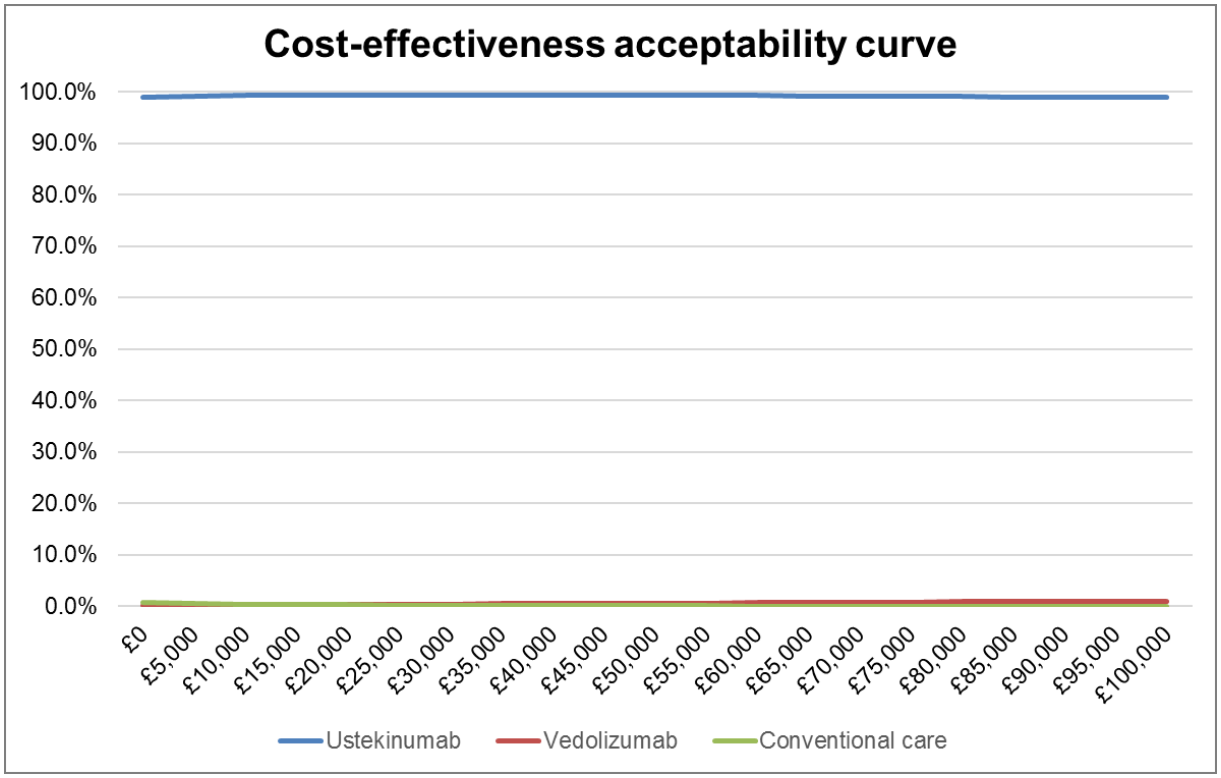


Figure 61: Cost-effectiveness acceptability curve: TNF failure



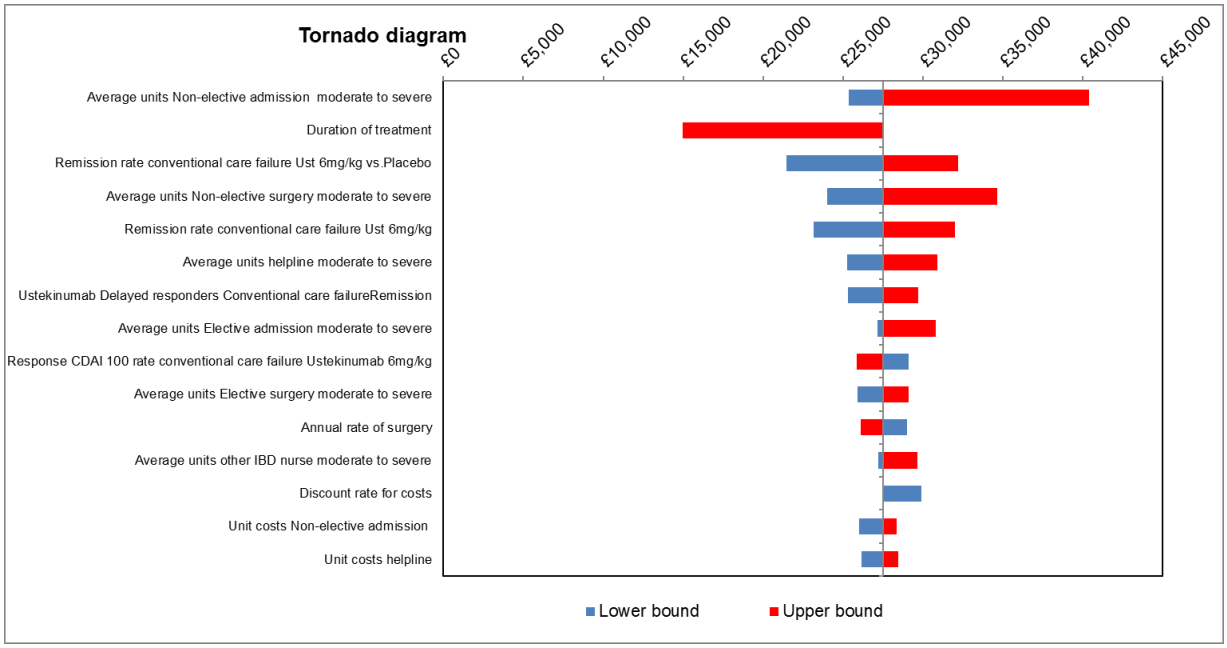
Key: TNF, tumour necrosis factor.

5.8.2 Deterministic sensitivity analysis

In a one-way sensitivity analysis (OWSA), variables were replaced with their upper or lower bounds. The model was then run with these values. Due to relatively small QALY gains between treatments, testing upper and lower bounds may result in ICERs moving between quadrants of the cost-effectiveness plane and can therefore be difficult to interpret. Therefore, OWSA results are shown in terms of net monetary benefit (NMB) using a WTP threshold of £30,000 as the NMB is easier to interpret where small QALY gains are concerned (NMB > £0 indicates cost-effectiveness at the specified threshold). The variables that had the biggest impact on NMB were plotted on tornado diagrams. Figure 62 and Figure 64 show the results for the conventional care failure and TNF failure populations, respectively. The results indicate that duration of biologic treatment, several resource use frequencies for the moderate to severe health state, and induction efficacy have large effects on the NMB for both populations. Figure 63 and Figure 65 show results versus adalimumab and vedolizumab in their respective populations. The results indicate that induction efficacy and resource use units for the moderate to severe health state have an impact on both comparisons, however duration of treatment has the largest impact on NMB versus adalimumab. The results demonstrate that the NMB remains above zero (and hence ustekinumab remains cost-effective) under extreme values of all parameters, for all treatments. Influential parameters versus biologics are in line with the findings of the economic evaluation SLR (see Section 5.1.2.1)

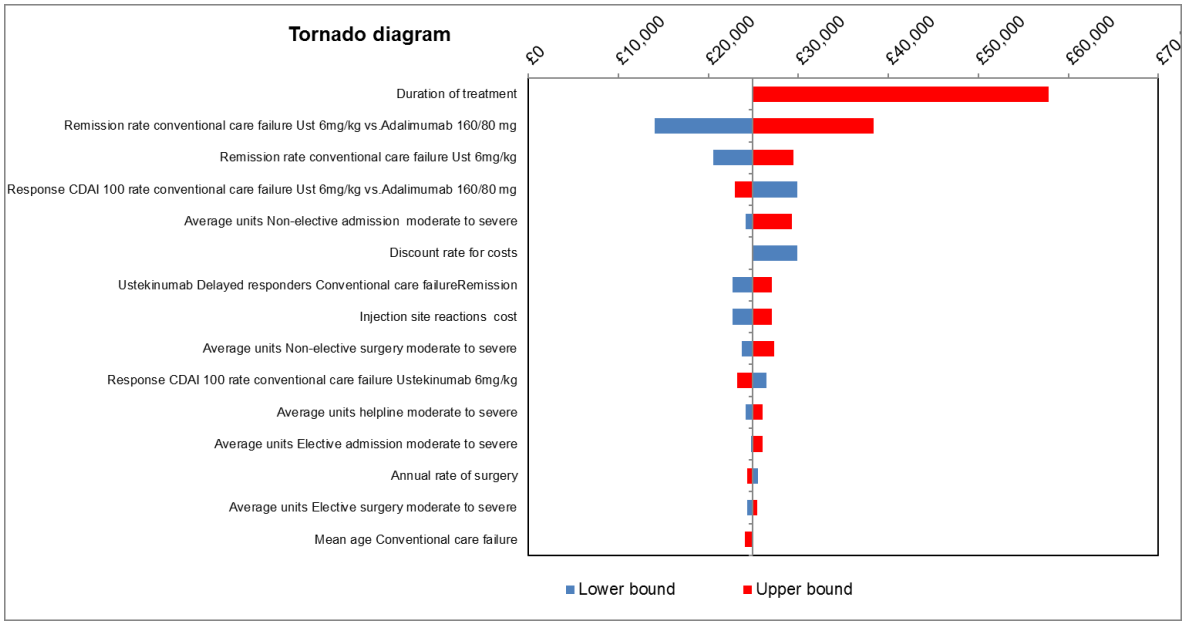
It is noted that for duration of treatment the lower bound is equal to the base case value.

Figure 62: Tornado diagram versus conventional care: conventional care failure population (base case NMB = £27,499)



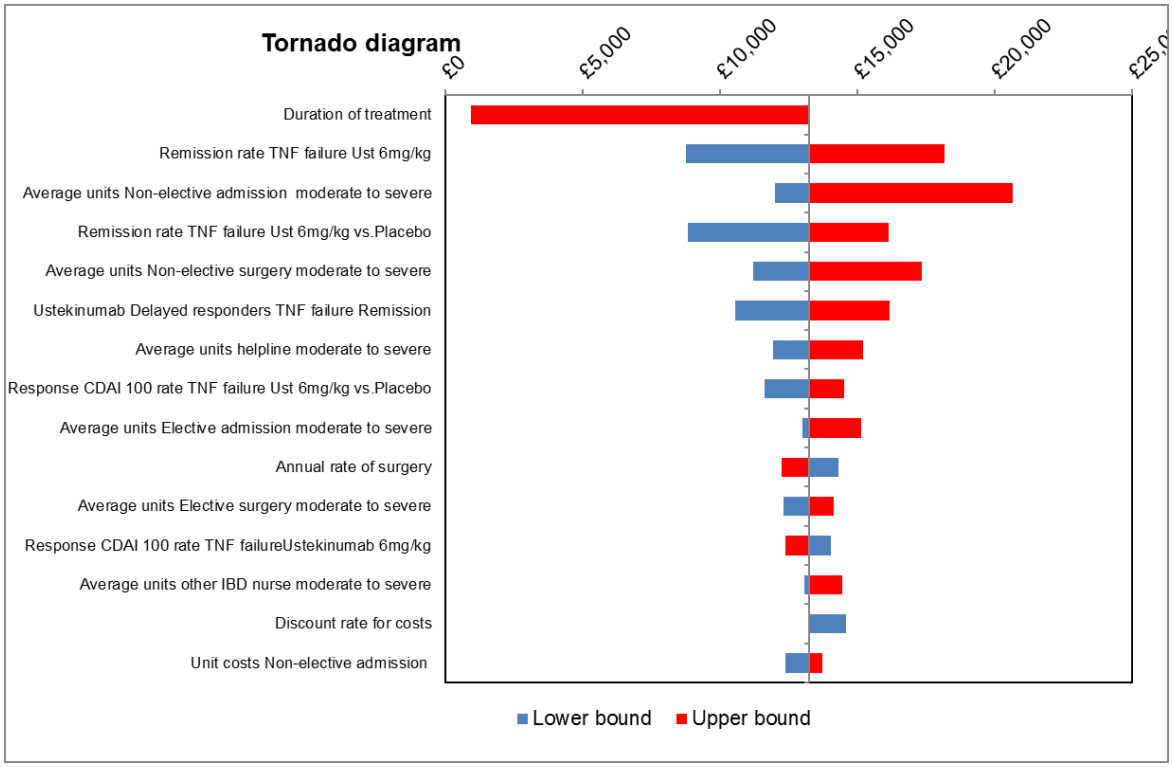
Key: IBD, inflammatory bowel disease; ust, ustekinumab.

Figure 63: Tornado diagram versus adalimumab: conventional care failure population (base case NMB = £24,888)



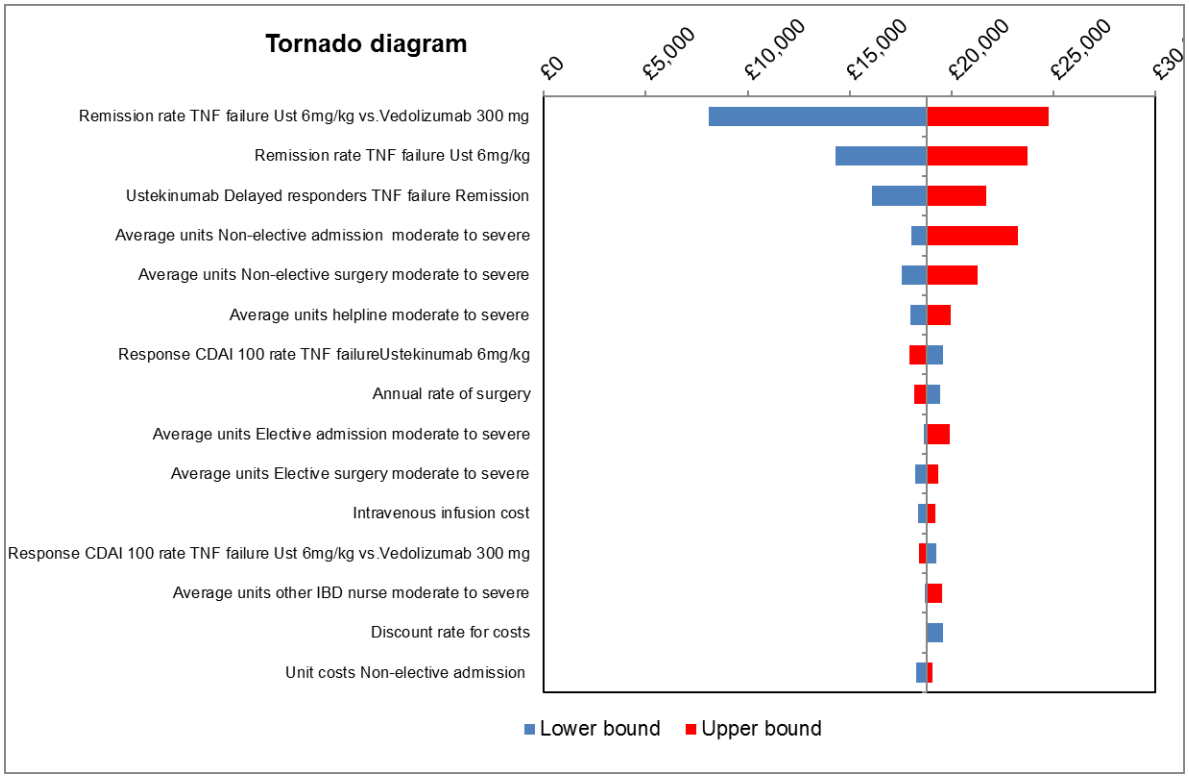
Key: IBD, inflammatory bowel disease; q8w, every 8 weeks; q812, every 12 weeks; ust, ustekinumab.

Figure 64: Tornado diagram versus conventional care: TNF failure population (base case NMB = £10,993)



Key: IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ust, ustekinumab.

Figure 65: Tornado diagram versus vedolizumab: TNF failure population (base case NMB = £17,422)



Key: IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ust, ustekinumab.

5.8.3 Scenario analysis

Many scenarios were tested within the model. The full list is presented in Table 79:

Table 79: Scenario analyses

	Scenario	Base case setting	Scenario setting	Justification
1	Base case	N/A	N/A	N/A
2	10-year time horizon	60 year time horizon	10-year time horizon	To explore the impact of alternative time horizons on the model results. 10-year time horizon was base case in TA352.
3	1-year time horizon		1-year time horizon	
4	2-year treatment duration	1-year treatment duration	2-year treatment duration	The duration of treatment is uncertain; data are available for comparison with other biologic treatments for 1 year of treatment. These scenarios explore the impact of extending the treatment duration.
5	3-year treatment duration		3-year treatment duration	

				IBD audit 2015 confirms that in practice patients may remain on biologic treatment beyond 1-year
6	No half cycle correction	Half-cycle correction applied	No half-cycle correction applied	To verify that this does not impact results given the short cycle-length used in the model.
7	Alternative utility source: IMUNITI SF-36	Utility source: IMUNITI IBDQ	Utility source: IMUNITI SF-36	To explore the impact of alternative utility values on the results of the analysis.
8	Alternative utility source: IMUNITI CDAI		Utility source: IMUNITI CDAI	
9	Alternative utility source: Bodger *et al.*		Utility source: Bodger *et al.*	
10	Response criteria: CDAI-70	Response criteria: CDAI-100	Response criteria: CDAI-70	Previous trials defined response using CDAI-70. This analysis explores the impact of assessing initial response to treatment based on CDAI-70.
11	Alternative source for resource use costs: TA352 resource use costs – original	Delphi panel resource use estimates used to derive costs.	Costs used in the original manufacturer's submission for TA352	Resource use costs were identified as a key driver of results. This explores the impact of using costs aligned with the most recent Crohn's disease NICE TA.
12	Alternative source for resource use costs: TA352 resource use costs – ACD responses		Costs used in the manufacturer's ACD response for TA352	
13	Ustekinumab dosing all q12w at start of maintenance phase	Ustekinumab dosing split between q12w and q8w at the start of maintenance based on clinician interpretation of the label	Ustekinumab dosing 100% q12w at the start of maintenance	The label for ustekinumab allows clinicians to use their judgement for dosing of ustekinumab. These scenarios explore the impact of the extreme situations.
14	Ustekinumab dosing all q8w at start of maintenance phase		Ustekinumab dosing 100% q8w at the start of maintenance	
15	No gradual decline in	Gradual decline in efficacy is	No gradual decline in efficacy is	The true impact on efficacy of biologic

	efficacy post-biologic maintenance phase	assumed following the end of the biologic maintenance phase	assumed following the end of the biologic maintenance phase	treatments following discontinuation at the end of maintenance is uncertain, this reflects the extreme and conservative scenario in which efficacy is lost immediately following cessation of treatment.
16	No dose escalation	Dose escalation is included	No dose escalation is included	To explore the impact of dose escalation on results.
17	Alternative maintenance data source: IMUNITI data	Maintenance data source: NMA transitions (calibrated)	Maintenance data source: IMUNITI transitions	To explore the impact of allowing transition probabilities to vary over time using data observed from the IMUNITI study. It is noted that this assumes that all biologic treatments have equal efficacy during maintenance which is a conservative assumption which is not in line with the results of the treatment sequence NMA.
18	AEs not included	AEs included	AEs not included	To explore the impact of AEs on the results of the analysis.
19	Adalimumab lower induction dose	Adalimumab induction dose 160/80	Adalimumab induction dose 80/40	To explore the impact of assuming the lower dose of adalimumab. It is noted that treatment sequence outcomes are only available for the 160/80 induction dose, and so the calibrated transition probabilities for the 80/40 induction dose assume the same treatment sequence outcome as for the 160/80 dose and therefore the efficacy of the 80/40 treatment sequence is likely to be over-estimated.
20	Ustekinumab induction efficacy lower bound	Ustekinumab induction efficacy (responders and	Ustekinumab induction efficacy (responders and	To explore the impact of assuming lower efficacy for ustekinumab during induction.

		remitters) based on mean	remitters) based on lower bound	
21	Disutility study included	Disutility study results used for disutilities associated with AEs and surgical complications	Disutilities due to AEs in line with TA352; no disutilities due to surgical complications	To explore the impact of an alternative source for disutilities due to AEs and the inclusion of disutilities due to surgical complications
Key: ACD, Appraisal Consultation document; AE, adverse event; CDAI, Crohn's Disease Activity Index; N/A, not applicable; q8w, every 8 weeks; q12w, every 12 weeks; SF-36; Short-form 36; TA, technology appraisal.				

Most scenarios tested did not affect the incremental cost-effectiveness decision. A few scenarios did affect the decision in both populations. A 1-year time horizon gave ICERs vs. conventional care of £55,771 and £122,877 in the conventional care failure and TNF failure populations, respectively. This is not considered to be a meaningful scenario given the chronic nature of Crohn's disease.

Using the original health state costs from TA352 gave ICERS for ustekinumab versus conventional care of £4,430 and £14,002 for the conventional care failure and TNF failure populations, respectively. Whilst ustekinumab is no longer dominant under this scenario, it remains the cost-effective treatment at a WTP threshold of £30,000 per QALY gained.

Use of a 2-year and 3-year treatment duration did not affect the decision for the conventional care population, but gave ICERs versus conventional care of £440 and £25,551, respectively, for the TNF failure population. Whilst ustekinumab is no longer dominant under this scenario, it remains the cost-effective treatment at a WTP threshold of £30,000 per QALY gained.

Using IM-UNITI transition probabilities gave ICERs for ustekinumab versus conventional care of £56,949 and £60,403 for the same populations, respectively. This scenario should be interpreted with extreme caution; as noted earlier IM-UNITI placebo arm, which portrays conventional care in this scenario, is not a true placebo arm as patients had previously received and responded to ustekinumab in the induction phase and were then randomised to placebo in the maintenance phase. The effect of ustekinumab induction coupled with longer half-life could potentially explain a smaller difference in efficacy between ustekinumab and conventional care which can be reflected in the increased ICERs.

The full results of each scenario are shown in Section 1.3 of this appendix.

5.8.3.1 Summary of sensitivity analyses results

The results of probabilistic and deterministic sensitivity analysis, and of pre-defined scenario testing demonstrate that ustekinumab remains dominant over comparator treatments in a range of scenarios. There are few circumstances in which the incremental result is changed.

5.8.3.2 Cost-minimisation

The results from the sensitivity indicate that a cost-minimisation approach may be more appropriate, as the ICER is subject to large differences due to the small QALY gains in the base case results. Ustekinumab is a cost-saving treatment option compared with all comparators.

A cost-minimisation analysis was conducted, using only the acquisition and administration costs of each biologic treatment (derived directly from the cost-effectiveness model). Costs of health states and adverse events were excluded as under a cost-minimisation analysis, the biologic treatments are assumed to have equal efficacy and comparable safety profiles. Conventional care has been excluded from this analysis as it is not reasonable to assume that biologic treatments and conventional care have equal efficacy.

The results of the cost-minimisation analysis in Table 80 and Table 81 indicate that ustekinumab is cost-saving versus other biologic treatments for the Conventional care failure and TNF failure populations, respectively.

Table 80: Cost-minimisation analysis: Conventional care failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
Ustekinumab	£9,979	£367	£10,346	
Adalimumab	£13,486	£0	£13,486	£3,140

Table 81: Cost-minimisation analysis: TNF failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
Ustekinumab	£10,278	£367	£10,645	
Vedolizumab	£20,307	£5,138	£25,445	£14,800

The difference between treatment acquisition cost in conventional care failure and TNF failure population is due a high use of dosing every 8 weeks in TNF population as patients are at a more advanced stage of disease.

Scenario analysis results (submission appendix 16)

The results of each scenario are shown in Table 64 and Table 65 for the Conventional care failure and TNF failure populations, respectively.

Table 64: Scenario analysis: conventional care population

	Ustekinumab			Adalimumab			Conventional care		ICER (full incremental analysis)		
#	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Ustekinumab	Adalimumab	Conventional care
1	***13.08***	£263,053	£25,805	***12.94***	£283,762	£27,716	12.68	£278,542		Dominated	Dominated
2	5.53	£101,061	£15,117	5.41	£120,913	£17,029	5.17	£114,496		Dominated	Dominated
3	0.66	£19,236	£8,913	0.66	£31,363	£10,793	0.59	£15,389	£55,771	Dominated	
4	13.10	£270,567	£34,813	12.87	£305,618	£37,359	12.68	£278,542		Dominated	Dominated
5	13.12	£276,684	£42,311	12.81	£325,425	£46,926	12.68	£278,542		Dominated	Dominated
6	13.08	£262,915	£25,808	12.94	£283,386	£27,720	12.68	£278,395		Dominated	Dominated
7	8.97	£263,053	£25,805	8.90	£283,762	£27,716	8.78	£278,542		Dominated	Dominated
8	13.17	£263,053	£25,805	13.01	£283,762	£27,716	12.72	£278,542		Dominated	Dominated
9	13.22	£263,053	£25,805	13.07	£283,762	£27,716	12.79	£278,542		Dominated	Dominated
11	13.08	£138,504	£25,805	12.94	£153,224	£27,716	12.68	£136,731	£4,430	Dominated	
12	13.08	£207,195	£25,805	12.94	£225,129	£27,716	12.68	£214,732		Dominated	Dominated
13	13.07	£263,073	£25,474	12.94	£283,762	£27,716	12.68	£278,542		Dominated	Dominated
14	13.11	£263,204	£27,825	12.94	£283,762	£27,716	12.68	£278,542		Dominated	Dominated
15	13.08	£263,326	£25,805	12.97	£282,187	£27,716	12.68	£278,542		Dominated	Dominated
16	13.07	£263,009	£25,346	12.91	£283,560	£25,995	12.68	£278,542		Dominated	Dominated
17	12.72	£284,399	£25,848	12.72	£296,691	£27,757	12.65	£280,455	£56,949	£3,111,715	
18	13.14	£212,120	£25,805	13.01	£221,737	£27,716	12.74	£226,706		Dominated	Dominated
19	13.08	£263,053	£25,805	13.01	£278,157	£26,287	12.68	£278,542		Dominated	Dominated
20	13.05	£264,881	£25,718	12.94	£283,762	£27,716	12.68	£278,542		Dominated	Dominated
21	13.13	£263,053	£25,805	13.00	£283,762	£27,716	12.73	£278,542		Dominated	Dominated

Table 65: Scenario analysis: TNF failure population

	Ustekinumab			Vedolizumab			Conventional care		ICER (full incremental analysis)		
#	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Ustek inumab	Adalimumab	Conventional care
1	***12.98***	£288,088	£24,713	***12.85***	£302,820	£29,727	12.76	£294,600		Dominated	Dominated
2	5.25	£117,145	£13,678	5.13	£130,883	£18,693	5.05	£121,992		Dominated	Dominated
3	0.61	£20,793	£7,518	0.59	£29,127	£12,786	0.58	£16,401	£122,877	Dominated	
4	12.97	£294,695	£31,214	12.84	£309,662	£35,547	12.76	£294,600	£440	Dominated	
5	12.97	£299,967	£36,400	12.84	£315,649	£40,610	12.76	£294,600	£25,551	Dominated	
6	12.98	£287,969	£24,717	12.85	£302,711	£29,732	12.76	£294,464		Dominated	Dominated
7	8.98	£288,088	£24,713	8.91	£302,820	£29,727	8.87	£294,600		Dominated	Dominated
8	13.02	£288,088	£24,713	12.87	£302,820	£29,727	12.77	£294,600		Dominated	Dominated
9	13.09	£288,088	£24,713	12.94	£302,820	£29,727	12.85	£294,600		Dominated	Dominated
11	12.98	£145,652	£24,713	12.85	£154,554	£29,727	12.76	£142,515	£14,002	Dominated	
12	12.98	£226,474	£24,713	12.85	£238,644	£29,727	12.76	£228,745		Dominated	Dominated
13	12.98	£287,818	£24,330	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated
14	12.99	£288,990	£25,998	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated
15	12.98	£288,078	£24,713	12.85	£302,765	£29,727	12.76	£294,600		Dominated	Dominated
16	12.98	£287,867	£24,437	12.85	£302,025	£28,972	12.76	£294,600		Dominated	Dominated
17	12.03	£344,394	£24,751	12.01	£352,781	£29,935	11.98	£341,046	£60,403	Dominated	
18	13.04	£235,958	£24,713	12.91	£250,696	£29,727	12.82	£241,709		Dominated	Dominated
19	12.98	£288,088	£24,713	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated
20	12.94	£290,377	£24,547	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated
21	13.04	£288,088	£24,713	12.90	£302,820	£29,727	12.81	£294,600		Dominated	Dominated

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: The British Society of Gastroenterology
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? No
- other? (please specify) Not employed by the BSG, but I am secretary of BSG IBD committee, chairman of the BSG IBD clinical research group and member of the clinical trial committee (ClinCom) of the European Crohn's and colitis organisation

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

What is the expected place of the technology in current practice?

- Crohn's disease is treated in line with NICE clinical guideline 152 with a stepwise progression through corticosteroids, immunosuppression, in the form of azathioprine, mercaptopurine and methotrexate, to anti-TNF antibody treatment with infliximab or adalimumab. NICE technology appraisal 352 recommends vedolizumab as an option for treating moderately to severely active Crohn's disease if TNF antibody treatment has failed, cannot be tolerated or is contraindicated. Many patients do not respond to current medical therapy, presenting an unmet need for more and different medical therapy.

- Ustekinumab is an antibody to the P40 subunit of interleukin 12 and 23 and as such it has widespread effects on downstream regulation of inflammation and has an established place in the management of psoriasis and psoriatic arthritis.

- The published evidence of efficacy of ustekinumab in Crohn's disease is limited to the licensing trials. In active Crohn's disease these are a phase 2a trial, a phase 2b trial and two phase 3 trials, and in maintenance of Crohn's disease there is one trial of maintenance therapy. In these trials there was evidence of a significant effect versus placebo in the UNITI-1 trial of patients who were anti-TNF refractory. The primary end point, a 100 point reduction in CDAI at week six, which reached 21.5 % of patients compared to lower dose ustekinumab 34.2 % and higher dose ustekinumab 33.7 % ($p=0.002$). Clearly in this trial the magnitude of the response in these resistant patients is modest with the delta against placebo of 12.2 to 12.8 %. In patients primarily anti-TNF naïve the same primary end point the result was placebo 28.7 %, lower dose ustekinumab 51.7 % and the higher dose ustekinumab 55.5 % ($p<0.001$). Analysis of secondary end points confirms the beneficial effects in both anti-TNF refractory and anti-TNF naïve patients.

- The higher response rate seen in TNF naïve patients than in patients who are anti-TNF resistant is also seen with trials of other biologics such as the use of a second anti-TNF agent or vedolizumab. There are no published comparative trials of ustekinumab with anti-TNF or anti-integrin treatment. As with other trials patients who are at highest risk of complications are understandably excluded, so it is impossible to assess the value of these agents in patients who would have been excluded from the trials such as those patients with previous malignancy or complications of their Crohn's disease such as stenosis or the presence of a stoma.

- The potential advantage of ustekinumab is that it targets a different inflammatory pathway to other biologics in Crohn's disease and may therefore be useful in patients who have had an unsatisfactory response to prior treatment, however at this stage there are no clinical trials to precisely quantify or define this advantage or to clearly define the patient group with most to benefit. Future trials of

ustekinumab versus second anti-TNF agent in patients who fail to have a lasting response to initial anti-TNF therapy or a head to head trial with Vedolizumab in patients after two anti-TNF agents would clarify this question.

- On the current evidence Crohn's disease patients who have failed one or two anti-TNF agents who are then treated with ustekinumab can expect a 33 % clinical response (versus placebo 20 %) by six to eight weeks. In the lower dose group there was a slight loss of response between week six and eight suggesting that perhaps the lower dose is sufficient but that maintenance treatment should be started at week six. Maintenance treatment in the clinical IM-UNITI resulted in clinical remission rates at week 44 in the placebo group of 35.9 % versus lower dose ustekinumab 48 % and higher dose ustekinumab 53 % of patients who had demonstrated a clinical response with induction therapy.

- The clinical trial data includes some data from the maintenance trial IM-UNITI that suggests week six may be too early assess for response. Patients who failed to show a predefined response by week eight received further ustekinumab and around 50 % appeared to show clinical response by week 16. There is no placebo comparative group in this observation (Sands et al. UEGW 2016. presentation 5).

- As with induction therapy there is currently insufficient published evidence to identify a subgroup of patients for whom the benefit of maintenance therapy is particularly useful.

- Ustekinumab for Crohn's disease may be most useful in patients who have primary non-response to anti-TNF treatment or secondary loss of response to such treatments despite having therapeutic drug levels of anti-TNF agents on board. In these patients a change to an alternative anti-TNF agent is unlikely to be useful. In this setting it needs to be considered head to head with Vedolizumab as both agents will appear to offer a treatment option in this situation. The sequential use of all available biologic agents is untested but may show a small but diminishing number of patients respond to each sequential agent.

- Ustekinumab is a novel biologic with robust trial evidence of a beneficial effect in active Crohn's disease and evidence of efficacy after an anti-TNF agent has failed. Further research is needed to accurately define its place in treatment in relation to alternative anti-TNF therapy or Vedolizumab. There are likely to be specific subgroups yet to be defined for whom each option represents the best choice of second line biologic.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

The advantages and disadvantages of the technology

- Ustekinumab is administered intravenously for the single induction dose and subcutaneously for the maintenance dose every eight to 12 weeks. This may be more convenient than other biologics for Crohn's disease but without head to head efficacy comparison the convenience is of uncertain value.

- Mucosal healing is beneficial in Crohn's disease. The patients who achieve this level of response have a lower relapse rate in follow up. The endoscopic healing data for induction and maintenance treatment with ustekinumab has been presented (Rutgeerts et al ECCO 2016). A sub study of the main phase 3 trials included patients who underwent colonoscopies at week 0, 8 and 44. The primary end point was the reduction in SES-CD endoscopic score. At week eight the mean SES-CD score changed by -0.7 from 12.33 to 11.63 in the placebo group (n=97) and by -2.8 from 14.16 to 11.36 in the ustekinumab group. This reduction appears to represent a statistically significant benefit (p=0.012). The secondary end point of a reduction of at least three in the SES-CD score was seen in 29.9 % of placebo versus 47.7 % of the ustekinumab group (p=0.005).

- Endoscopic remission (4 % versus 8 %) and mucosal healing (4 % versus 9 %) were not commonly seen in either group (NS). There was a trend towards benefit with ustekinumab therapy measured by endoscopic outcome.

- Similar non-significant data for endoscopic healing was seen at the end of the maintenance treatment with a trend to some benefit confirmed to the eight weekly injections and not seen with the 12 weekly injections.

- The endoscopic sub study is probably too small to assess the magnitude of the endoscopic benefit derived from ustekinumab therapy. There are trends in favour of treatment supported by the other secondary end points such as faecal calprotectin response and IBD Q.

- One advantage of ustekinumab is that it is already established as a treatment for psoriasis. This access to a large safety population albeit in a different disease population and at a lower dose. The PSOLAR psoriasis registry North America has reported on 40,388 patient years of follow up including 4,364 patients treated with ustekinumab comprising of approximately one third of the study population. There was no signal of increased infection or malignancy rate in this population. (Papp K. et al J. Drugs Dermatology 2015 volume 14: 706-714 and Kalb R. et al JAMA Dermatology DOI:10.1001/jamadermatol.2015.0718).

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Any additional sources of evidence

- There is little available experience with ustekinumab in Crohn's disease outside clinical trials at present.

Implementation issues

- If recommended by NICE the delivery of ustekinumab treatment could be accommodated within existing facilities for the NHS management of Crohn's disease.

- Ustekinumab treatment for Crohn's disease would be used in hospital Gastroenterology Units familiar with treating complex Crohn's disease.

Equality

- No issues regarding particular populations except for the problem, which is common to all Crohn's trials, the patients with previous surgery resulting in a stoma have been excluded from the clinical trials but are still likely to benefit if the technology is applied to active Crohn's disease in patients who already have a stoma.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Crohn's and Colitis UK
Your position in the organisation: [redacted]
Brief description of the organisation:

Crohn's and Colitis UK is a national charity leading the battle against Crohn's Disease and Ulcerative Colitis. We're fighting to achieve a better quality of life for the 300,000 people in the UK suffering physically and emotionally due to these and other forms of Inflammatory Bowel Disease (IBD). Ultimately, we want to find a cure. For more than 35 years, we've been working with and for patients and their families, the nurses, doctors, and all those that work in healthcare that treat them, and the policymakers who can bring about change.

We provide high quality information and support as well as fund and partner in life-changing research and campaign vigorously – for more knowledge, better services and more support for people affected by IBD.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Symptoms:
Crohn's Disease is a chronic condition that causes inflammation of the digestive system (gastrointestinal tract or gut) anywhere between the mouth and the anus. Common symptoms include: cramping pains in the abdomen, diarrhoea (sometimes with blood and mucus), weight loss and profound fatigue (comparable to that reported in cancer patients[i]).

Anaemia is a common complication, which can be caused by a variety of factors including: a lack of iron in the diet or poor absorption of iron from food; low intake or poor absorption of certain vitamins, such as vitamin B12 or folic acid; or some of the medications used, such as sulphasalazine or azathiopurine.

Other symptoms associated with this condition include:

- inflammation of the joints affecting the elbows, wrists, knees and ankles, in about one in three people with IBD, and more rarely affecting the spine and pelvis in the form of ankylosing spondylitis
- skin conditions including mouth ulcers, erythema nodosum which affects about one in seven and, more rarely, pyoderma gangrenosum
- liver complications, including gallstones (experienced by one in 4 people with Crohn's) and Primary Sclerosing Cholangitis (affecting one in 25 people)
- eye problems such as episcleritis, scleritis and uveitis, affecting one in 20 people with IBD[ii]
- bone thinning, due to the inflammatory process itself, poor absorption of calcium, low calcium levels in the diet or the use of steroid medication
- blood clots in the veins, including deep vein thrombosis (DVT) – people with Crohn's are about twice as likely to develop clots.

Crohn's Disease is often associated with anal problems such as fissures, tags, abscess and fistulas[iii].

The condition follows an unpredictable, relapsing and remitting course, with variation in the pattern and complexity of symptoms. It commonly first presents in the teens and twenties and affects men and women equally.

When diagnosed in childhood the disease is often more severe than if presenting in adulthood, with major consequences for lifelong morbidity. People with Crohn's Disease (depending on the extent of the disease, severity of inflammation and duration) are at an increased risk of developing bowel cancer [iv]. At least 50% of people with Crohn's Disease may require surgery within ten years of diagnosis and 70-80% during their lifetime[v].

Broader impact of Crohn's Disease

***Psychosocial*:**
Anxiety and depressive illness are higher in people with IBD[vi]. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning. Emotionally, people with IBD can experience difficulties in coping with their lives and feelings of anger, embarrassment, frustration, sadness and fear of needing surgery or developing cancer.

For many individuals, the fear of incontinence or experiencing 'an accident' in public is a constant worry. This can have a devastating impact on their ability to engage in activities away from the home such as going to work, shopping and socialising, which may lead to isolation. In 2007, a Crohn's and Colitis UK survey of 974 young people with IBD found that 246 respondents stated that their IBD made socialising almost impossible.

Personal relationships and family life:
Crohn's Disease can have an effect on personal relationships and family life - both in terms of creating new relationships and maintaining existing ones. For example:

"My wife states that I have changed since being diagnosed, I never thought I had, but looking back, she is right. We are battling this illness together ... it's not just me it affects, It's everyone, my wife, work and family".

Caring for very young children can be difficult and social activities and holidays can become restricted. Taking children to and from school or attending school events can become problematic[vii]. Pain and tiredness can make parents more likely to be irritable with their children and to lack the energy needed to look after, play with and deal with the behaviour of younger children[viii].

Some people living with Crohn's Disease may require significant support from their carers and families, for example, support with cleaning themselves, or washing clothes, floors, bedding and/or toilets following involuntary evacuation of the bowel and support with dressing and remaking beds.

Ability to work or engage with education:
Crohn's Disease can affect a person's ability to work and the career decisions they make as a result[ix]. A 2016 research study identified common

problems experienced at work included poor concentration, low working pace and delayed work production. Education and employment may also be disrupted by the unpredictable occurrence of flare-ups. Sick leave was associated with lower quality of life and higher anxiety and depression rates[x].

Research undertaken by Crohn's and Colitis UK with the Work Foundation involving interviews with 1,906 people (1,107 with Crohn's Disease and 799 with Ulcerative Colitis) identified the significant impact of IBD on the productivity of workers, from the start of their career through to retirement. This found that:

- 66% were concerned about not being able to do their work adequately
- 69% felt that their IBD had prevented them from reaching their full educational potential
- Four out of five respondents reported working when they were unwell.

More recent research published in 2016, *Working Well: Promoting job and career opportunities for those with IBD*[xi], echoed many of these findings.

The above demonstrates the extent to which quality of life can be impacted by Crohn's Disease and why effective treatment options are so important.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment outcomes important to patients are those that reduce physical symptoms, stabilise the disease course and induce remission, in order that they can resume 'normal' life. For example:

"Having Crohns that is in control is fairly routine, it doesn't affect my life. However, flaring Crohns is another story. I experience debilitating pain every day, I am constantly exhausted, I am careful of what I eat, cannot eat/drink what I like and I always have to know where the toilet is. I have had numerous accidents where I have not been able to make it to the bathroom on time, this is embarrassing. I am hopeful that better treatment will come for us suffering with this condition."

"I am 23 years old and I have had to leave my university place studying Mental Health Nursing three times due to my Crohn's Disease. My life has been on hold for years due to this illness and I have lost 3 years of income, which has been a great burden."

Patient-centred care should be responsive to individual needs and take account of age, preferences, personal values and goals[xii]. These may include:

- feeling better; reduction in pain, more energy or going to toilet less
- retaining or returning to employment, education and training
- going on holiday or being able to travel
- being able to socialise and return to hobbies and activities
- starting a family
- regaining their sense of self and control over their life.

Patient-reported outcome measures should be used to inform shared decision-making, monitoring and research.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

There is currently no medical or surgical cure for Crohn's Disease.

Current available treatments are aimed at inducing and maintaining remission and improving quality of life.

Corticosteroids are commonly used as a first line treatment. However, there are significant short and long-term side effects with these, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis. Their use is also limited to induction of remission.

Immunosuppressants – azathioprine, mercaptopurine or methotrexate – may be added if necessary. However, up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them. In the majority of patients who do respond, the benefits take three to six months to appear. Significant risks of thiopurines including non-Hodgkin's lymphoma (as high as 4-5 fold compared with unexposed IBD patients and further increased when used in combination with anti-TNFs). Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment. Methotrexate is an alternative for people with Crohn's Disease who are unresponsive to thiopurines. It has lower mucosal healing rates compared to biologics and azathioprine. Most frequently observed side effects are myelosuppression and liver damage. It has an absolute contraindication in pregnancy.

Anti-TNFs - where first line treatments have been found to be ineffective, are not tolerated or are contraindicated, anti-TNF therapies, such as infliximab and adalimumab are used, sometimes in combination with immunosuppressants. These are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality

of life for patients. However, up to 40% of patients treated with anti-TNF therapy do not respond to induction therapy. In the approximately one third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time[xiii]. The side effect profile is significant, including increased susceptibility to infections and increased risk of some cancers, particularly lymphoma.

Vedolizumab is an option for treating moderately to severely active Crohn's disease if anti-TNF therapies have failed, cannot be tolerated or are contraindicated. This is a newer drug which offers a different mode of action and is gut selective. It takes longer to act than the anti-TNFs and its long-term profile is still relatively unknown, although more data are becoming available.

Surgery - as mentioned above, 70-80% of patients may require surgery during their lifetime, often in combination with medical therapies. Different kinds of surgery may be required, including removal of damaged sections of intestine, strictureplasty, colectomy, surgery for abcesses and fistulas.

Due to the nature of Crohn's Disease and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again.

Overall, **current treatments are suboptimal** and there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Crohn's Disease to resume their lives and restore their quality of life.

"I have been in that situation for 15 years having had two major surgeries and had every drug available, yet still the illness persists. My outlook at present is to be condemned to never working again, having no social life, depression and having a diet limited to less than ten food items. My current intake of 16,376 tablets and 30 injections every year will just roll over year after year after year unless a new drug treatment is successful."

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health

- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Ustekinumab would offer an important additional treatment option for those patients for whom conventional therapies have failed, who have lost response to anti-TNF therapies, or for whom anti-TNF therapies are contraindicated. As highlighted above, current treatment options for Crohn's Disease are suboptimal and there are patients who have exhausted all options available who feel condemned to an extremely low quality of life.

Below are quotes we have received from ustekimumab trial participants:

"It sounds like a cliché, but this moment really was a turning point in my life. I started to get better. My symptoms subsided and I was feeling the best I ever felt in years. I only went to the emergency department one other time soon after being put on the drug [ustekimumab]. *But that was the last time I went to hospital in the last 3 years. Since going on the drug in 2012, I still feel great today. Sure, I still have moments when I get abdominal pain, or I have trouble with going to the toilet. But that is so much better than what could of been if I hadn't gone on the trial. I actually feel like a healthy normal person most of the time. I am really grateful for this drug...This is really important for someone with a chronic illness. We just want to feel normal.*

"It [ustekinumab] *meant I was able to live my life, working, seeing friends, being a happy and healthy wife instead of being cooped up housebound afraid to go out for fear of not finding a toilet in time and lacking in energy to manage going out anyway."*

"I was diagnosed with Crohn's Disease when I was just nine years old, and I'm now 28. It's safe to say that up until four years ago, I'd known nothing other than being unwell for as long as I can remember. I have tried most drugs approved for use for Crohn's Disease (different kinds of steroids, chemotherapy, and the standard immunosuppressants and anti-inflammatories), and nothing - until ustekinumab - has really worked for any length of time. Before I started on ustekinumab I was probably going to the loo about 20 times a day – and sometimes this would be completely red with blood. Now, I probably go to the loo between 2-4 times a day. I'm finally managing to maintain a stable weight and to eat normal portions of food – rather than picking at meals because I can't face eating. I'm also

pretty much completely without pain – whereas before I started on the trial I was often in excruciating pain. The combined effect of this reduction in symptoms is that I'm living my life in a relatively normal way – and most importantly, I'm without any real fear of feeling as horribly unwell as I did before I started on the trial. It has given me a real sense of hope that my Crohn's, which has always been severe, might be able to be managed effectively by drugs. Ask any of my family or close friends what a difference they have seen in my outlook on life, my appetite, my energy, and my ability to do things that I'd never contemplated before, and they won't hesitate to tell you that I've never been as well as I have been since being on this trial. Only two months ago, I completed my first ever half marathon – having taken up running 18 months before. To have had the opportunity to have ustekinumab has been nothing less than life-changing. Crohn's is such a debilitating, frustrating and life-limiting disease – so to have found a drug that lifts that burden from me to such an extent has been wonderful. It's my sincere hope that I can continue to take this drug for as long as it continues to work for me."

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

While the initial dose of ustekinumab is given intravenously, further doses are subcutaneous. Patients commented to us that this was convenient for them, reducing the amount of time they spent at hospital and reducing costs involved in travel and time away from other activities, such as work.

"The treatment being in injection form is also a massive bonus as it means less time away from work compared to lengthy infusions which often end up taking half a day, resulting in more time away from work."

"I found it was straightforward injections and handy to take."

"Ustekinumab sounded like a much better option than other biologics because it had a long half-life and I could have it subcutaneously. Just a small injection into the skin... It is not invasive to my life."

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

We are not aware of any.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

As described above, current treatments for Crohn's Disease are suboptimal. This can result in a significant detrimental impact on quality of life and new and different treatment options are very much welcomed by those who are struggling to get their condition under control.

Please list any concerns patients or carers have about the treatment being appraised.

The main disadvantages from a patient perspective would be potential treatment failure for those who will be relying on this to work for them, having exhausted other available options and the time it takes to produce a beneficial effect which, as with vedolizumab, is longer than for the anti-TNFs.

Safety monitoring needs to be managed more carefully with treatments of this type which do not require people to be in the hospital on such a regular basis.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We are not aware of any.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Those patients for whom currently available therapies are ineffective, intolerant or contraindicative will gain most benefit. In this population group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This

may include highly undesirable long-term steroid use, potential repeated surgeries, unproven unconventional therapy or, where available, the uncertain outcome of a clinical trial.

"I was left without any treatment options in the UK. My Crohn's Disease was so widespread that it was inoperable and surgeons refused to consider surgery. I was then told that I would have to be kept on steroid treatment until something else became available or a trial was found for me. I was left for several months suffering very badly and I felt like I had no hope of ever getting better.

"I was diagnosed with Crohn's disease in 2003 at the age of 20. I worked my way through all of the conventional treatments, sadly none of which worked for me due to intolerance to the medicines - the worst reaction being 2 x bouts of pancreatitis following azathioprine. I was lucky enough to be offered the chance to try biologics. Infliximab was first - a great effect on my symptoms but sadly another reaction after my second infusion. Then humira which was excellent for 5 years but ended when I developed antibodies meaning it stopped working for me. I was devastated as humira allowed me to feel well, confident and fulfil a dream of travelling for two months. I went into a major flare, and was off work (as a physiotherapist) for two months. I was awaiting the call for surgery when I was offered the chance to try Stelara in 2012 on a drug trial. It was a huge life changer for me. I was on Stelara for a year and went in to remission. I went back to work, and after stopping it (voluntarily) in Nov 2013, stayed well enough to have a successful pregnancy resulting in my oldest son. In fact I have managed to have another son 6 weeks ago, something I'm sure would have been delayed massively were it not for stelara, this is by far the biggest impact.

"I am a 28 year old who has currently failed infliximab and adalimumab. In September 2014 I had a right hemicolectomy which removed some scarred bowel, however, I gained inflammation quickly in my remaining bowel. By 2015, my calprotectin was over 3,000. I started vedolizumab in December 2015 and, despite initial promising results, there are now some indications that this drug might be failing too. I am now running out of options. I have gone from a young woman with a bright future (top of my class at university, distinction for my MA) to one who is barely able to function on a day-to-day basis. I am having to give up employment, despite all my efforts to keep going. At 28 years old I am beginning to run out of options. I know that if the vedolizumab fails I will need further surgery and a stoma. However, I also know from painful experience that surgery does not cure Crohn's, it is likely to return in another area - and then what? I understand that I have been particularly unlucky with my disease course, however, I am now terrified of my future. For me, it is vital that new options are on the horizon, such as ustekinumab. Without the option to try this drug, I am left with the prospect of enduring disability without hope of respite. Unfortunately, I know that I am not the only young person with Crohn's who is facing such an uncertain future."

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

More data is needed to accurately answer this question.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The patient experience reflected through this submission is from patients who have been involved in the clinical trials as the treatment is not widely available as part of routine NHS care for Crohn's Disease. Due to the necessarily limited nature of trial participants, there may be some variation in experience when used as part of routine care and additional data will usefully inform clinical practice and shared decision-making about appropriate treatment options.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Phase III trial data show significantly improved health-related quality of life for patients with Crohn's Disease receiving ustekinumab through clinical trials based on data from IBDQ, a commonly used Patient-Reported Outcome Measure (PROM) which captures data across 32 different items of importance to patients, including fatigue, social engagement, pain, anxiety and sleep disorders.

Due to the nature of selection of appropriate patients for inclusion in trials, for example excluding those at highest risk of complications, it may be that there will be some differences in relation to the population that would ultimately receive treatment.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but

have emerged during routine NHS care?

Ustekinumab is already used in the NHS for other indications. This means that it has an existing safety profile. However, it might not be possible to transfer these risks from psoriatic patients to subjects with Crohn's due to the difference in pharmacokinetics and pharmacodynamics in these two distinct diseases. Moreover, ustekinumab has been predominantly used as monotherapy in psoriasis. Data on the added risk of concomitant immunosuppression in Crohn's are not yet available.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

Some relevant survey data and research on patient views on the impact of the condition have been outlined in response to question 2. The patient comments we have included throughout this submission provide further evidence of patient views of the condition and existing treatments. Additionally, we have supported research on the impact of fatigue[xiv]. Research currently in development includes understanding the experiences and needs of adolescents with IBD and the challenges facing mothers-to-be with IBD[xv].

Earlier this year, the findings of a large-scale national IBD survey conducted by Crohn's and Colitis UK echoed the comments made by people with IBD who contributed to a House of Commons digital debate. Both found that lack of awareness and understanding of the full impact of the condition were major concerns for people with IBD affecting many areas of life, including education, employment and access to toilets, together with the unpredictable and debilitating nature of physical symptoms, including extraintestinal manifestations and fatigue.

We would be pleased to provide further information in relation to any of the above.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

For certain religious groups, such as Muslims, the impact of active disease and the effects of surgery may interfere with requirements relating to religious practices and cause particular distress, which could be alleviated by an additional medical therapeutic option[xvi].

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Patients who are uncomfortable with injections would be likely to have difficulties with the treatment.

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Ustekinumab has a different mode of action from currently available drugs for Crohn's. Unlike the current treatments, it targets interleukin 12 and interleukin 23, naturally occurring proteins that regulate the immune system and immune-mediated inflammatory disorders. This drug treatment will allow clinicians to target other inflammatory pathways and switch out of class[xvii].

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of

your submission.

- Active Crohn's Disease can present a major barrier to people's ability to participate in daily life
- Currently available therapies for Crohn's Disease are suboptimal
- Ustekimumab offers a new class of therapeutic treatment for Crohn's Disease
- Ustekinumab has been shown to be clinically effective in stabilising Crohn's Disease and inducing remission, enabling people to resume "normal life"
- Ustekinumab may delay or prevent surgery in patients with Crohn's Disease.

---

[i] Minderhoud IM, Oldenburg B, van Dam PS et al. High prevalence of fatigue in inflammatory bowel disease is not related to adrenal corticol insufficiency. Am J Gastroenterol 2003; 98;1088-93.
[ii] Crohn's and Colitis UK (2013) Crohn's Disease. Crohn's and Colitis UK St Albans.
[iii] Ibid
[iv] Ibid
[v] Mowat et al, 2011, Guidelines for the Management of Inflammatory Bowel Disease in Adults
[vi] Graff LA et al. Stress coping, distress and health perception in inflammatory Bowel Disease: a review of co-morbidty and management. Inflammatory Bowel Disease. 2009 Jul: 15)7):1105-18.
[vii] Mukherjee, S. and Sloper P. Understanding The Impact Of Inflammatory Bowel Disease On Parents And Their Children. York: University of York
[viii] Ibid
[ix] Gay et al., 2011
[x] Employment status, difficulties at work and quality of life in inflammatory bowel disease patients http://journals.lww.com/eurojgh/Abstract/2016/10000/Employment_status,_difficulties_at_work_and.4.aspx
[xi] http://www.theworkfoundation.com/DownloadPublication/Report/377_IBD%20Report%20Final.pdf
[xii] IBD Standards 2013 Update, www.ibdstandards.org.uk
[xiii] Profile of ustekinumab and its potential in patients with moderate-to-severe Crohn's disease
[xiv] http://www.fatigueinibd.co.uk
[xv] https://www.crohnsandcolitis.org.uk/research/projects
[xvi] Iqbal F, Zaman S, Bowley D and Vaizey C. Quality of life after restorative protocolectomy in Muslim patients. *Gut* 2014; 63:1197-1198.
[xvii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4699281/

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: UKCPA
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **No**

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **No**

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

What is the expected place of the technology in current practice?
Ustekinumab offers clinicians an alternative monoclonal antibody or biologic with a different mode of action to those all already licenced and approved by NICE. It's place in therapy should probably be if there is a loss of response or contra-indication or intolerance to these other biological agents – not a first line option or replacement.

The SPC states:
"STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

In terms of drug costs (eg biosimilar infliximab) and experience of biologics in this patient group I think most clinicians and commissioners would use anti-TNF agents, if possible, first. This would also be more in line with the NICE TA wording for vedolizumab in Crohn's (which does not match the SPC licence for use).

The pharmacological and surgical therapeutic management of Crohn's disease is well supported by national and international guidance (NICE, ECCO) which has reduced some geographical variation in practice. However, there will undoubtedly remain some variation in appropriate use and access to biologics due to the knowledge and expertise of gastroenterologists in specialist vs non specialist centres.

The current mainstay of biological treatment for Crohn's disease is the anti-TNF antagonists (infliximab, adalimumab) which are well established therapies. However, a significant proportion of patients with Crohn's disease do not respond adequately to these agents. The α4β7 integrin antagonist (vedolizumab) has recently been licenced and NICE approved although efficacy in CD is relatively modest (remission data better in UC).

Some patients will be primary non-responders to the aforementioned agents or will lose response over time despite dose increases, or have contra-indications or intolerances. Access to an agent with a different mode of action and targeting an alternative disease mechanism such as ustekinumab is welcomed and may enable us to avoid surgery and its potential complications.

Biologics should only be started by clinicians with experience of their use in IBD and their clinical benefit should be reviewed regularly.

Study designs and patient populations are sufficiently different between studies of different biological agents used in IBD and therefore any direct comparisons of efficacy should be viewed with caution.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Ustekinumab has already been approved by NICE for treating active psoriatic arthritis (TA340) and for the treatment of adults with moderate to severe psoriasis (TA180).

The advantages and disadvantages of the technology
Ustekinumab will be a useful addition to the choice of biologics we can offer patients.

Any ambiguity with the wording such as definition of "prior therapy" should be avoided to avoid different interpretation by specialists and commissioners**.**

There should be clear guidance on duration of treatment if no response is seen.

Use in clinical practice of ustekinumab in this patient group is currently limited.

Subcutaneous route of administration allows self-administration and can therefore potentially avoid the need for hospital admission and therefore impact on capacity. This also lends itself to homecare delivery and therefore VAT savings on the overall costs. Note : The final scope wording only mentions administration by intravenous infusion but this only for induction – maintenance is subcut.

The frequency of clinic follow up should remain the same as for all biologics.

The safety profile of ustekinumab appears to be favourable from clinical trials however ustekinumab has been shown to increase the risk of serious infections and reactivate latent infections including therefore chest x-ray is mandatory prior to starting treatment. Treatment should not be given in those patients with current of previous malignancies. Post marketing surveillance has shown serious hypersensitivity reactions which may be delayed. This may stop some clinicians not wishing patients to receive treatment at home.

Published evidence, most notably the TAXIT trial, suggests that measuring anti-TNF drug levels and antibodies enables us to have better medicines optimisation and

therefore a more clinical and cost effective delivery of disease control. The use of similar assays with ustekinumab would enable better optimal dosing in individual patients. The effects of concommitant immunomodulators on antibody formation is unclear.

Any additional sources of evidence
No

Implementation issues
The numbers of patients initially are unlikely to be large if post anti-TNF and/or vedolizumab. The overall number of patients on biological treatment will undoubtedly increase

Ambiguous wording to avoid variation in interpretation of the guidance by specialists and commissioners. A clear treatment pathway for place in therapy agreed between specialist and commissioners should be made.

Patients will require education on self- administration if to inject at home and a checklist to do so safely e.g. check for infection etc.

For other NICE approved conditions a patient access scheme is in place so all doses, regardless of weight are similarly priced. The induction dose of ustekinumab is weight based. Consideration for a similar pricing scheme may be warranted.

Finally, as with all biologics, appropriate prescribing, in line with guidance, should involve a specialist pharmacist. IBD Audit clearly states the need for a specialist pharmacist in IBD as part of the MDT. Patients receiving biologics should be closely monitored clinically. These agents are also high cost. Pharmacy have an important role in the clinical and cost effective use and safety of these agents.

Equality
Do not think there are any obvious issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **British Society for Gastroenterology** and consequently I will not be submitting a personal statement.

Name: .....John Mansfield.....

Signed: .....

Date: .....13 feb 2017.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy [ID843]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
James Lindsay

Name of your organisation
Barts Health NHS Trust (THE Royal London Hospital)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **X**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **X**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **X**

  I am on the IBD clinical research group of the British Society of Gastroenterology and I am the Education Officer and a Governing Board member of the European Crohn's and Colitis Organisation (ECCO)

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

All agree that chronic active Crohn's disease has a marked negative impact on QOL and work productivity. It is progressive and if left under treated results in complications that may mandate life changing surgery. There are both European (ECCO) and British (BSG) guidelines for the management of Crohn's disease that have subtle differences but in general agree that patients with disease that is refractory or dependant on corticosteroids and / or refractory to immunomodulators (Thiopurines / methotrexate) should be treated with a biologic such as anti TNF. This should be given prior to complications arising for best effect. It should be monitored both for safety and efficacy, and that it should be optimised (perhaps via drug level monitoring) to ensure best impact. The benefit of these agents should be assessed after induction to ensure primary response and then at one year to see whether the drug can be stopped (complete remission) or should be continued (clinical benefit but ongoing evidence of active disease). This is how the disease should be treated across the NHS and this is the message that I take from the TA for Anti TNF agents in CD. However there is still wide variation in the use of anti TNF agents mainly to interpretation by commissioners of the NICE TA. Vedolizumab is appropriate for patients with active disease who fail anti TNF. Surgery should always be considered as an option.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

This is an area of active research and most studies are not validated / retrospective. However, patients diagnosed at young age, patients with deep ulceration on colonoscopy, patients with complex perianal disease, extensive small bowel disease or disease affecting a site where surgery is inappropriate (rectum / oesophagus) have a worse prognosis. Smoking negatively impact prognosis. There is no doubt that patients who have previously failed anti TNF therapy do less well with ustekinumab than patients who are naïve. However, this is the same with all biologics (ie the incremental benefit from sequential biological therapies diminishes)

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This should only be prescribed by gastroenterologists with an interest in IBD supported by an MDT. The infusion has to be given in hospital. The SC injections

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

can be given at home. Each centre would need to have an IBD specialist nurse to ensure appropriate governance and monitoring.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Available for psoriasis (with different dosing strategy).

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The current guidelines (ECCO and BSG) do not include its use as they have not been upated since its phase III trials were published. Both are moving from Oxford evidence levels to GRADE methodology.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Will be the same to use as currently available anti TNFs. It will require similar monitoring but less infusion capacity than infliximab.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Need to be aware of the nuances of the phase III induction and maintenance data re assessing primary response and the placebo effect in the maintenance arm. The induction effect seems to increase beyond 8 weeks and the drug should certainly be continued to week 16 prior to declaring no response. Likewise do remember that the placebo arm in the IMUNITI trial did receive an induction dose and that the effect of this carries over until week 16ish. So I would assess for primary response at week 8 and week 16. I would continue for one year and then re-assess as per anti TNF TA

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

This is a difficult answer. The clinical trials measure efficacy – which the drug clearly has. They use a primary endpoint in the induction trial (week 8) that is probably too early. In reality the effectiveness in clinical practice will be greater. Also the population studied in clinical trials are by definition quite niche – however, there are no concerning safety signal from the CD trial or the psoriasis registry to suggest that the results should not be extrapolated to all populations.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The data from the CD phase III program is reassuring – no additional safety signals. The data from the psoriasis PSOLAR registry is also reassuring. No new adverse events from clinical practice.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

My only comment here would be that the panel should not underestimate the disabling impact of chronic active crohn's disease which has a worse QOL than NY grade III heart failure.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The mucosal healing data has been presented an congresses (UEGW / ECCO) – this is encouraging. There was one real world data presentation from a small series presented at ECCO last week. No new signals are coming from this

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction. Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.
How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
No new staff, no significant new training, no monitoring over and above that used for currently approved biologic therapies. Issue will be relative cost effectiveness of the technology which will of course depend on price! But again, please do not underestimate the cost of a patient with chronic active CD who is partially responding to escalated doses of the currently approved biologics. These problems do not go away, they just stay on sub optimal therapy, or get admitted to hospital!

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Ustekinumab for previously treated moderate to sever active Crohn's disease [ID843]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. *About you*

Your name: Nicholas Cox

Name of your nominating organisation: Crohn's and Colitis UK
Do you know if your nominating organisation has submitted a statement?

☑ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☑ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☑ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☑ No

- a patient organisation employee or volunteer?
-

☐ Yes ☑ No

Do you have experience of the treatment being appraised?

☑ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. *Living with the condition*

What is your experience of living with the condition as a patient or carer?

I was diagnosed with IBD, initially as having UC, in 1999 after an episode in which I lost 52lbs/20kg or a more than a quarter of my body weight in about 4 weeks. I was going to the toilet hourly, day and night, often passing blood and mucus. I would sometimes soil my underwear. As a father of two young boys it was desperate to have to let them see me in that state. After primarily being treated with steroids, and later azathioprine, to which I had a severe allergic reaction, I was admitted to hospital in 2002. I benefitted from a stage 1 trial of basiliximab in 2003, which put me in almost total remission for about 6 years. However from 2009 the condition became active, and by the autumn of that year I was unable to work properly, was passing blood in most of the 10-12 motions a day, sometimes vomiting up food rather than being able to keep it down. I felt very depressed. It was then that infliximab infusions were tried, to no avail as my condition continued to worsen. Work was proving a problem.

I was admitted again early 2010 following significant weight loss, and placed on an intravenous steroid drip. The condition was stabilised with the heavy doses of steroids, and I was then given adalimumab, which had some success, before joining the ustekinemab trial. The diagnosis was then amended to Crohn's.

Before the first bout of the disease I was an extremely active person. I exercised regularly, was heavily involved in coaching in local sport and had just started a family. By 1999 I was less able to climb stairs than my then 89 year old grandmother. I missed my younger son's' first week at school in 2002 through illness.

The symptoms of the disease made it impossible to operate as a normal human being during periods when the disease was active. At its worst I was

bed-ridden and unable to function, visiting the bathroom to pass motion up to 20 times a day. Sleep deprivation and fatigue prevented me from working normally, or properly taking part in bringing up my family. In 2009 I was having to go back to bed for 2-3 hours a day after my children had gone to school and my work was limited to a couple of hours a day from home.

Even in periods where the condition improved, which it did in part with the adalimumab, things were never normal. In 2011 I was still taking heavy doses of steroids and whenever these were reduced the condition would start to flare up again. I often had stomach pains and was passing motion 5-6 times a day.

The effect of the disease is of course not just physical. The uncertainty or the future hangs over you all the time. Worries about not finding a toilet and soiling underwear, which for a grown man is very difficult, are at one end of the scale. Concerns about the need for surgery – or where a doctor tells you that surgery is not a real option in Crohn's – and about the effects of the disease in the longer term are ever present. It makes you feel less able and less confident. I believe the condition played a part in hindering my efforts to secure a judicial appointment in early 2010.

For me, another worry is the effect that having the disease has on one's immediate family, and on those with whom I work. I have been fortunate to be well-supported by my business colleagues, and of course by my wife, who for several periods has had to provide childcare unsupported by me.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I would hope to remain healthy and independent, and to lead a fulfilling and productive life, to be normal and free from anxiety, as much as is possible.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I have not found any previous treatment totally satisfactory.

The infliximab did not seem to have any notable effect, and the time taken over the infusions sometimes caused difficulties with my work commitments.

I have been taking mercaptopurine now for many years, but it does not seem to work on its own. I worry about its long-term side effects.

The adalimumab was partially successful, but only when coupled with mercaptopurine and steroids. The self-administration was painful and left me feeling sick for a short period afterwards, although it was convenient to be able to self-administer at home.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

It consists of one injection every two months, so it impacts little on the rest of my life. If administered closer to home it would be easier still.

I responded to treatment quickly and positively. Within six months I was feeling and acting normally, going on walking holidays and playing sport. I am now as fit and healthy as I have been for almost 10 years. I have much more energy and do not fatigue easily, which is fortunate for someone who is in partnership in a local business employing 70 people.

I now experience stomach pain very rarely, and that tends to be because I have eaten too much red meat that my gut now seems to tolerate less well.

I have noticed no significant adverse reaction to the drug.

I hope it will keep me as healthy as I feel now.

I feel much less anxious about the future.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

It is more easily administered than infliximab, or the blood-cleaning treatments I have witnessed, as it does not require specialist expertise or equipment. With training it could easily be self-administered, like insulin, saving time and money.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

No.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Several have potentially harmful both short -term and long-term effects. Prolonged use of steroids or of immuno-suppressants may cause different and equally difficult issues of their own.

Please list any concerns you have about the treatment being appraised.

It may not suit people who dislike injections, or who find it difficult to self-administer.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Any patient for whom other treatments have failed and those who might have problems with attending hospital for other treatments to be administered, due to mobility issues or just ones of distance, if they are able to self-administer.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I really couldn't say.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☑ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are

important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☑ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Not believe so.

9. Other issues

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

From the little I understand I believe that it works in a different way to other available treatments.

It seems to me to have produced a relatively quick positive response, with no appreciable contra-indications.

Is there anything else that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This treatment seems relatively easy to administer.
- It offers relatively swift response times (in my experience)
- It has no obvious contra-indications.
- The doses only have to be given relatively infrequently (for me bi-monthly)
- It seems to work; I have been in effective remission for four years.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Claire Purkiss
Name of your nominating organisation: Crohns and Colitis UK
Do you know if your nominating organisation has submitted a statement?

X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

☐ a patient with the condition?

X Yes ☐ No

☐ a carer of a patient with the condition?

☐ Yes X No

☐ a patient organisation employee or volunteer?

☐ Yes X No

Do you have experience of the treatment being appraised?

X Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed, initially with Colitis, in 2003 whilst at University studying Physiotherapy. Years of poorly controlled, debilitating, illness followed as I worked my way through the conventional medical therapies available with little effect, or side effects that were worse than the disease itself. For many years the only thing able to give any respite from my symptoms were high doses of steroids, which once weaned led to a gradual increase in symptoms again (not to mention the undesirable side effects of steroids, which for me, included low mood, weight gain and irritability). I was eventually fortunate enough to start Infliximab in 2007, following a second bout of pancreatitis induced by Azathioprine. Two doses in and my symptoms were so much better, but I developed a hyper-sensitivity reaction leading to severe joint pain meaning I could no longer take it. I then started Adalimumab-this resulted in 5 years of health! I couldn't believe I could leave the house without worrying whether there was a toilet nearby, attend music festivals with friends, stay over at friends houses without worrying about embarrassing toilet trips, go on holiday without panicking about needing the toilet on the flight, eat and drink foods I had previously had to avoid, go to work as a physiotherapist and be able to fulfil my very physical job (without taking time off for hospital appointments and tests and ill health), not worry about carrying toilet roll everywhere I went and panicking about incontinence. I was living the life of a 'normal' 20 something year old. Sadly after 5 years I lost response to the drug and found myself in a terrible flare up that was not responding to treatment. I had 2 months off work, I was stuck in the house with terrible joint pain, stomach pain and unrelenting diarrhoea. My husband could not believe I was the same person he had met and then married and, although he was very supportive, it became hard for him too as he was faced with this new 'ill' version of me. I

was scheduled to have surgery (total colectomy) when I received the devastating news that my latest colonscopy had shown granulation tissue meaning I actually had Crohns disease and not Colitis as originally thought. I was so upset-the only comfort of surgery was that at last I would be rid of this disease, but now I was faced with the reality that I would never be rid of it. At the age of 30 this seemed incredibly daunting and depressing. How would I carry on at work? How would I get to work on the tube/train/bus? Would I have problems with incontinence? How would I go on holiday? Have children- or care for children if I could have them? How would my husband cope being married to a chronically ill person? What other drugs were there for me to try? Would they work? Thankfully I was offered the chance to try Ustekinumab as part of drug trial. I can honestly say it changed my life. I returned to work within 2 months, I was able to leave the house, and use public transport and had energy again. My joint pain cleared up and I began to enjoy food again as the diarrohea slowly resolved. I began to feel hopeful again. I stopped the drug trial volountarily in November 2013 in order to start a family. I was lucky enough to give birth to my son in November 2014 and had a brilliantly healthy pregnancy and subsequent year. I then went on to have another son in September 2016, and I remain in remission still. I am sure I would have required surgery had it not been for this drug. And I am equally sure that this would have delayed my ability to have a family and increased my time off of work. Crohns disease is a daunting illness that almost robbed me of a ‘normal’ youth. It leads to pain and isolation, and the need to put a ‘brave face on’ to all those around you. I was so fortunate to have the chance to try this drug and for the effect it had on my disease. I still occasionally worry about ‘what ifs’. What if it returns? What if eventually all the drug therapies are exhausted and nothing works for me? What if I have surgery and then it comes back somewhere else? That is why we need more therapy options available.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Reduction in bowel movements and more 'normal' bowel movements-this is the most important to me as this is what makes leaving the house with any confidence so hard. My commute to work is difficult if flaring as there are no toilets on the train, and it takes at least an hour door to door. Also caring for children if needing to constantly run to the toilet is impossible.

Reduction in joint pain-this is the second most important for me as when struggling with back and joint pain it makes day to day tasks very hard e.g-getting to work, caring for children, housework.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Aminosalicylates: These were ineffective for me and resulted in a worsening of my symptoms.

Corticosteroids: I have had several courses throughout my illness. They are great at helping me to feel better very quickly, however long term I struggle when taking them. They make me very low in mood and irritable and I dislike the cosmetic side effects of 'moon face'. They are however very easy to take and good as a 'rescue therapy' in terms of acting quickly. Long term I would be concerned regarding the effects on bone mass density.

Immunosupressants: These were ineffective for me. I developed pancreatitis whilst taking Azathioprine and 6-MP, despite a second attempt at slow induction.

Anti-TNFs: Excellent effect on disease, but poor reaction to Infliximab as stated above. I also lost response to Adalimumab after 5 years, however I thought it was an excellent drug. I had no side effects whilst taking it, and

found the method of delivery being an injection much more preferable to infusion in terms of not taking so much time off of work, and being able to travel without needing to think about attending hospital appointments for therapy.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

I would hope to expect similar outcomes as to when I was on the drug trial. This would mean a huge improvement in symptoms. A reduction in bowel movements from many times a day (sometimes 20+) to 1-2, and no longer having severe abdominal and joint pain. Also no longer having diarrhoea, but more formed bowel movements.

I know this drug has a massive impact on quality of life. If symptoms are under control then this means being able to carry out my role at work, not taking time off for investigations, ill health or appointments. This results in less stress on my team at work, as they have a me as a manager present to support them. It also means the ability for them to provide an effective service to our patients at a busy NHS hospital as they are not having to absorb my work load. My employer would probably find this treatment preferable to an infusion, as an

injection takes less time to administer than an infusion meaning less time off work.

I also prefer injection as a route of administration in terms of ease of delivery. For the trial we had to be in hospital to receive the drug , I'm unsure if it would continue like this or be possible to inject at home? If at home this is even better in terms of ease of treatment delivery.

I would expect to be well enough to care for and play with my two young boys (5 months old and 27 months old)-to have the energy to keep up with them instead of the fatigue that comes with Crohns flare ups. I would also be able to support my husband-by being a partner in terms of sharing child care, going out to work to contribute financially and having the energy to listen to him, have fun together and so maintain our relationship. Equally maintaining friendships would be much easier as I would no longer need to cancel plans, or avoid making them all together due to fatigue, pain and diarrhoea.

All of the above would clearly have a profound effect on mental health. If you are able to carry out all of the above due to good health, that leads to a positive mental outlook, and the converse is true when dealing with the symptoms of Crohns. It is hard to maintain a happy disposition when struggling with the smallest of tasks on a day to day basis.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

It provides an alternative therapy when others have failed.

It potentially avoids the need for surgery, or at least postpones it. This means the ability to avoid adhesions post surgery that I believe may potentially cause problems with conceiving-extremely important to consider particularly as Crohns disease typically effects a young population.

The ease of use with the treatment being in injection form rather than infusion should not be undervalued.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I know of none.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

If the treatment needs to still be given in a hospital then this would impact on taking more time off work than therapies that could be delivered at home.

Please list any concerns you have about the treatment being appraised.

I have none.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I have none

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Those that have tried other drugs and failed them. I say this only because if there is a therapy that can be taken in tablet form that is effective on the course of the disease then this is probably preferable to most patients than an injection.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Not to my knowledge

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes X☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It works on different pathways to other medical therapies available.

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This drug had a huge impact on my symptoms and quality of life
- It is easy to deliver in injection form
- As my experience shows previously effective treatments can suddenly stop working meaning there is a need for more treatment therapies to become available.
- Surgery does not cure Crohns disease therfore medical therapy to delay it is vital
- Crohns disease limits many aspects of those affected's life-work, family, and friendships

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Ustekinumab for treating moderately to severely active CD after prior therapy

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD
Authors	Robert Hodgson, Lead Health Economist, CRD Mousumi Biswas, Research Fellow, CRD Teumzghi Mebrahtu, Research Fellow, CRD Matthew Walton, NIHR Fellow, CRD Melissa Harden, Information Specialist, CRD Nerys Woolacott, Senior Research Fellow, CRD
Correspondence to	Nerys Woolacott, Senior Research Fellow, CRD, University of York, York YO10 5DD
Date completed	Date completed (10/02/2017)

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 16/10/12.

Declared competing interests of the authors

None

Acknowledgements

We would like to thank Professor Alan Lobo, Consultant Gastroenterologist and Honorary Professor of Gastroenterology at the University of Sheffield for their clinical advice throughout the project. We would also like to thank Phillip Morgan for his help in preparing the cost effectiveness sections of this report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Hodgson R, Biswas M, Mebrahtu T, Walton M, Harden M,Woolacott N, Ustekinumab for treating moderately to severely active CD after prior therapy: A Single Technology Appraisal. CRD/CHE, University of York, 2017.

Contributions of authors

Please refer to the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals see http://www.icmje.org/

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

ADA	Adalimumab
AE	Adverse event
ASAs / 5-ASAs	Aminosalicylates
BNF	British National Formulary
CD	CD
CDAI	CD Activity Index
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CrI	Credible Interval
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
DMARD	Disease modifying anti-rheumatic drug
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
ERG	Evidence Review Group
GI	Gastrointestinal
HE	Health economics
HRQoL	Health-related quality of life
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Incremental cost-effectiveness ratio
INF	Infliximab
ITT	Intention-to-treat
IV	Intravenous

MIMS	Monthly Index of Medical specialties
MP / 6-MP	6-mercaptopurine
MTX	Methotrexate
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network Meta-Analysis
NR	Not reported
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QALYs	Quality adjusted life years
RCT	Randomised Controlled Trial
RR	Relative risk
SC	Subcutaneous
SD	Standard deviation
SES-CD	Simple Endoscopic Score for CD
SF-36	Short Form Questionnaire – 36 Items
SPC	Summary of product characteristics
STA	Single Technology Appraisal
TB	Tuberculosis
TNF/TNFα	Tumour necrosis factor alpha
UST	Ustekinumab
VDZ	Vedolizumab

1 Summary

Crohn's Disease (CD) is an immune-mediated condition that causes inflammation of the gastrointestinal system that predominantly affects young adults, with age-specific incidence peaking at between 15 to 30 years of age. The clinical features of CD are variable and are determined partly by the site of the disease. Common symptoms include diarrhoea, abdominal pain, extreme tiredness, unintended weight loss and blood and mucus in stools. Less common symptoms include fever, nausea, vomiting, arthritis, inflammation and irritation of the eyes, mouth ulcers and areas of painful, red and swollen skin.

CD is incurable long-term progressive disease. CD patients may have periods of remission; the management of CD is, however, a life-long requirement. The treatment aims are therefore to control manifestations of active disease, reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects (AEs).

There are currently at least 115,000 people in the UK with CD. It is estimated that over 4,000 patients in England and Wales have failed all available therapies in current practice.

CD is treated with conventional therapies as a first line and biologics as an option if symptoms don't subside or exacerbate. Ustekinumab is a biologic drug with its marketing authorisation granted by the European Commission (EC) granted in November 2016 for the treatment of moderate to severe CD.

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

The population for this submission are people with moderately to severely active CD in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-α inhibitors (anti-TNF), or who are intolerant to either of them; this is in line with NICE scope definition. For conventional care failures the company submission presents evidence mainly for conventional care failures who are not necessarily anti-TNF naïve; it is unclear how well this will reflect the NHS population.

The intervention treatment for the submission is ustekinumab administered initially as a single intravenous (IV) ~6mg/kg induction dose. This matches the licensed induction dose specifies a number of vials according to patient's weight category: <55kg 2x 130mg vials; >55kg to < 85kg 3x130mg vials; and >85kg 4x130mg vials. Eight weeks after the induction dose patients receive maintenance therapy: subcutaneous (SC) injection solution 90mg every 12 weeks (can be titrated up to every 8 weeks).

The comparators for this submission are: conventional therapy (which can include drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or

methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate); tumour necrosis factor-α inhibitors (anti-TNFs) (infliximab and adalimumab); and vedolizumab. Biologic therapies are given in addition to conventional care.

The outcome measures for the submission are: disease activity (remission, response, and relapse); mucosal healing; surgery; adverse effects of treatment; and, health-related quality of life. This is in agreement with the NICE scope definition.

1.2 Summary of clinical effectiveness evidence submitted by the company

Four well conducted placebo-controlled, double-blind RCTs provided data on the licensed dose of ustekinumab in Crohn's disease. Three trials were of induction therapy (single dose of ~6mg/kg followed-up for 8 weeks (dose in CERTIFI was exactly 6mg/kg)): two trials were of a population who had failed anti-TNFs (UNITI-1 and CERTIFI), one was of patients who had failed conventional care (UNITI-2). One trial (IM_UNITI) was of maintenance therapy treatment (up to ~one year, with follow-up data to two years) and investigated the effect of treatment withdrawal in those who had responded to ustekinumab induction. This trial included a mixed population of conventional care failure and anti-TNF failures.

Based on the short term clinical effectiveness results, ustekinumab appears to be more effective than placebo in terms of both clinical response and remission in both the conventional care failure and anti-TNF failure populations. The ERG calculated Relative Risks and 95% CI for Clinical (CDAI-100) response at week 6 were: UNITI-1 1.57 (1.17 to 2.11); UNITI-2 1.93 (1.51 to 2.47); and CERTFI 1.69 (1.16 to 2.46). The Relative Risks and 95% CI for Clinical remission (CDAI <150) at week 6 were: UNITI-1 2.07 (1.29 to 3.34); UNITI-2 1.97 (1.40 to 2.79); and CERTIFI 1.15 (0.59 to 2.26). Endoscopic response outcomes were also more likely to be achieved by those patients randomised to ustekinumab over placebo in UNITI-1 and -2, with a greater change in SES-CD score from baseline, and a higher chance of endoscopic remission at week 8. Differences in inflammatory biomarker levels between the treatment arms were generally non-significant, though patients randomised to ~6mg/kg ustekinumab in the UNITI-1 and UNITI-2 trials had a greater reduction of CRP levels at 8 weeks (UNITI-1: PLA +3.30 vs UST -5.55; UNITI-2: PLA -0.14 vs UST -8.56).

The results of IM_UNITI indicate that around half of patients who respond to ustekinumab are in clinical remission at week 44. A higher proportion of patients randomised to the two ustekinumab dosages (UST 90mg every 8 weeks or 12 weeks) retained their responder status and a higher proportion were in remission at Week 44 than those randomised to placebo (53%, 49% and 36% respectively).

The results of the follow-up of placebo responders from UNITI-1 and -2 also indicate that placebo response in Crohn's disease is common and can be sustained. Of the placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% achieved clinical response (CDAI-100) and 48% achieved clinical remission at one year.

The trials provide no evidence on the effect of ustekinumab in Crohn's disease in the long term, i.e. beyond two years.

Results of the four trials show that the adverse event profile of ustekinumab is similar to that of placebo during the induction and maintenance phase follow-up. Data on adverse effects in long term are lacking.

Since there were no head-to-head comparative trials available to allow direct comparisons of ustekinumab with its comparators in CD, network meta-analyses (NMA) were conducted for the response outcomes: clinical response (reduction in CDAI> 70; reduction in CDAI >100) and remission (CDAI$\leq$150). Separate analyses were conducted for the induction phase and maintenance phase of treatment. These analyses were conducted separately for conventional care failure patients and anti-TNF-failure patients.

The relative and absolute treatment effects of the biologics from the NMA were presented in the CS. In the conventional care failure population, the probability (OR and 95% CrI) of achieving CDAI-100 was 3.12(2.08 to 4.68), 3.03 (1.60 to 5.89) and 1.69(1.02 to 2.84) for ustekinumab ~6mg/kg, adalimumab 160/80 mg and vedolizumab 300mg. The probability of achieving clinical remission (CDAI<150) during the same period was 31.34 (4.50 to 963.60), 3.92 (1.86 to 8.95), 2.69 (1.38 to 5.59) and 2.50 (1.60 to 3.98) for infliximab 5mg, adalimumab 160/80 mg, vedolizumab 300mg, and ustekinumab ~6mg/kg, respectively. In the anti-TNF failure population, the probability (OR and 95% CrI) of achieving CDAI-100 was 2.02 (1.28 to 3.20), 1.87 (1.26 to 2.80) and 1.79 (1.20 to 2.70) for adalimumab 160/80 mg, ustekinumab ~6mg/kg and vedolizumab 300mg. The probability of achieving clinical remission (CDAI<150) during the same period was 3.65 (1.90 to 7.38), 2.34 (1.37 to 4.08) and 1.53 (0.87 to 2.76) adalimumab 160/80 mg, ustekinumab ~6mg/kg, and vedolizumab 300mg, respectively.

Overall, the results of the induction phase NMA indicate that ustekinumab is not the most clinically effective biologic both in the conventional care failure and anti-TNF failure subpopulations in terms of achieving an initial clinical response to or achieving remission.

The analysis of effectiveness in the maintenance phase was not straight forward and required a 'treatment sequence' analysis. This found that ustekinumab was comparable in terms of clinical response and remission with the other biologics for both populations. However, the analysis is complex and uncertain and these results may be unreliable. No evaluation of the relative effectiveness of the biologics beyond one year was possible as data are lacking.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS described a systematic review which was conducted to identify all studies containing clinical data on patients with moderately to severely active CD treated with biologics. Although the reporting of the review process lacked detail in the submissions, and results were largely omitted from the submission, the review as originally conducted was likely to have found all relevant literature. *Application of selection criteria lacked clarity in places; it was also not clear why studies identified in the updated searches were excluded from the NMA'* . Methodology, where reported, was generally appropriate.

All the relevant ustekinumab trials were included, although one Phase II trial (CERTIFI) was not included consistently across all analyses.

The UNITI and CERTIFI trials comparing ustekinumab against placebo during treatment induction were generally well-conducted studies with high internal validity, though their applicability to clinical practice and the UK CD population as a whole is questionable due to a number of reasons. The limited duration of follow-up (6 weeks) provided only a brief opportunity to compare the active treatment to conventional management based on only a single dose. In addition, the use of CDAI as the primary outcome does not reflect clinical opinion and practice in the UK, and is thought of as unreliable and subjective. The trial populations may not be wholly generalisable to NHS practice: patients with disease severity CDAI>450 were excluded and 20 to 30% of patients were not taking any background conventional medication for CD. Regarding the conventional failure trial, the population was a mixture of anti-TNF naïve and experienced patients (though none were anti-TNF failures). It is unclear whether this reflects the NHS population eligible for ustekinumab or whether or not it implies that the results from the trial may overestimate the benefit likely to be achieved in practice.

The clinical evidence for the assessment of ustekinumab relative to its comparators was based on 13 RCTs encompassing all four relevant biologics (adalimumab, infliximab, ustekinumab a vedolizumab). It appropriately included two types of patient subpopulations: conventional care failure and TNF failure patients and both the induction and maintenance treatment phases.

The induction phase comparator studies were, on average, good quality trials although the majority of the trials either did not give information or did not used optimal missing data handling methods. As for the ustekinumab trials the time point for the assessment of treatment response to induction was rather short. The data for infliximab were limited to one very small trial and no data for infliximab from an anti-TNF failure population were available.

All the maintenance trials were withdrawal trials of responders to the respective active treatment rather than continuing the placebo controlled comparison from the induction phase. As such they were not ideal source of evidence to evaluate the relative effectiveness of the biologics in the one year maintenance phase.

Since there were no head-to-head comparative trials available to allow a direct comparison of ustekinumab with its comparators in CD, network meta-analyses (NMA) were conducted. Separate analyses were conducted for the induction phase and maintenance phase of treatment. Analyses were conducted separately for conventional care failure patients and anti-TNF-failure patients.

For the induction phase NMA eight trials were included. These trials had generally been conducted to a high-standard, although four trials reported questionable handling of missing data. The trials included were generally comparable, but the ERG had some concerns about the differences in the timing of primary endpoints between biologics, and treatment history and prior anti-TNF exposure / nature of anti-TNF failure of the various patient populations included also varied between the trials. The company adopted standard NMA under Bayesian framework that the ERG considered this to be the appropriate method. Comparison of the NMA results with the actual trial results for ustekinumab and comparator biologics found them to be very similar so results can be considered credible.

The CS recognised the lack of a true common comparator between the four maintenance trials, and that it was inappropriate to conduct a standard NMA. A 'treatment sequence analysis' was instead conducted, constructing a network using 13 studies. The trials share the comparability issues with those in the induction NMA, and the maintenance trials varied in terms of re-randomisation criteria upon entry into maintenance phase. There were several serious methodological flaws identified in these analyses and their interpretation within the CS. The methods by which the control arm was constructed introduced considerable potential for unobservable confounding of results, and may have inflated the relative effectiveness of ustekinumab. Outcome measures (CDAI-70 and CDAI-100) and response rates between trials were inconsistent but were aggregated; such inconsistencies were again likely to make ustekinumab appear better than its comparators. The ERG believes the results of the treatment sequence analysis are highly unreliable, and do not represent a realistic long-term comparison of ustekinumab and its comparators.

1.4 Summary of cost effectiveness submitted evidence by the company

The *de novo* analysis presented by the company compared the cost-effectiveness of ustekinumab in patients with moderate to serve Crohn's disease. The company's analysis is presented for two patient groups, patients who have failed convention care and, patients who have previously failed anti-TNF therapy. The comparator therapies in the conventional care failure subpopulation were adalimumab and conventional care. Conventional care consisted of a mix of non-biologic therapies including 5-ASAs, immunomodulators and corticosteroids. In a scenario analysis infliximab was also included as a comparator therapy. In this scenario analysis comparison of two biosimilar Remsima and Inflectra are also considered assuming equal effectiveness to Remicade (infliximab). In the anti-TNF failure subpopulation the economic model include the comparator therapies vedolizumab and conventional care.

The model structure used by the company consisted of a short-term induction phase, represented by a decision tree, and a longer-term maintenance phase, represented by a Markov model). The model used a consisted of 3 primary health states based on the CDAI score remission CDAI <150, mild disease CDAI 150> to <220 and moderate to severe disease CDAI score >220. Two additional health states surgery and death were also include in the model. The analysis was undertaken from the perspective of the NHS over a 60 year life-time time horizon. Costs and benefits were discounted by 3.5% consistent with NICE reference case.

Within the conventional care failure subgroup, the company's model estimates ustekinumab to be dominant (lower costs greater effectiveness) compared with adalimumab and conventional care. In the scenario analysis including infliximab, the biosimilar Inflectra is the most cost-effective therapy with an ICER of £504 per QALY compared with ustekinumab and dominating all other therapies. Within the anti-TNF failure subgroup, the company's model estimates ustekinumab to be dominant compared to vedolizumab and conventional care.

In addition to the base-case analysis, the company also presented a series of one-way sensitivity analyses and scenario analyses to assess the impact of uncertainty around key input variables and assumptions on the ICER estimates. The results of these indicated that the base-case cost-effectiveness estimates were most sensitive to: (i) duration of therapy; (ii) use of alternative transition probabilities based on IM-UNITI IPD data; (iii) the source of health state costs data; and (iv) the time horizon of model.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic analysis presented by the company was inadequate to fully address the decision problem specified in NICE's scope. The structure of the model, although accommodating key clinical outcomes in the short-term, does not fully characterise the chronic life-long relapsing-remitting nature of CD nor does it accurately incorporate the impact of surgery on both future prognosis and HRQoL. The impact of these structural failures in the model presented by the company is difficult to ascertain and the ERG is unclear whether correction of the identified structural issues would lead to an increase or decrease in the estimate ICER.

The ERG is also concerned about the clinical data used to populate the company's model. Specifically, the ERG is concerned about the way in which the company has interpreted the results of the treatment sequence analysis which is used in the model to populate the maintenance phase of the model. The use of the treatment sequence analysis to populate the transitions in this phase of the model makes the implicit assumption that non-responders to induction therapy remain in the moderate to severe health state for the entire maintenance period. The ERG considers this assumption to be unreasonable and that is likely to overestimate the cost-effectiveness of ustekinumab relative to conventional care. The ERG is also concerned with the methods used generate the transition matrices used in the economic model as they are highly dependent on arbitrary starting values used in the generation process.

There is substantial uncertainty regarding the duration of treatment with biologic therapy such as ustekinumab; the base-case analysis assumes that the maximum duration of treatment with a biologic is 1 year. Evidence from the annual UK IBD audit suggests that the vast majority (~ 90%) of patients continue on currently used biologic therapy for more than one year. Sensitivity analysis presented by the company show that increasing the duration of treatment with ustekinumab treatment has a significant impact on the estimated cost-effectiveness of ustekinumab relative to conventional care. Scenario analysis carried out by the ERG show that the company's base-case analysis is likely to represent be an optimistic interpretation of the input data and is likely to considerably overestimate the benefits ustekinumab relative to conventional care. It is not possible to ascertain the benefits of ustekinumab over currently used biologic therapies due to a lack of appropriate effectiveness data.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical

The evidence presented for the effectiveness of ustekinumab was identified through a systematic review and primarily based on good quality RCT evidence. The effectiveness of usektinumab was compared with generally relevant comparators and the outcomes assessed were appropriate.

Cost effectiveness

The model structure adopted was based on a previous cost-effectiveness model developed by Bodger et al a version of which was also used in the appraisal of the comparator therapy vedolizumab (TA352). The company's economic model attempts to address a number of issues raised inTA352, however, a number of substantive issue remain, see weaknesses below.

1.6.2 Weaknesses and remaining areas of uncertainty

Clinical

Regarding the clinical evidence the following weakness and areas of uncertainty have been identified:

There is some uncertainty regarding the induction response rates across the trials because the time point used in the trials was generally too short.

The data available on the effectiveness of infliximab in CD is very uncertain, and completely lacking for the anti-TNF experienced population.

There is no reliable estimate of the one year effectiveness of ustekinumab relative to conventional care (placebo) nor relative the comparator biologics.

There is a complete lack of real long term (longer than 92 weeks) data for ustekinumab in CD. As Crohn's disease is a chronic condition further research is required to establish the benefit or other wise of continuing treatment (continuously or intermittently as patients' disease relapses and remits) indefinitely.

Cost effectiveness

The health economic model submitted by the company is subject to a number of issues which limit the credibility of the company's results. The principal issues identified by the ERG are outlined in brief below.

- Omission of key aspects of CD in the model structure including the relapsing-remitting nature of CD and the role of surgery. The impact of these structural failure is difficult to ascertain and the ERG unclear whether correction of the identified structural issues would lead to increase or decrease in the estimated ICER.
- The clinical effectiveness data used to parametrise the model is subject to a number of significant problems relating to both the interpretation of the NMA results and the methods used to generate the transition matrices used. These issues are likely lead to a significant overestimation of the benefits of the ustekinumab therapy compared with conventional care.
- The maximum duration of treatment biologic therapy was assumed to be 1 year in the base-case analysis. Evidence from the annual IBD audit, however, suggest that the vast majority (~90%) of patients continue on currently used biologic therapies for more than one year. Increasing the maximum duration of ustekinumab treatment has the effect of reducing the cost-effectiveness of ustekinumab relative to conventional care.
- The health state cost used in the model potentially overestimate the costs associated with monitoring and managing patients with CD. They are also inconsistent with values used in TA 352.

1.7 These Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of exploratory analyses to explore uncertainty in a number of model assumptions and inputs. The number of scenarios was limited given challenges arising from making changes to the model structure: The results of this analysis are summarised Table 1 and Table 2 below.

Table 1 Summary results of key assumptions considered by ERG including CS scenario analysis – Conventional care failure population

	Ustekinumab *				Infliximab-Remicade $				Adalimumab				Conventional care	
scenario	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**
CS base-case (corrected)	*£263,292*	*13.08*	*Dominant*	*£27,152*	*£279,739*	*12.85*	*£7,017*	*£3,921*	*£283,714*	*12.94*	*£19,787*	*£2,670*	*£278,542*	*12.68*
ERG base-case (CDAI-100)	£114,670	13.18	£109,279	-£5,456	£117,767	13.17	£190,612	-£8,946	£119,479	13.19	£170,228	-£10,156	£107,150	13.11
ERG base-case (CDAI-70)	£114,782	13.18	£111,878	-£5,624	£122,331	13.22	£144,669	-£12,075	£120,188	13.19	£171,435	-£10,800	£107,097	13.12
ERG's additional scenario analyses														
Alternative utility values	£263,292	13.54	Dominant	£27,108	£279,739	13.31	£7,054	£3,894	£283,714	13.40	£19,899	£2,625	£278,542	13.14
Alternation reaction cost	£233,895	13.08	Dominant	£26,540	£250,173	12.85	£9,619	£3,477	£246,647	12.94	Dominant	£9,727	£248,532	12.68
Starting matrices A	£323,420	12.06	£3,084	£3,536	£329,080	12.02	£68,822	-£3,421	£336,652	12.04	£115,580	-£10,098	£323,015	11.93
Starting matrices B	£322,932	12.07	£365	£4,075	£328,960	12.02	£69,163	-£3,442	£336,488	12.05	£114,802	-£10,051	£322,881	11.93
Time horizon 5-year	£57,315	3.08	Dominant	£16,385	£69,273	2.93	£30,638	-£80	£74,802	2.99	£49,312	-£3,674	£65,420	2.80
Time horizon 10-years	£101,282	5.53	Dominant	£24,084	£116,449	5.32	£12,380	£2,781	£120,867	5.41	£26,426	£862	£114,496	5.17
5 years treatment	£289,392	13.14	£23,320	£3,108	£322,842	12.70	£1,761,960	-£43,546	£357,500	12.74	£1,258,380	-£77,076	£278,542	12.68
10 years treatment	£312,533	13.20	£65,208	-£18,353	£350,275	12.65	Dominated	-£72,626	£403,470	12.67	Dominated	-£125,363	£278,542	12.68
Lifelong treatment	£345,065	13.28	£111,037	-£48,550	£367,670	12.63	Dominated	-£90,758	£433,453	12.63	Dominated	-£156,417	£278,542	12.68
ERG also considers the following CS scenario analyses and included in the ERG's preferred base-case														
Inclusion of IM-UNITI	£284,428	12.72	£57,327	-£1,894	£288,309	12.70	£139,741	-£6,168	£296,667	12.72	£221,635	-£14,018	£280,455	12.65
CDAI-70	£264,727	13.05	Dominant	£24,550	£266,426	13.17	Dominant	£26,260	£286,409	12.91	£35,775	-£1,322	£278,219	12.69
TA352 original cost	£138,589	13.08	£4,684	£10,044	£145,133	12.85	£49,251	-£3,284	£153,192	12.94	£62,978	-£8,620	£136,731	12.68

*Ustekinumab remains dominant or best active treatment in all scenarios; $ Results of other infliximab biosimilar are presented in section 6; ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years

Table 2 Summary results of key assumptions considered by ERG including CS scenario analysis - TNF failure population

	Ustekinumab *				Vedolizumab				Conventional care	
scenario	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. Conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. Conventional care**	**Total costs**	**Total QALYs**
CS base-case (corrected)	*£287,780*	*12.99*	*Dominant*	*£13,643*	*£302,258*	*12.85*	*£83,169*	*-£4,896*	*£294,600*	*12.76*
ERG base-case (CDAI-100)	£129,531	12.52	£110,967	-£4,544	£136,581	12.49	£408,844	-£12,303	£123,303	12.46
ERG base-case (CDAI-70)	£129,792	12.52	£110,507	-£4,760	£137,322	12.50	£368,806	-£12,920	£123,259	12.46
ERG's additional scenario analyses										
Inclusion of CERTIFI	£292,754	12.90	Dominant	£12,897	£307,102	12.77	£92,782	-£5,441	£299,062	12.68
Alternative utility values	£287,780	13.44	Dominant	£13,670	£302,258	13.30	£82,952	-£4,889	£294,600	13.21
Alternation reaction cost	£257,666	12.99	Dominant	£13,137	£272,125	12.85	£88,460	-£5,383	£263,979	12.76
Starting matrices A	£338,103	12.13	£8,201	£2,141	£348,156	12.07	£288,639	-£9,729	£337,298	12.03
Starting matrices B	£342,790	12.05	£5,146	£2,559	£353,270	11.99	£314,337	-£9,959	£342,260	11.95
Time horizon 5-year	£68,263	2.87	Dominant	£6,312	£79,863	2.78	£164,785	-£7,887	£70,220	2.72
Time horizon 10-year	£116,863	5.25	Dominant	£11,093	£130,341	5.13	£103,823	-£5,936	£121,992	5.05
5 years treatment duration	£308,961	12.96	£70,728	-£8,270	£323,423	12.84	£355,422	-£26,391	£294,600	12.76
10 years treatment duration	£324,333	12.95	£158,631	-£24,110	£336,472	12.83	£563,104	-£39,641	£294,600	12.76
Lifelong treatment duration	£338,068	12.93	£249,766	-£38,247	£347,406	12.83	£767,844	-£50,743	£294,600	12.76
ERG also considers the following CS scenario analysis and included in the ERG's preferred base-case										
Inclusion of IM-UNITI	£344,308	12.03	£59,313	-£1,612	£352,400	12.01	£365,137	-£10,422	£341,046	11.98
CDAI-70	£289,088	12.97	Dominant	£9,909	£302,954	12.85	£132,983	-£7,455	£293,328	12.78
TA352 original cost	£145,491	12.99	£13,085	£3,847	£154,102	12.85	£125,827	-£8,824	£142,515	12.76

*Ustekinumab remains dominant or best active treatment in all scenarios; ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life year

The ERG also presented an alternative base-case based on a combination of a number of these scenario analyses and additional scenarios presented by the company. The ERG base-case made the following assumptions:

- Inclusion of CERTIFI trial to estimate efficacy during induction phase for TNF failure population;
- Inclusion of alternative utility values from the GEMINI studies;
- Inclusion of alternative cost value of £1621 applied for injection site reactions;
- Inclusion of IM-UNITI data to estimate maintenance phase efficacy;
- Health state costs are based on the health state costs used in theTA352 original submission.

The ICER for the ERG base-case analysis in the conventional care failure population was £109,279 per QALY relative to conventional care. Ustekinumab was estimated to be cost effective relative to adalimumab. The ICER for the ERG base-case analysis in the anti TNF failure population was £110,967 per QALY relative to conventional care. Ustekinumab was estimated to be cost effective relative to vedolizumab. The ERG was carried assuming the alternative response definition of CDAI 70 (70 point drop in CDAI score). This allows infliximab to be included in the analysis for the conventional care failure population. The ICER using the ERG's base-case assumptions and the CDAI-70 response criteria in the conventional care failure population was £111,878 per QALY relative to conventional care. Ustekinumab was estimated to be cost effective relative to both adalimumab and infliximab. The ICER using the ERG's base-case assumptions and the CDAI-70 response criteria in the TNF failure population was £110,507 per QALY relative to conventional care. Ustekinumab was estimated to be cost effective relative to vedolizumab.

The ERG preferred base-case assumed a maximum treatment duration of one year for biologic therapy. This parameter is however subject to considerable uncertainty. The ERG therefore presents additional scenario using the ERG base-case to explore the impact of alterative assumptions about the maximum duration of biologic treatment. These analyses consider the alternative maximum treatment durations of 2, 3, 5, 10 years and life longer treatment. The results of this analysis are summarised in Table 3 and Table 4.

Table 3 Summary results of ERG's preferred base-case (CDAI-100/CDAI-70) with alternative assumptions of treatment duration – Conventional care failure population

	Ustekinumab				Infliximab-Remicade $				Adalimumab				Conventional care	
scenario	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**
CS base-case (corrected)	*£263,292*	*13.08*	*Dominant*	*£27,152*	*£279,739*	*12.85*	*£7,017*	*£3,921*	*£283,714*	*12.94*	*£19,787*	*£2,670*	*£278,542*	*12.68*
ERG's analysis including CDAI-100														
ERG base-case (CDAI-100)	£114,670	13.18	£109,279	-£5,456	£117,767	13.17	£190,612	-£8,946	£119,479	13.19	£170,228	-£10,156	£107,150	13.11
2 years treatment	£122,848	13.23	£131,811	-£12,125	£127,615	13.20	£224,802	-£17,735	£131,049	13.23	£204,447	-£20,393	£107,150	13.11
3 years treatment	£129,529	13.28	£132,910	-£17,328	£136,142	13.24	£235,817	-£25,304	£142,763	13.27	£226,897	-£30,905	£107,150	13.11
5 years treatment	£143,111	13.36	£143,101	-£28,422	£153,547	13.29	£257,770	-£40,997	£164,487	13.34	£250,727	-£50,477	£107,150	13.11
10 years treatment	£168,889	13.51	£154,201	-£49,728	£187,582	13.40	£279,627	-£71,803	£206,277	13.48	£272,181	-£88,201	£107,150	13.11
Lifelong treatment	£208,149	13.74	£160,165	-£82,081	£247,714	13.59	£293,572	-£126,200	£281,612	13.72	£287,939	-£156,286	£107,150	13.11
ERG's analysis including CDAI-70														
ERG base-case (CDAI-70)	£114,782	13.18	£111,878	-£5,624	£122,331	13.22	£144,669	-£12,075	£120,188	13.19	£171,435	-£10,800	£107,097	13.12
2 years treatment	£123,334	13.24	£134,400	-£12,612	£139,308	13.28	£193,652	-£27,220	£132,808	13.24	£206,256	-£21,971	£107,097	13.12
3 years treatment	£130,260	13.29	£134,765	-£18,007	£154,010	13.34	£211,904	-£40,271	£145,567	13.28	£228,687	-£33,423	£107,097	13.12
5 years treatment	£144,339	13.37	£144,448	-£29,507	£184,024	13.44	£240,556	-£67,333	£169,214	13.36	£252,241	-£54,729	£107,097	13.12
10 years treatment	£171,062	13.53	£155,115	-£51,594	£242,721	13.62	£268,329	-£120,461	£214,690	13.51	£273,274	-£95,781	£107,097	13.12
Lifelong treatment	£211,760	13.77	£160,769	-£85,132	£346,426	13.95	£286,578	-£214,275	£296,671	13.77	£288,657	-£169,871	£107,097	13.12

$ Results of other infliximab biosimilar are presented in Appendix 10.4; ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years

Table 4 Summary results of ERG's preferred base-case (CDAI-100/CDAI-70) with alternative assumptions of treatment duration – TNF failure population

	Ustekinumab				Vedolizumab				Conventional care	
scenario	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. Conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. Conventional care**	**Total costs**	**Total QALYs**
CS base-case (corrected)	*£287,780*	*12.99*	*Dominant*	*£13,643*	*£302,258*	*12.85*	*£83,169*	*-£4,896*	*£294,600*	*12.76*
ERG's analysis including CDAI-100										
ERG base-case (CDAI-100)	£129,531	12.52	£110,967	-£4,544	£136,581	12.49	£408,844	-£12,303	£123,303	12.46
2 years treatment	£135,126	12.57	£111,122	-£8,631	£143,036	12.52	£324,022	-£17,906	£123,303	12.46
3 years treatment	£139,616	12.61	£107,907	-£11,777	£149,081	12.55	£305,823	-£23,249	£123,303	12.46
5 years treatment	£148,542	12.69	£110,477	-£18,385	£158,972	12.58	£297,430	-£32,071	£123,303	12.46
10 years treatment	£165,013	12.83	£114,282	-£30,760	£173,212	12.63	£296,691	-£44,862	£123,303	12.46
Lifelong treatment	£188,386	13.02	£116,268	-£48,289	£182,801	12.66	£297,416	-£53,496	£123,303	12.46
ERG's analysis including CDAI-70										
ERG base-case (CDAI-70)	£129,792	12.52	£110,507	-£4,760	£137,322	12.50	£368,806	-£12,920	£123,259	12.46
2 years treatment	£135,919	12.58	£111,359	-£9,250	£144,983	12.54	£301,774	-£19,565	£123,259	12.46
3 years treatment	£140,792	12.63	£108,035	-£12,665	£152,196	12.56	£289,887	-£25,942	£123,259	12.46
5 years treatment	£150,479	12.71	£110,577	-£19,835	£163,961	12.61	£286,213	-£36,436	£123,259	12.46
10 years treatment	£168,356	12.86	£114,361	-£33,267	£180,903	12.66	£288,698	-£51,654	£123,259	12.46
Lifelong treatment	£192,310	12.70	£290,700	-£61,926	£193,725	13.07	£116,326	-£52,293	£123,259	12.46

ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life year

2 Background

2.1 Critique of company's description of underlying health problem.

The CS described Crohn's Disease (CD) as an immune-mediated condition that causes inflammation of the gastrointestinal (GI) system.[1, 2] CD predominantly affects young adults, with age-specific incidence peaking at between 15 to 30 years of age.[3, 4] Males and females are equally affected, but CD is more common in White people than in Hispanic and Asian people, and there is a greater incidence observed in the Jewish population. [3]

The clinical features of CD are variable and are determined partly by the site of the disease. Common symptoms include diarrhoea, abdominal pain, extreme tiredness, unintended weight loss and blood and mucus in stools. Less common symptoms include fever, nausea, vomiting, arthritis, inflammation and irritation of the eyes, mouth ulcers and areas of painful, red and swollen skin.

CD is not medically or surgically curable. Studies have shown that the natural course of CD is progressive.[5-8] The CS reports that whilst patients may have periods of remission, management of CD is a life-long requirement. Treatment aims are therefore to control manifestations of active disease to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects (AEs).

Life expectancy is relatively unaffected by CD, and epidemiological studies suggest that overall mortality rates for patients with IBD in England are similar to those of the general population.[9] The key consideration for patients and carers is therefore how to manage disease and minimise the impact of CD on patient quality of life.

There are currently at least 115,000 people in the UK with CD. [9] It is estimated that over 4,000 patients in England and Wales have failed all available therapies in current practice.[10, 11]

The ERG believes that the CS presented sufficient information the underlying health problem.

2.2 Critique of company's overview of current service provision

The NICE guidance recommends that monotherapy with a conventional gluco-corticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) or 5‑aminosalicylate (5‑ASA) treatments are recommended as to induce remission in people with a first presentation or a single inflammatory exacerbation of CD in a 12‑month period. Then azathioprine, mercaptopurine and methotrexate can be added if there are two or more inflammatory exacerbations in a 12-month period or glucocorticosteroid dose cannot be tapered. [9] If conventional therapy failed or contraindicated,

infliximab and adalimumab, within their licensed indications, are recommended. [12]Then, if infliximab and adalimumab have failed or contraindicated, vedolizumab is recommended.[11]

The current NICE guidance seems to indicate that anti-TNFα treatments are discontinued after 12 months and remission is sustained afterwards, 'with treatment continued only if there is clear evidence of ongoing active disease'. However, based on the chronic nature of CD as described in the CS and clinical advice to the ERG, treatments do not necessarily stop after 12 months and remission may not be sustained after discontinuation. The clinical advisor also indicated that anti-TNFα failure patients may be given a second anti-TNFα therapy. For example, patients who fail for infliximab (or adalimumab) may be given another anti-TNFα drug before vedolizumab.

The CS states that ustekinumab offers a new biologic treatment option for patients who have moderately to severely active CD who have failed, or are contraindicated to conventional therapy and/or TNFα inhibitor therapy. No additional tests or investigations are needed for treatment eligibility, outside of those required for the diagnosis of moderately to severely active CD in need of further treatment (following conventional and/or anti-TNFα therapy).

The CS also states that ustekinumab is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of CD. Induction treatment must be administered through IV infusion. The CS also assumes that hospital units already have the staffing and infrastructure needed for the IV administration of biologic drugs so ustekinumab would utilise this existing resource.

Maintenance treatment is administered through SC injection. Janssen funds a homecare service, already in place for existing ustekinumab indications, where the SC injection is delivered to patients at home with an optional service of nurse administration. Homecare service with nurse administration is available for the entire maintenance phase without additional resource burden to the NHS for the administration of ustekinumab during maintenance treatment. After proper training, patients or their caregivers may inject ustekinumab without the assistance of a health care professional (HCP), if a physician determines that it is appropriate.

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection and the treatment plan changed in the case of active TB. Treatment of latent TB infection should be initiated prior to administering ustekinumab; anti-TB therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients should be monitored closely for signs and symptoms of active TB

during and after treatment. Patients should also be monitored for early signs of cancer as immunosuppressants like ustekinumab have the potential to increase the risk of malignancy.

The CS recommends that all patients should receive an IV induction dose followed by a maintenance SC dose at Week 8. After this, dosing every 12 weeks is recommended. Patients who have not shown adequate response 8 weeks after the first SC dose (Week 16) may receive a second SC dose at this time. Patients who lose response on maintenance dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks; patients may subsequently be dosed every 8 or 12 weeks according to clinical judgement.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by Week 16 or 16 weeks after switching to the 8-weekly dose. If therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective

3 Critique of company's definition of decision problem

3.1 Population

The CS described the relevant population for the evidence as,

"People with moderately to severely active CD in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-α inhibitor, or who are intolerant to either of them".

This population is appropriate and the description matches the NICE's scope exactly. All the clinical study evidence presented in the CS is relevant to this population. There is an issue for consideration about whether or not a population of patients who has responded inadequately to, or is no longer responding to conventional therapy includes only patients who have never taken an anti-TNFα (anti-TNFα naïve), or includes patients who have previously taken an anti-TNFα but not 'failed'. This issue arises in trials of CD because biologic therapy is recommended only for a period of one year, with treatment being stopped if patients are in remission. It is likely that a group patients who have previously responded but not failed' are more likely to respond than a group of patients who have not been tested. This is discussed further in Section 4.2.

3.2 Intervention

The intervention presented by the CS is ustekinumab, which matches the NICE scope. The scope did not specify a dose of ustekinumab but marketing authorisation specifies

Ustekinumab is administered initially as an intravenous (IV) ~6mg/kg induction dose. The licensed induction dose specifies a number of vials according to patient's weight category: ≤55kg 2x 130mg vials; >55kg to ≤ 85kg 3x130mg vials; and >85kg 4x130mg vials. This dosing approximates to 6mg/kg. Then, maintenance subcutaneous (SC) injection solution is dosed at 90mg. All patients should receive an IV induction dose followed by a maintenance SC dose at Week 8. After this, dosing every 12 weeks is recommended. Patients who have not shown adequate response 8 weeks after the first SC dose (Week 16) may receive a second SC dose at this time.

Patients who lose response on maintenance dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks; patients may subsequently be dosed every 8 or 12 weeks according to clinical judgement. Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by Week 16 or 16 weeks after switching to the 8-weekly dose. If therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective

The CS stated that ustekinumab had received a positive opinion from the CHMP on 15 September 2016.

3.3 Comparators

The CS presented three comparators:

- Conventional therapy (which can include drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate);
- Tumour necrosis factor-α inhibitors (infliximab and adalimumab); and,
- Vedolizumab

The comparators in the CS decision problem match the final NICE's scope. In clinical practice the biologics are given in addition to conventional care.

3.4 Outcomes

The outcome measures considered by the CS include:

- Disease activity (remission, response, relapse)

- Mucosal healing
- Surgery
- Adverse effects of treatment
- Health-related quality of life

The outcomes considered by the CS match the NICE final scope.

3.5 Other relevant factors

Location of CD was also included as a subgroup to be considered in the NICE scope. CD can be in the ileum, colon or perianal area. This was addressed very briefly in the CS, with a statement that in subgroup analysis, across the UNITI trial programme, ustekinumab was shown to be effective irrespective of location of CD.

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review

The company conducted one systematic literature review designed to identify all studies containing clinical data on patients with moderately to severely active CD treated with biologics. The results of this broad review were later used to answer more refined questions specific to particular decision problems, and no single coherent methodology was provided for the review of clinical effectiveness data. As such, the presentation of review methodology and results in the CS is fragmented, inconsistent, irrelevant or outdated in places, and generally lacking in detail and transparency.

The ERG recognises that the SLR as originally conducted is not of precise relevance to the decision problem or UK practice, due to inclusion of trials of unlicensed biologic therapies and dosages, but the way the review process was reported in the CS was not clear, and it was difficult to ascertain the way in which the trials eventually included in the NMA were identified and appraised from beginning to end. The distinction between the broad original SLR process and selection and appraisal of trials to be included in the NMA is blurred at times in the CS. Due to the lack of information provided regarding the methodology of the original SLR, both this and the study selection and appraisal for the NMA is also presented here. A more in-depth critique of the NMA methodology can be found in Section 4.3.

4.1.1 Searches

The MS described the search strategies used to identify relevant studies of clinical data related to moderately to severely active CD. The search strategies were briefly described in the main body of the submission in Section 4.1.1 and full details were provided in Appendix 2.

The searches were carried out in July 2015 and updated in October 2016. The following electronic databases were searched: MEDLINE, MEDLINE In Process, EMBASE, the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Health Technology Assessment database (HTA)). To supplement the electronic database searches, several sources of grey literature were searched. The manufacturer hand searched the proceedings of four conferences, from 2012 onwards: European Crohn's and Colitis Organisation, American College of Gastroenterology, United European Gastroenterology Week and Digestive Disease Week. Ongoing trials were sought from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform Search Portal. In addition, several UK, European and International HTA agency websites were searched.

The methods used to identify both published and unpublished studies for the systematic review were mostly appropriate. Some mistakes within the reporting of the searches were highlighted by the ERG in the points for clarification, and the manufacturer provided corrections in their response document in Section D: Erratum. Taking these corrections into account, the reporting of the searches was clear with sufficient detail to allow the searches to be reproduced.

The manufacturer also clarified that although search terms for ustekinumab are missing from the original searches carried out in 2015, they are included in the October 2016 update search without a date restriction. Therefore all relevant RCTs of ustekinumab are likely to have been retrieved by the strategies presented. All of the appropriate generic and brand names for the other drugs licensed for CD (infliximab, adalimumab, vedolizumab, certolizumab and natalizumab) have been included in the strategies presented in Appendix 2, although an English language limit was applied to the strategies in MEDLINE and EMBASE. Therefore any foreign language papers would not have been retrieved by the searches.

As the searches for MEDLINE and EMBASE were limited to RCTs only, any relevant reviews of ustekinumab, or the other drugs for CD listed in the search strategy, would not have been identified by these searches in MEDLINE or EMBASE. Although DARE was searched for relevant reviews, it was closed in March 2015. Therefore, it is possible that any relevant reviews published after this date would not have been retrieved. No specific searches were carried out for non-RCT evidence.

Therefore data on adverse effects from non-RCT studies of ustekinumab, or any of the other drugs for CD named in the search strategy, may not have been identified by the searches.

The ERG deems the search strategies for clinical effectiveness to be generally appropriate and reported in accordance with the PRISMA guidelines, with flow diagrams presented for the original search process in Figure 6 of the CS and of the updated searches in Figure 1 of Appendix 2. The searches were limited to studies of randomised controlled trials only, which is appropriate for a review of effectiveness; although including other designs such as observational studies may have yielded useful safety information. Overall, the ERG believes the search strategies were of sufficient quality, and it is unlikely that any relevant studies have been overlooked at the searching stage of the review. It is made not entirely clear, however, how the results of the updated searches were added to the review and narrative synthesis, as little information is provided on these processes. The ERG cannot be certain these omissions had no impact upon the NMA, as no studies identified in the updated searches were included in the network, nor were reasons for their exclusion provided.

4.1.2 Inclusion criteria

The methods used to screen and select the relevant literature were generally of a good standard, with two reviewers independently screening titles and abstracts for inclusion. Full-text screening according to the inclusion/exclusion criteria was then performed on those publications identified as being potentially relevant, with disagreements resolved by a third reviewer.

Inclusion criteria for the original SLR were presented in Table 9 of the CS. The review included randomised controlled trials of any design which compared ustekinumab, infliximab, adalimumab, vedolizumab, certolizumab, and natalizumab to any other treatment, including placebo and no treatment, in patients with active moderate to severe CD. Outcomes of interest were a variety of efficacy endpoints; safety endpoints included surgery and treatment withdrawal, dose escalations and measures of quality of life were also included in screening. Eligibility criteria relating to comparator treatments were not explicitly reported in the CS. Further selection criteria were applied to the results of the original SLR to obtain those studies included in the NMA, focusing on license and dosing to select evidence relevant to UK practice.

A total of 4,767 unique citations were retrieved for screening, of which 246 underwent full-text assessment for eligibility for inclusion, yielding a total of 41 publications and reporting results of 31 trials to be included in the original review. Of the 31 trials identified in the SLR, 18 were deemed ineligible for inclusion (though the reasons for exclusion were not always clear in the CS), and one further trial was excluded from the induction NMA. The updated searches carried out in October 2016 identified a further 75 publications of eight trials (three previously unidentified) which were included

in the SLR. This results in a total of 34 relevant trials, however, following the application of unclear selection criteria, only eight trials were deemed acceptable for inclusion in the induction phase NMA, with a further four in the maintenance phase NMA and another in the treatment sequence analysis. It is not clear why those studies identified in the updated searches were omitted from the NMA, nor were the biologics involved mentioned; no details of these trials were provided in the submissions.

As little detail of the study selection processes for the NMAs was presented, the ERG is unable to assess whether any trials were incorrectly excluded. The ERG questions the exclusion of the CERTIFI ustekinumab trial results from the induction phase NMA on the basis of dosing, and deems it sufficiently similar to the other ustekinumab trials to be included. Further explanation and a critique of this study can be found in Section 4.2.5, and an alternative version of the induction NMA in which CERTIFI is included is presented in Section 4.5.

There was one study identified by the ERG that was excluded from the NMA with no reasoning provided; this study was a Phase-II a double-blind, placebo controlled, randomised controlled trial of ustekinumab in patients with moderate to severe CD, comparing four different treatment regimens against placebo. [13] According to the inclusion criteria listed on Page 56 of the CS, the ERG believes this study should have been included, or reasons for its exclusion given greater prominence, as they are not made clear in the CS. One arm of this trial used an induction dose of 4.5mg/kg of IV ustekinumab at week 0 in 26 patients with outcomes assessed six weeks after treatment administration, exhibiting a statistically significant relative treatment effect of 2.42. While this data should technically have been included according to the inclusion criteria provided in the CS, the ERG deems its omission reasonable given that the trial used a different induction dosage from that licensed in the UK (~6mg/kg).

4.1.3 Critique of data extraction

The CS presented the number of studies identified as eligible for inclusion in the systematic review but a data extraction plan was not provided; the CS states only that data was extracted and verified against the source by a second reviewer. While the ERG believes that reporting of data extraction procedures was not adequate, the data reported in the clinical effectiveness section of the CS matches the scope and was without significant obvious errors.

4.1.4 Quality assessment

There was no quality assessment of all 34 trials identified in the systematic literature review presented in the CS, nor was full methodology reported. The CS does however present a quality assessment of 30 trials identified for inclusion in an unpublished NMA from the original searches, reported in Table 9 of the CS appendices. It is not clear from the evidence provided which risk of bias assessment tool

was used, and there are a great deal of irrelevant studies included. Therefore the ERG conducted its own assessment of the studies included in the CS NMA using the Cochrane risk of bias assessment tool, the results of which are presented in Appendix 10.1 and discussed in Section 4.3.3. Risk of bias assessments for UNITI-1, UNITI-2, IM-UNITI and CERTIFI are reported in Section 4.2. There were full quality assessments of the three UNITI trials presented in Section 4.6 of the CS; these were performed in accordance with Centre for Reviews and Dissemination guidelines and as such are deemed appropriate by the ERG.

4.1.5 Evidence synthesis

The CS states that a narrative synthesis of the 41 publications identified in the original searches was performed; however, evidence of this, or any information on the methodological approach was not presented in the submission documents, nor was there any mention of the studies identified in the review update. As such, there is a hypothetical risk that bias could have been introduced into the analyses at this stage due to a lack of transparency in this process.

Evidence synthesis in support of the decision problem took the form of two sets of network meta-analyses, for induction treatment, induction and maintenance treatment, these included separate analyses for the conventional care failure subpopulation, and for the anti-TNFα failure subpopulation, and the different outcome measures reported. There were a total of 13 trials included in the quantitative synthesis presented in the submission, with 13 used in the network meta-analyses. Of the 13 trials, four were for ustekinumab and the remainder were studies on the UK licensed comparators vedolizumab, adalimumab, and infliximab. A full critique of the NMA can be found in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company presented a review of three pivotal Phase III randomised controlled trials (RCTs) that provided data for 8-week induction period (UNITI-1 and UNITI-2 trials) and 44-week maintenance period (IM-UNITI trial). The ERG has also identified a fourth trial which is relevant to the submission. The four trials are listed in Table 5 with basic study characteristics in Table 6 and Patients' baseline characteristics in Table 7. As IM-UNITI is in fact the maintenance phase of UNITI-1 and -2 it is not included in tables 2 and 3. Further details will be described in each of the individual trials sections (4.2.1, 4.2.2, 4.2.3, and 4.2.4).

Table 5 List of relevant trials

Trial name (NCT number)	Population	Intervention	Comparator
UNITI-1 (NCT01369329)	Adult patients with moderately to severely	Ustekinumab 130mg IV (n=245)	Placebo (n=247)

	active CD who have failed or are intolerant to TNFα inhibitor therapy	Ustekinumab ~6mg/kg IV (n=249)	
UNITI-2 (NCT01369342)	Adult patients with moderately to severely active CD who have failed conventional therapy	Ustekinumab 130mg IV (n=209) Ustekinumab ~6mg/kg IV (n=209)	Placebo (n=210)
CERTIFI	Adult patients with moderately to severely active CD who have failed or are intolerant to TNFα inhibitor therapy	Ustekinumab 6mg/kg IV (n=131)	Placebo (n=132)
IM-UNITI (NCT01369355)	Adult patients with moderately to severely active CD induced into clinical response with ustekinumab in the induction studies UNITI-1 or UNITI-2	Ustekinumab 90mg SC q12w (n=132) Ustekinumab 90mg SC q8w (n=132)	Placebo (n=133)

Table 6 Key study characteristics of UNITI-1, UNITI-2 and CERTIFI trials

	UNITI-1	UNITI-2	CERTIFI
Population	Adult patients with moderately to severely active CD who have failed or are intolerant to anti-TNFα therapy	Adult patients with moderately to severely active CD who have failed conventional therapy	As UNITI-1
Treatments	**Ustekinumab ~6mg/kg**: The exact doses were: • Ustekinumab 260mg (weight ≤55kg) • Ustekinumab 390mg (weight >55kg and ≤85kg) • Ustekinumab 520mg (weight >85kg) **Placebo**: patients received a matching IV placebo		One of 3 doses: 1mg/kg, 3mg/kg, or 6mg/kg (Maintenance Phase ustekinumab dose 90mg)
Location	177 locations worldwide	226 locations worldwide	153 centres Europe, USA and Canada
Trial design	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study. Randomisation was stratified by study region, CDAI score,(and initial response to anti-TNFα)		Phase II RCT Randomisation was stratified by study region, and initial response to anti-TNFα
Eligibility criteria for participants – disease criteria	Inclusion criteria: • Male or female ≥18 years of age. • CD or fistulising CD of at least 3 months duration, with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography histology, and/or endoscopy • Active CD, defined as a baseline CDAI score of ≥220 and ≤450.		
Eligibility criteria for participants – additional disease criteria		An abnormal CRP (>0.3mg/L) at screening, OR Calprotectin >250mg/kg at screening, OR Confirmed by endoscopy within 3 months prior to baseline.	
Eligibility criteria for participants	Have received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of	Has failed conventional therapy:	As UNITI-1

– previous therapy	CD, AND were primary non-responder or secondary non-responders), or were intolerant to the medication.	Is currently receiving corticosteroids and/or immunomodulators (i.e. AZA, MTX, or 6-MP) at adequate therapeutic doses, OR Has a history of failure to respond to or tolerate an adequate course of corticosteroids and/or immunomodulators (i.e. AZA, MTX, or 6-MP), OR Is corticosteroid dependent or has had a history of corticosteroid dependency Has not previously demonstrated inadequate response or intolerance to anti- TNF	
Primary outcome	The primary endpoint was clinical response at Week 6, defined as a reduction from baseline in the CDAI score ≥100 points. Patients with a baseline CDAI score ≥ 220 to ≤ 248 points were considered to be in clinical response if a CDAI score <150 was attained.		
Major secondary outcomes	• Clinical remission at Week 8 (CDAI <150 points) • Clinical response at Week 8 • CDAI ≥70-point response at Week 6 • CDAI ≥70-point response at Week 3 Safety assessments were based on reported AEs, clinical laboratory test results, vital sign measurements, physical examinations, ECG findings and TB testing.		Clinical remission at Week 6 (CDAI <150) Clinical response at Week 4

Other outcomes	• Clinical response/remission over time
	• Inflammatory biomarkers
	  ○ serum CRP
	  ○ faecal calprotectin
	  ○ faecal lactoferrin
	• IBD-specific and general HRQL measures
	  ○ IBDQ
	  ○ SF-36
	• Medical resource utilisation and health economics
	• Relationship between efficacy and pharmacokinetics
	• Relationship between efficacy and antibodies to ustekinumab status
	Mucosal healing was also assessed by ileocolonoscopy in patients at participating sites who consented to inclusion in the endoscopic sub-study		

Permitted and disallowed concomitant medication	The following medications were permitted provided dosing had been stable for at least 3 weeks prior to baseline, unless otherwise specified: • Oral 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) providing patients had been taking them for ≥12 weeks, and dosing had been stable dose for at least 4 weeks prior to baseline • Oral corticosteroids (e.g. prednisone, budesonide) at a prednisone-equivalent dose of ≤40 mg/day or ≤9 mg/day of budesonide • Antibiotics being used as a primary treatment for CD. Patients were not to initiate treatment with any of the following concomitant CD-specific therapies: • Oral or rectal 5-ASA compounds • Immunomodulators (AZA, 6-MP, MTX) • Oral, parenteral or rectal corticosteroids • Antibiotics as a primary treatment for CD • Total parenteral nutrition as a primary treatment for CD The following medications were prohibited: • Immunomodulatory agents other than 6-MP/AZA or MTX • Immunomodulatory biologic agents (including but not limited to natalizumab, abatacept) Experimental CD medications (including but not limited to thalidomide, briakinumab, vedolizumab, traficet, AMG 827)		

Pre-planned subgroup analyses	Subgroup analyses were carried out based on the following characteristics: • Demographic • Baseline disease characteristics • CD medication history • Concomitant CD medication use at baseline • Centre location, and • Initial response to TNFα inhibitor therapy (primary or secondary non-responders or intolerant). Subgroup analyses were planned when the number of patients in the subgroups permitted.	

Key: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; CDAI, CD activity index; CRP, C-reactive protein; HRQL, health-related quality of life; IBD, irritable bowel disease; IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; MTX, methotrexate; SF-36, 36-item short form health questionnaire; TNF, tumour necrosis factor.

Table 7 Baseline characteristics of included induction trials

	UNITI-1		UNITI-2		CERTIFI	
	UST ~6mg/kg	**Placebo**	**UST ~6mg/kg**	**Placebo**	**UST 6mg/kg**	**Placebo**
Randomised	249	247	209	210	131	132
Male (%)	101 (40.6)	118 (47.8)	90 (43.1)	99 (47.1)	48 (36.6)	64 (48.5)
Age, years, mean (SD)	37.3 (12.5)	37.3 (11.8)	38.4 (13.1)	40.2 (13.1)	39.4 (13.2)	39.5 (13.1)
Weight, kg, mean (SD)	69.5 (19.5)	71.5 (17.7)	71.9 (18.8)	74.0 (19.9)	74.1 (21.4)	74.4 (20.5)
CD characteristics						
Disease duration, years, mean (SD)	12.7 (9.2)	12.1 (8.4)	8.7 (8.4)	10.4 (9.8)	12.7 (8.9)	12.4 (9.1)
CDAI score, mean (SD)	327.6 (62.0)	319.0 (59.7)	302.2 (58.9)	302.2 (61.7)	338.0 (67.3)	312.4 (64.2)
C-reactive protein, mg/L, median	9.9	8.5	7.8	8.5	12.6	9.3
Faecal calprotectin, mg/kg, median	530.2	515.8	523.2	415.5	NA	NA
GI areas involved, n (%)						
Ileum only	37 (14.9)	28 (11.4)	49 (23.4)	44 (21.0)	34 (44.1)	33 (27.3)
Colon only	40 (16.1)	48 (19.5)	43 (20.6)	37 (17.6)	30 (43.3)	39 (15.4)
Ileum and colon	171 (68.7)	166 (67.5)	117 (56.0)	129 (61.4)	55 (30.9)	46 (28.3)
Proximal GI tract	54 (21.7)	45 (18.3)	29 (13.9)	32 (15.2)	NA	NA
Perianal GI tract	107 (43.0)	107 (43.5)	61 (29.2)	57 (27.1)	NA	NA
Medications for CD taken at baseline, n (%)						
One or more medications	174 (69.9)	185 (74.9)	170 (81.3)	158 (75.2)	92 (70.2)	101 (76.5)
Immunosuppressant	78 (31.3)	81 (32.8)	72 (34.4)	73 (34.8)	35 (26.7)	30 (22.7)
Aminosalicylate	50 (20.1)	54 (21.9)	93 (44.5)	89 (42.4)	25 (19.1)	24 (18.2)
Glucocorticoid	108 (43.4)	111 (44.9)	92 (44.0)	75 (35.7)	59 (45.0)	73 (55.3)
History of disease refractory to treatment with TNF antagonist, n (%)	246 (98.8)	246 (99.6)	NA	NA	NA	NA
No history of TNF antagonist treatment, n (%)	NA	NA	144 (68.9)	131 (62.4)	NA	NA
History of TNF antagonist treatment failure, n (%):						
Patients who received 1 drug	120 (48.2)	112 (45.3)	NA	NA	66 (50.4)	71 (53.8)
Patients who received 2 or 3 drugs	126 (50.6)	134 (54.3)	NA	NA	64 (48.9)	60 (45.5)
Primary non-response	72 (28.9)	74 (30.0)	NA	NA	36 (27.5)	44 (33.3)
Secondary non-response	171 (68.7)	170 (68.8)	NA	NA	95 (72.5)	91 (68.9)

Unacceptable side effects	105 (42.2)	87 (35.2)	NA	NA	47 (35.9)	41 (31.1)

Key: CDAI, CD activity index; GI, gastrointestinal; NA, not applicable; SD, standard deviation; TNF, tumour necrosis factor

Generalisability of the ustekinumab trials to NHS clinical practice

The trial populations, based on their inclusion and exclusion criteria and the baseline characteristics can be considered reasonably generalisable to UK CD population.

The ustekinumab trials included patients with a CDAI score between 220 and 450; and therefore excluded patients at the higher end of the CDAI spectrum (CDAI > 450). Advice from the clinical advisor to the ERG suggests that the number of patients with a CDAI score in excess of 450 is likely to be small and therefore the exclusion of patients is likely to have only a limited impact on the representativeness of the UNITI trials. It is however, uncertain whether patients with a CDAI score of 450 or greater would benefit to the same degree as patients with less severe disease.

Biologics for CD are given against a background of conventional care, i.e. almost all patients in clinical practice will be receiving some form of conventional therapy as well as the biologic. In the ustekinumab trials (Table 7) only 70 to 80% of patients were taking any medication for CD at baseline. As a population they may therefore not be as optimally treated with conventional care as the clinical practice patients should be; the benefits of ustekinumab seen in the trials may be greater than those achieved in practice.

4.2.2 The UNITI-1 trial

The UNITI-1trial investigated the clinical effectiveness of ustekinumab in 741 adult patients with moderately to severely active CD who have failed or are intolerant to TNFα inhibitor therapy. The trial consisted three arms, that is, two arms of intervention treatment (Ustekinumab 130mg IV and Ustekinumab ~6mg/kg IV) and one arm of a comparator (placebo). The trial was a double-blind multicentre study conducted in 177 locations worldwide with an 8-week follow-up period. The primary outcome was “clinical response” at week 6 which was defined as a reduction of CD activity index (CDAI) score of ≥100 from baseline. Further details of the trial are summarised in Table 6.

The ERG has the following comments about the UNITI-1 trial. First, the follow-up period for the primary (6 weeks) and secondary (8 weeks) outcomes were very short. In fact, patients had received only one IV dose of active treatment or placebo. The committee of human medicinal products (CHMP) guidance recommends that primary outcome (endpoint) should be considered after at least 2 cycles of therapy. Therefore, the ERG believes that the follow-up period was not sufficient.

Second, the primary outcome measure used was CDAI. The CDAI is a composite of 8 items (components) which is prone to errors due to high inter-observer variability and subjectivity. Based on our clinical expert's opinion, this measurement is thought of as 'soft' and unreliable; the "endoscopic response" is a more objective outcome measure than CDAI. Therefore, outcome results based on this tool may be biased or may not reflect disease status accurately.

Third, those biomarkers used in these studies are indicators of any inflammation in the body, and are not CD-specific. This becomes a problem when concomitant inflammatory diseases are present as this may exaggerate biomarker levels. Therefore, these measurements alone may not reflect the actual CD status of a person.

Fourth, IBDQ was used as a tool for health related quality of life (HRQL) patient reported outcomes. However, in addition to being a composite of items, IBDQ is a tool which is prone to recall bias as participants may not accurately remember their historical health status indicators.

4.2.2.1 Participant flow in the UNITI-1 trial

A Consort diagram of the patient disposition has been presented both in the CS (Figure 8 page 78 of the CS) and CSR (Figure 2 page 48 of the CSR). The ERG considers the diagrams to provide sufficient information on the flow of participants during the 8-week follow-up period.

4.2.2.2 Baseline characteristics of the UNITI-1 Trial population

The CS presented baseline data of the UNITI-1 trial population (Table 13 page 83-84 of the CS) based on demographic (age, sex, weight), CDs characteristics, gastrointestinal areas involved, previous CD medication, history of disease refractory to treatment with anti-TNFα, and history of anti-TNFα treatment failure, see summary in Table 7 above. The CSR has also reported baseline information of the trial in more detail (Table 2 page 51; attachment TSICM0-Attachment TSICM04 page 119-122, TSIDEM03 page 127 and Attachment TSIMH01 page 134 of the CSR). The CS and CSR concluded that the baseline characteristics of the trial were balanced.

The ERG agrees that the baseline characteristics were balanced across the three arms. Apart from the omission of those patients with a CDAI >450 as discussed above, the trial population appears generalisable to the CD population in UK practice who have failed or become intolerant to anti-TNFα therapies.

4.2.2.3 Study quality of the UNITI-1 Trial

The CS presented a quality assessment of the UNITI-1 trial based on a "NICE checklist" and concluded that the trial's risk of bias was low (Table 14 page 85-86 of the CS). The ERG conducted its own quality assessment of the trial using the Cochrane risk of bias assessment tool, see Table 8 below. The ERG

considers that the risk of bias was low in most of the Cochrane tool's criteria; however, there is a concern about handling of missing data in the trial.

The SC states that (see Table 12 page 73-74 of the CS):

> *"The CDAI score was calculated for a visit only if 4 or more of the 8 components were available at that visit. When at least 4 of the 8 components were available, any missing components were imputed by carrying forward the last non-missing component, with the exception of a missing haematocrit value. If the CDAI score could not be calculated (i.e. <4 components available) at a visit, the CDAI score was considered missing. Patients with a missing CDAI score at Week 6 were considered to not have achieved clinical response at Week 6"*

Based on this statement, the ERG identifies the following issues. First, it is not clear why "4" was used a cut-off value for the number of available (complete) components. It is not clear as to why imputing missing data was only applicable to those who had at least 4 components available. In fact, this method would unfairly exclude participants with 3 available components. Therefore, the ERG considers the approach to be inconsistent.

Second, although participants may have had 3 components available, they were assumed to be non-responders. In fact, based on the number of components available, there were 2 types of non-responders (i.e. those with <4 components available and those who had <100 CDAI score change). This introduces additional uncertainty to the results of the trial.

Third, the ERG also noticed that the CS adopted last observation carried forward (LOCF) method to impute missing data as a primary method. However, the ERG considers that LOCF may lead to bias due to the fact that this *ad hoc* method does not account for the uncertainty surrounding the missing values. The multiple imputation (or maximum likelihood) data should have been used as a primary missing data estimation method, and LOCF as a sensitivity analysis method. The ERG notes that sensitivity analyses (page 67 of the CSR) using complete cases, multiple imputation and worst cases were carried out for the primary outcome data (i.e. clinical response outcome at week 6) and all the methods appear to have reached at the same conclusion.

Table 8 Quality assessment of UNITI-1 trial using Cochrane risk of bias tool

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	Patients were randomised using permuted block randomisation with stratification for key prognostic factors.
Allocation concealment	Low	Randomisation implemented via a centralised IVRS/IWRS.

Baseline comparability	Low	Patient demographics and other baseline characteristics were balanced although the proportion of males was moderately higher in the placebo group than the two ustekinumab arms.
Blinding of participants and personnel	Low	Patients and investigators remained blinded to the study allocation throughout.
Blinding of outcome assessment	Low	Investigators remained blinded throughout.
Incomplete outcome data	Unclear	Primarily, last observation carried forward (LOCF) was used to estimate missing values. Sensitivity analysis using complete cases, multiple imputation and worst case were carried out only for the primary outcome. However, all participants with <4 components available were forced to be non-responders instead of their missing component values estimated and CDAI scores aggregated.
Selective reporting	Low	Reported outcomes data matches the outcome measures in the protocol of the study

4.2.2.4 Summary results of UNITI-1 Trial

Responses – CDAI

The UNITI-1 trial consisted of two arms (ustekinumab and a placebo arm). Reported primary and secondary outcomes in the CS (Table 15 of page 88 of the CS) and the CSR (Table 6 page 66, Table 7-8 page 68, Table 9-10 page 69 of the CSR) are summarised below in Table 9 with the ERG's calculated relative risks and 95% confidence intervals included. As only the ~6mg/kg dose is licensed, only these results are presented here.

Table 9 Summary results of key outcomes for UNITI-1 trial

	Arm	Participants who achieved the outcome (%)	Relative Risk and 95% CI *
Clinical (CDAI-100) response at week 6[a]	Placebo	53/247 (21.5)	Ref
	UST ~6mg/kg	84/249 (33.7)	1.57 (1.17 to 2.11)
Clinical remission (CDAI <150) at week 6[b]	Placebo	22/247 (8.9)	Ref
	UST ~6mg/kg	46/249 (18.5)	2.07 (1.29 to 3.34)
Clinical remission (CDAI <150) at week 8[b]	Placebo	18/247 (7.3)	Ref
	UST ~6mg/kg	52/249 (20.9)	2.87 (1.72 to 4.75)
Clinical (CDAI-100) response at week 8[b]	Placebo	50/247 (20.2)	Ref
	UST ~6mg/kg	94/249 (37.8)	1.86 (1.39 to 2.50)
CDAI-70 response at week 6[b]	Placebo	75/247 (30.4)	Ref
	UST ~6mg/kg	109/249 (43.8)	1.44 (1.14 to 1.82)
CDAI-70 response at week 3[b]	Placebo	67/247 (27.1)	Ref
	UST ~6mg/kg	101/249 (40.6)	1.50 (1.16 to 1.93)
Clinical remission (CDAI <150) at week 3[b]	Placebo	14/247 (5.7)	Ref
	UST ~6mg/kg	32/249 (12.9)	2.27 (1.24 to 4.14)

Key: *, calculated by ERG; [a] primary outcome; [b] secondary outcome; CDAI , CD activity index; UST, ustekinumab

The results indicate that patients randomised to ~6mg/kg ustekinumab had a higher probability of achieving response (CDAI-100 and -70) and clinical remission (CDAI <100) at weeks 3, 6 and 8 than those who were randomised to placebo.

The ERG's conclusion is in line with both the CS and CSR that participants who were randomised to the intervention treatments had a better chance of achieving disease improvement, although the follow-up period was short.

Inflammatory biomarkers

Based on the CS's information on page 97-99 and the CSR (Attachment TEFCRP02 page 186, Attachment TEFFECL01 page 187 and Attachment TEFFECL03 page 189 of the CSR), participants who were randomised to ~6mg/kg ustekinumab showed a significantly higher reduction of CRP and faecal lactoferrin during the 8-week follow-up period than those who were randomised to placebo (Table 10).

Table 10 Mean change of inflammatory biomarkers concentration from baseline (and SD) through week 8 for the UNITI-1 Trial

	Week 3	Week 6	Week 8

CRP	Placebo (N=247)	2.37 (19.62)	2.74 (18.52)	3.30 (18.59)
	UST ~6mg/kg (N=249)	-6.89 (19.74)	-5.66 (20.80)	-5.55 (20.52)
Faecal lactoferrin	Placebo(N=239)	N/R	0.17 (293.12)	N/R
	UST ~6mg/kg (N=243)	N/R	-57.27 (237.77)	N/R
Faecal calprotectin	Placebo (N=237)	N/R	-50.87 (2242.88)	N/R
	UST ~6mg/kg (N=239)	N/R	-239.13 (1242.71)	N/R

Key: N, total sample; N/R, not reported; SD, standard deviation; UST, ustekinumab

Patient reported outcomes

Health related quality of life outcomes at 8 weeks for the UNITI-1 trial using patients' self-administered questionnaires (i.e. SF-36 and IBDQ scores) were available in the CS and CSR. Based on the CS (Table 17 page 101 of the CS) and CSR's (Attachment TEFSF01-Attachment TEFSF02, page 196-199 of the CSR) reported outcomes, the mean changes (and SDs) from the baseline values for the physical component summary and the mental component of the SF-36 are summarised in Table 11.

The physical component summary mean differences as calculated by the ERG is 0.95 (95% CI: -0.20 to 2.1) for ~6mg/kg vs placebo. The respective mental component summary mean differences was 2.67 (95% CI: 1.10 to 4.25), see Table 11.

The CS also reported IBD scores (Table 17 page 101 of the CS and Attachment TEFIBDQ01 page 191 of the CSR) which are summarised in Table 11.. The mean difference as calculated by the ERG for placebo vs 6mg/kg is 10.2 (95% CI: 5.35 to 15.05), see Table 11. Based on these SF-36 results, the ERG considers that on average, there appears to be little improvement in in physical components summary, although there a significant improvement in the mental components summary, over the placebo group during the 8-week follow-up period. However, the results also suggest that those who were randomised to ustekinumab ~6mg/kg dosage appeared to have their IBD symptoms reduced significantly during the follow-up period.

Table 11 Summary of patient-reported outcomes at week 8 in UNITI-1 trial

	Arm	Mean score (SD) change from baseline	Mean change difference and 95% CI *
IBD score	Placebo (n=247)	11.9 (26.5)	Ref
	UST ~6mg/kg (n=249)	22.1 (28.6)	10.2 (95% CI: 5.35 to 15.05)
SF-36 Physical component summary	Placebo (n=247)	2.62 (6.5)	Ref
	UST ~6mg/kg (n=249)	3.57 (6.6)	0.95 (95% CI: -0.20 to 2.1)
SF-36 Mental component summary	Placebo (n=247)	2.19 (8.5)	Ref
	UST ~6mg/kg (n=249)	4.86 (9.3)	2.67 (95% CI: 1.10 to 4.25)

Key: *, calculated by ERG; IBD, Inflammatory bowel disease; Ref, reference, SF-36, 36-item short form health questionnaire; SD, standard deviation.

Endoscopic response

Endoscopic response results were presented in the CS, although UNITI-1 and UNITI-2 results across both the 130mg and ~6mg/kg doses of ustekinumab were combined (Table 19, page 107 of the CS). After a request by the ERG to Janssen, separate results for UNITI-1 and UNITI-2 were made available (Table 14 of the Janssen's response to clarification letter). Participants randomised to the ustekinumab achieved better endoscopic response outcomes than the placebo group, see Table 12 below. However, it must be noted that the endoscopic response population comprised only those who were willing to participate in the sub-study, so may not be representative of the UNITI-1 trial population, nor CD patients in the UK.

Table 12 Summary of endoscopic outcomes in the UNITI-1 at week 8

	Placebo	Ustekinumab*
Patients with eligible SES-CD score at baseline	41	66
Baseline SES-CD score, mean (SD)	12.3 (6.7)	14.6 (8.3)
Change from baseline in SES-CD, mean (SD)	0.2 (3.2)	-2.3 (5.2)
Patients with ≥3 point reduction from baseline in SES-CD score, n (%)	7 (17.1)	29 (43.9)
Patients in endoscopic response, %	0 (0.0)	9 (13.6)
Patients in endoscopic remission, %	0 (0.0)	2 (3.0)

Key: *, 130mg and 6mg/kg dosages combined.

Subgroup analyses

Subgroup analysis results of clinical response at week 6 and clinical remission at week 8 were presented in appendix 4 of the CS (Figure 3-Figure 8, page 24-33 of the appendices of the CS) and the CSR (Attachment GEFCRES10-Attachment GEFCRES15, page 153-162;Attachment

GEFCREM05-Attachment GEFCREM10, page 143-152; Attachments GEFCRES10-GEFCRES15, page 153-162 of the CSR).

The results show that participants for whom at least one TNFα inhibitor had failed demonstrated similar efficacy (clinical response at Week 6 and clinical remission rates at Week 8) to those patients for whom TNFα inhibitors are not suitable because of intolerance or contraindication. The analyses also indicate that the odds of a response to ustekinumab is higher in females than in males (OR 2.4 (95% CI 1.4 to 4.2) vs 1.2 (95% CI: 0.7 to 2.3), as were the odds of achieving remission (OR for remission 6.1 (95% CI 2.5 to 8.2) vs 2.1 (95% CI: 0.9 to 4.8), though no test for interaction was conducted.

4.2.3 The UNITI-2 trial

The UNITI-2 trial compared the clinical effectiveness of ustekinumab and placebo in 627adult patients with moderately to severely active CD who have failed conventional therapy. The trial was composed of three arms (Ustekinumab 130mg IV, Ustekinumab ~6mg/kg IV, and placebo). The trial was conducted in 266 locations worldwide with a follow-up period of 8 weeks. The trial's characteristics were identical to the UNITI-1 trial apart from the eligibility criteria of participants, that is, participants in the UNITI-1 trial were those who had failed anti-TNFα therapies, whereas participants in the UNITI-2 trial were those who had failed conventional therapy. The UNITI-2 trial patients may have had a history of receiving anti-TNFα medications but not a history of *failure or intolerance* to the treatments. See Table 6 for more details.

The ERG's concerns about the UNITI-1 trial (see section 4.2.2) also apply to this trial: (i) the follow-up period for the primary (6 weeks) and secondary (8 weeks) outcomes were very short (ii) the use of CDAI and IBDQ may not reflect the disease status accurately and (iii) inflammatory biomarker measurements may not reflect the actual CD status of a person.

4.2.3.1 Participant flow in the UNITI-2 trial

Both the CS (figure 9 page 79 of the CS) and CSR (figure 2 page 51 of the CSR) presented consort diagrams of patient disposition of the UNITI-2 trial which the ERG considers that the diagrams provide enough information about the follow-up population.

4.2.3.2 Baseline characteristics of the UNITI-2 Trial population

The CS presented baseline data of the UNITI-2 trial population (Table 13 page 83-84 of the CS) based on demographic characteristics (age, sex, and weight), CD characteristics, GI areas involved, and previous conventional and anti-TNFα medications. See summary in Table 7 above The CSR also presented more detailed information about baseline characteristics of the UNITI-2 trial population

(Table 2 page 54, Attachment TSICM01 page 126, Attachment TSICM02 page 127, Attachment TSIDEM03 page 132-133, and Attachment TSIDEM09 page 136 of the CSR). The CS concluded and the ERG agrees that there was no significant imbalance in baseline characteristics among the three arms of the trial.

In addition the study population appears generalisable to UK clinical practice. There is an issue for consideration about whether the trial population truly reflects the 'conventional care failure' population to be treated in NHS practice. It can be argued reasonably that patients who have previously responded to but not 'failed' an anti-TNFα are more likely to respond to ustekinumab than a group of patients who have not been exposed. The proportion of anti-TNFα exposed patients in UNITI-2 is 42% and therefore the response rates in this trial may overestimate that to be expected in NHS clinical practice.

As already stated, the UNITI trials included patients with a CDAI score between 220 and 450; and therefore excluded patients at the higher end of the CDAI spectrum (CDAI > 450) and therefore, it is uncertain whether the UNITI-2 trial results are generalisable to patients with a CDAI score of 450 or greater.

4.2.3.3 Study quality of the UNITI-2 Trial

The CS conducted a quality assessment of the UNITI-2 trial based on a "NICE checklist" and concluded that the trial's risk of bias was low (Table 14 page 86-87 of the CS). The ERG conducted its own quality assessment of the trial using the Cochrane risk of bias assessment tool, see Table 13 below. The ERG considers that that the overall risk of bias for the UNITI-2 trial may be low. However, there a possibility of bias due to missing data for the same reasons that are highlighted in UNITI-1, see section 4.2.2.3.

Table 13 Quality assessment of UNITI-2 trial using Cochrane risk of bias tool

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	Patients were randomised using permuted block randomisation with stratification for key prognostic factors.
Allocation concealment	Low	Randomisation implemented via a centralised IVRS/IWRS.
Baseline comparability	Low	Patient demographics and other baseline characteristics were balanced although the proportion of who had previously taken anti-TNFα medication was significantly higher in the placebo group than the 130mg ustekinumab dosage group.
Blinding of participants and personnel	Low	Patients and investigators remained blinded to the study allocation throughout.
Blinding of outcome assessment	Low	Investigators remained blinded throughout.
Incomplete outcome data	Unclear	Primarily, last observation carried forward (LOCF) was used to estimate missing values. Sensitivity analysis using complete cases, multiple imputation and worst case were carried out only for the primary outcome. However, all participants with <4 components available were forced to be non-responders instead of their missing component values estimated and CDAI scores aggregated.
Selective reporting	Low	Reported outcomes data matches the outcome measures in the protocol of the study

4.2.3.4 Summary results of UNITI-2 Trial

The UNITI-2 trial consisted of two ustekinumab arms and a placebo arm. The reported primary and secondary outcomes are summarised below. As only the~6mg/kg dose is licensed, only the results for this are presented by the ERG.

Response - CDAI

The UNITI-2 trial's primary and major secondary clinical effectiveness outcomes were presented in the CS (Table 15 of page 88 of the CS) and the CSR (Table 6 page 71, Table 7 page 72, Table 8 page 73, Table 9-10 page 74 of the CSR). The reported outcomes along with the ERG's calculated relative risks and 95% confidence intervals are summarised in Table 14 below.

The results show that patients randomised to the ~6mg/kg had higher probability of achieving response and remission when compared with those randomised to placebo.

The ERG's conclusion agrees with both the CS and CSR that participants who were randomised to the ustekinumab treatments had a better chance of achieving disease improvement.

Table 14 Summary of key outcomes for UNITI-2 trial

	Arm	Proportion of participants who achieved the outcome (%)	Relative Risk and 95% CI *
Clinical (CDAI-100) response at week 3 [b]	Placebo	45/209 (21.5%)	Ref
	UST ~6mg/kg	81/209 (38.8%)	1.8 (1.32 to 2.45)
Clinical (CDAI-100) response at week 6 [a]	Placebo	60/209 (28.7)	Ref
	UST ~6mg/kg	116/209 (55.5)	1.93 (1.51 to 2.47)
Clinical (CDAI-100) response at week 8 [b]	Placebo	67/209 (32.1)	Ref
	UST ~6mg/kg	121/209 (57.9)	1.81 (1.44 to 2.27)
Clinical remission (CDAI < 150) at week 3 [b]	Placebo	24/209 (11.5%)	Ref
	UST ~6mg/kg	48/209 (23.0%)	2 (1.27 to 3.14)
Clinical remission (CDAI < 150) at week 6 [b]	Placebo	37/209 (17.7%)	Ref
	UST ~6mg/kg	73/209 (34.9%)	1.97 (1.40 to 2.79)
Clinical remission (CDAI < 150) at week 8 [b]	Placebo	41/209 (19.6)	Ref
	UST ~6mg/kg	84/209 (40.2)	2.05 (1.49 to 2.82)
CDAI-70 response at week 6 [b]	Placebo	81/209 (38.8)	Ref
	UST ~6mg/kg	135/209 (64.6)	1.67 (1.37 to 2.03)
CDAI-70 response at week 3 [b]	Placebo	66/209 (31.6)	Ref
	UST ~6mg/kg	106/209 (50.7)	1.61 (1.26 to 2.04)

Key:*, calculated by ERG; [a] primary outcome; [b] secondary outcome; CDAI = CD activity index; UST= ustekinumab

Inflammatory biomarkers

Inflammatory biomarker outcomes have been summarised in Table 15 below based on the CS (Figure 18 page 98 and information on page 97-99) and CSR (Attachment TEFCRP02 page 197, Attachment TEFFECL01 page 198 and Attachment TEFFECL03 page 200 of the CSR) reported results. Participants who were randomised ustekinumab showed a significantly higher reduction of CRP biomarkers during the 8-week follow-up period than those who were randomised to placebo, see Table 15 below. The faecal lactoferrin and faecal calprotectin results also show that there was significant difference in mean change between the ustekinumab groups and placebo.

Table 15 Mean change of inflammatory biomarkers concentration (and SD) from baseline through week 8 for the UNITI-2 Trial

		Week 3	Week 6	Week 8
CRP	Placebo (N=247)	-0.18 (14.15)	1.03 (17.53)	-0.14 (14.66)
	UST 6mg/kg (N=249)	-8.61 (20.14)	-8.41 (20.97)	-8.56 (19.60)
Faecal lactoferrin	Placebo (N=239)	N/R	3.63 (191.84)	N/R
	UST 6mg/kg (N=243)	N/R	-106.49 (250.05)	N/R
Faecal calprotectin	Placebo (N=237)	N/R	19.43 (893.98)	N/R
	UST 6mg/kg (N=239)	N/R	-312.69 (1110.04)	N/R

Key: N, total sample; N/R, not reported; SD, standard deviation; UST, ustekinumab

Patient reported outcomes

Based on the CS (Table 17 page 101of the CS) and CSR's (Table TEFSF01 page 207 of the CSR) reported outcomes, the mean changes (and SDs) from the baseline values for the physical component and mental component summaries of the SF-36 are summarised in Table 16 below. The physical component summary mean differences as calculated by the ERG are ~6mg/kg vs placebo. The respective mental component summary mean difference was and 3.55 (95% CI: 1.46 to 5.64), See Table 16 below.

The CS also reported IBD scores (Table 17 page 101 of the CS and Table TEFIBDQ01 page 203 of the CSR) which indicate that the mean IBDQ score changes and SDs from baseline for the three arms were 14.7 (26.96) and 35.3 (36.05) for the placebo and ~6mg/kg , respectively. The mean change differences as calculated by the ERG are as follows: placebo vs ~6mg/kg was 20.6 (95% CI: 14.47 to 26.7), See Table 16 below.

Based on these SF-36 and IBDQ results, the ERG considers that participants who were randomised to the intervention treatment achieved better health related quality of life outcomes than the placebo group during the 8-week follow-up period.

Table 16 Summary of patient-reported outcomes at week 8 in UNITI-2 trial

	Arm	Mean score (SD) change from baseline	Mean change difference and 95% CI*
IBD score	Placebo (n=207)	14.7 (26.96)	Ref
	UST ~6mg/kg (n=207)	35.3 (36.05)	20.6 (95% CI: 14.47 to 26.7)
SF-36 Physical component summary	Placebo (n=207)	2.59 (5.88)	Ref
	UST ~6mg/kg (n=207)	6.01 (7.7),	3.42 (95% CI: 2.05 to 4.79)
SF-36 Mental component summary	Placebo (n=207)	3.25 (9.47)	Ref
	UST ~6mg/kg (n=207)	6.8 (11.34)	3.55 (95% CI: 1.46 to 5.64)

Key: *, calculated by ERG; IBD, Inflammatory bowel disease; Ref, reference, SF-36, 36-item short form health questionnaire; SD, standard deviation.

Endoscopic response

Endoscopic response results for 145 participants of the UNITI-2 trial were provided by the Company in their clarification response, though the results for the licensed 6mg/kg dose were combined with those for the 130mg dose. The results indicated that participants who were in the ustekinumab dosages and placebo appear to have similar endoscopic response outcomes, see Table 17 below. However, the ERG noted that participation in the endoscopic sub-study was dependent on willingness of patients and that they may not be representative of the UNITI-2 trial population.

Table 17 Summary of endoscopic outcomes in the UNITI-2 at week 8

	Placebo	Ustekinumab*
Patients with eligible SES-CD score at baseline	56	89
Baseline SES-CD score, mean (SD)	12.4 (8.3)	13.9 (8.0)
Change from baseline in SES-CD, mean (SD)	-1.4 (5.9)	-3.1 (6.0)
Patients with ≥3 point reduction from baseline in SES-CD score, n (%)	22 (39.3)	45 (50.6)
Patients in endoscopic response, %	4 (7.1)	10 (11.2)
Patients in endoscopic remission, %	13 (23.2)	23 (25.8)

Key: *, both the 130 mg and 6mg/kg dosages combined

Subgroup analyses

Subgroup analyses results of the clinical response at week 6 and clinical remission at week 8 are presented in appendix 4 of the CS (Figure 9-Figure 12, page 31-41 of the appendices of the CS) and the CSR (Attachment GEFCRES10- Attachment GEFCRES13, page 164-171; Attachment GEFCREM05-Attachment GEFCREM08, page 156-163 page; and Attachments GEFCRES10-GEFCRES13, page 164-171 of the CSR).

The results show that participants for whom at least one TNFα inhibitor had failed demonstrated similar efficacy (clinical response at Week 6 and clinical remission rates at Week 8) to those patients

for whom TNFα inhibitors are not suitable because of intolerance or contraindication. Patients who had not previously received a TNFα inhibitor (TNF-naïve) demonstrated similar efficacy (clinical response and clinical remission rates at Week 6) to those patients who had previously been exposed to a TNFα inhibitor (but who did not meet the failure criteria specified for UNITI-1). The analyses also indicate that the odds of a response to ustekinumab is higher in males than females in (OR 3.7, (95% CI: 2.0 to 7.0) vs 2.9 (95% CI: 1.6 to 5.0)), as were the odds of or of achieving remission (OR for remission (OR 3.4 (95% CI: 1.7 to 6.7) vs 2.5 (95% CI: 1.4 to 4.4)) though no test for interaction was conducted.

4.2.4 The IM-UNITI study

The trial included 1,281 participants who had completed the induction studies (UNIT-1 and UNITI-2 trials). The study had two designated subgroups of participants: (i) 'randomised' group that included 397 (31%) participants and (ii) 'non-randomised with 884 (69%) participants. The 'randomised' subgroup are those who were randomised to the two ustekinumab dosages (130mg and ~6mg/kg) in theUNITI-1 and UNITI-2 trials and achieved clinical response by the end of the 8-week follow-up period. The 'non-randomised' subgroup are those who were randomised to ustekinumab dosages but did not achieve clinical response during induction period (UNITI-1 and UNITI-2 follow-up period), and those who were randomised to placebo in the same trials irrespective of clinical response achievement during the induction period.

4.2.4.1 The IM-UNITI randomised trial

The IM-UNITI randomised trial was primarily aimed at investigating the clinical remission of participants with moderately to severely active CD induced into clinical response with ustekinumab in the induction studies (i.e. UNITI-1 and UNITI-2) and who then continued to receive maintenance doses of ustekinumab (i.e. 90mg q12w and 90mg q8w) and placebo for about 44 weeks.

The trial consisted of three arms: ustekinumab 90mg SC q12w, ustekinumab 90mg SC q8w, and placebo. The trial was a multicentre study conducted in 220 locations worldwide for about 44 weeks of follow-up. The primary response outcome was "clinical remission" at week 44 which was defined as defined as a CDAI score <150 points. Further details of the trial are summarised below in Table 18.

The ERG considers that whilst the IM-UNITI randomised trial provides vital information about long-term loss of response and safety of ustekinumab it must be noted that participants of the trial were only those who were randomised to ustekinumab and had achieved clinical response at week 8 of the UNITI-1 and UNITI-2 trials. Those who were randomised to placebo during the induction period (irrespective of the clinical response), and those non-responders who were randomised to the ustekinumab dosages, were not included in the randomised trial part of IM_UNITI. This means that

results from the IM-UNITI randomised trial are not applicable to the wider CD patient population. Those who were randomised to placebo during the induction period (irrespective of the clinical response), and those non-responders who were randomised to the ustekinumab dosages, were followed as part of the open label arm of IM-UNITI.

Second, the IM-UNITI trial included all participants who responded to ustekinumab during induction irrespective of the dose they received (130 mg or ~6mg/kg), whilst ~6mg/kg is the only licensed induction dosage. No separate analysis of data has been presented in the CS or CSR for patients originating from the different ustekinumab induction arms.

Table 18 Key study characteristics of the randomised IM-UNITI trial

Population	Adult patients with moderately to severely active CD induced into clinical response with ustekinumab in the induction studies UNITI-1 or UNITI-2
Treatments	**Ustekinumab 90mg q12w:** patients received an SC dose every 12 weeks **Ustekinumab 90mg q8w:** patients received an SC dose every 8 weeks **Placebo:** patients received a matching SC placebo Patients who lost response were eligible to move to the ustekinumab 90mg SC q8w dose (patients already on this schedule continued on it). Patients who showed no improvement 16 weeks after dose adjustment were discontinued from the study and considered as treatment failures (responders continued at this dose).
Location	220 study locations worldwide: Australia, Belgium, Brazil, Bulgaria, Canada, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Iceland, Ireland, Israel, Japan, Korea, Netherlands, New Zealand, Poland, Russia, Serbia, South Africa, Spain, UK, USA.
Trial design	The same as UNITI-1 and UNITI-2
Eligibility criteria for participants	Patients were taken from the two induction trials: UNITI-1 and UNITI-2. Patients who achieved clinical response on ustekinumab were included in the randomised portion of this trial that made up the primary study population. Other patients from the induction trials (i.e. responders to placebo and non-responders) could also be included in the study, but were not included in the randomised portion of the trial.
Primary outcome	The primary endpoint was clinical remission at Week 44, defined as a CDAI score <150 points. Safety of the two maintenance regimens of ustekinumab was also considered a primary endpoint.
Major secondary outcomes	Secondary endpoints included: • Clinical response at Week 44 • Clinical remission at Week 44 for patients in clinical remission to ustekinumab at Week 0 • Corticosteroid-free remission at Week 44 • Clinical remission at Week 44 in the subset of patients who were refractory or intolerant to TNFα inhibitor therapy i.e. patients from UNITI-1 Safety assessments were based on reported AEs, clinical laboratory test results, vital sign measurements, physical examinations, ECG findings and TB testing.

Other outcomes	Other endpoints included:
	• Change in the CDAI score and the CDAI component scores
	• Corticosteroid endpoints and fistula response
	• Analyses to assess the effect of dose adjustment
	• Inflammatory biomarkers
	  ○ serum CRP
	  ○ faecal calprotectin

	○ faecal lactoferrin • IBD-specific and general HRQL measures ○ IBDQ ○ SF-36 • Medical resource utilisation and health economics • Relationship between efficacy and pharmacokinetics • Relationship between efficacy and antibodies to ustekinumab status Mucosal healing was also assessed by ileocolonoscopy in patients at participating sites who consented to inclusion in the endoscopic sub-study
Permitted and disallowed concomitant medication	• The same as UNITI-1 and UNITI-2. With the exception of corticosteroids for which tapering was recommended, dosing of concomitant medications was to remain stable through Week 44.
Pre-planned subgroup analyses	Subgroup analyses were conducted based on the following characteristics: • Demographic (i.e. age, sex and weight) • Induction baseline disease characteristics • CD medication history (including TNFα inhibitor therapy) • CD medication use at induction baseline, and centre location. Subgroup analyses were planned when the number of patients in the subgroups permitted.
Key: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, azathioprine; CDAI, CD activity index; CRP, C-reactive protein; HRQL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; MTX, methotrexate; SF-36, 36-item short form health questionnaire; TNF, tumour necrosis factor.	

4.2.4.2 Participants flow in the IM-UNITI randomised trial

A Consort diagram of the patient disposition of the IM-UNITI trial has been presented both in the CS (Figure 10 page 80 of the CS) and CSR (Figure 3 page 55 of the CSR). The ERG considers the diagrams to provide sufficient information on the flow of participants during the follow-up period.

4.2.4.3 Baseline characteristics of the IM-UNITI randomised Trial population

Baseline data of the IM-UNITI trial are presented in Table 13 of the CS (for the IM-UNITI patients at the start of UNITI-1 and -2 induction) and also in Table 8 page 23 of the CS appendices document for the start of maintenance. However the items reported in Table 8 do not match those reported in Table 13. As would be expected measures of CD hwere improved CDAI mean scores, proportion of participants with faecal calprotectin >250mg/kg and faecal lactoferrin 7.24µg/g. However, the information does not allow other differences between the ustekinumab responders and the true baseline populations to be checked.

4.2.4.4 Study quality of the IM-UNITI Trial

The CS presented a quality assessment of the UNITI-1 trial based on a "NICE checklist" and concluded that the trial's risk of bias was low (Table 14 page 85-86 of the CS). The ERG conducted its own quality assessment of the trial using the Cochrane risk of bias assessment tool, see Table 19 below. The ERG considers that the trial had low risk of bias in 4 of the tool's components. However, the ERG believes that blinding of patients, personnel and investigators was broken for patients who

lost response (placebo and ustekinumab 90mg q12w weeks dosage groups) when they switched to ustekinumab 90mg q8w. In addition, the ERG considers that the risk of bias due missing data remains unknown, see Table 19 for details.

Table 19 Quality assessment of IM-UNITI trial using Cochrane risk of bias tool

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	Although the CS states that "patients were randomised using permuted block randomisation with stratification for key prognostic factors" the 'sample' for the IM-UNITI study does not represent real world patients.
Allocation concealment	Low	Randomisation was implemented via a centralised IVRS/IWRS, the study considered only those participants who were initially randomised to the ustekinumab dosages and achieved clinical response for inclusion.
Baseline comparability	Low	Patient demographics and other baseline characteristics appeared to be balanced.
Blinding of participants and personnel	High	Patients who were randomised to placebo and ustekinumab 90mg every 12 weeks were switched to ustekinumab 90mg q8w dosage at the time of loss of response.
Blinding of outcome assessment	High	It is highly likely that investigators knew the switching-over of patients who lost response onto ustekinumab 90mg q8w dosage.
Incomplete outcome data	Unclear	See UNTI-1 (Table 8) and UNITI-2 (Table 13) trials.
Selective reporting	Low	Reported outcomes match the protocol.

4.2.4.5 Summary results of IM-UNITI Trial

Maintenance of response - CDAI

The IM-UNITI has reported primary and secondary outcomes in the CS (Table 16 of page 91 of the CS) and the CSR (Table 5 page 84, Table 6 page 88, Table 7 page 89, Table 8 page 90 of the CSR). The results are summarised below in Table 20. The IM-UNITI trial results are not presented separately for the two induction dose groups (fixed 130 mg or the licensed ~6mg/kg dose).

Table 20 Summary results of key outcomes for IM-UNITI trial

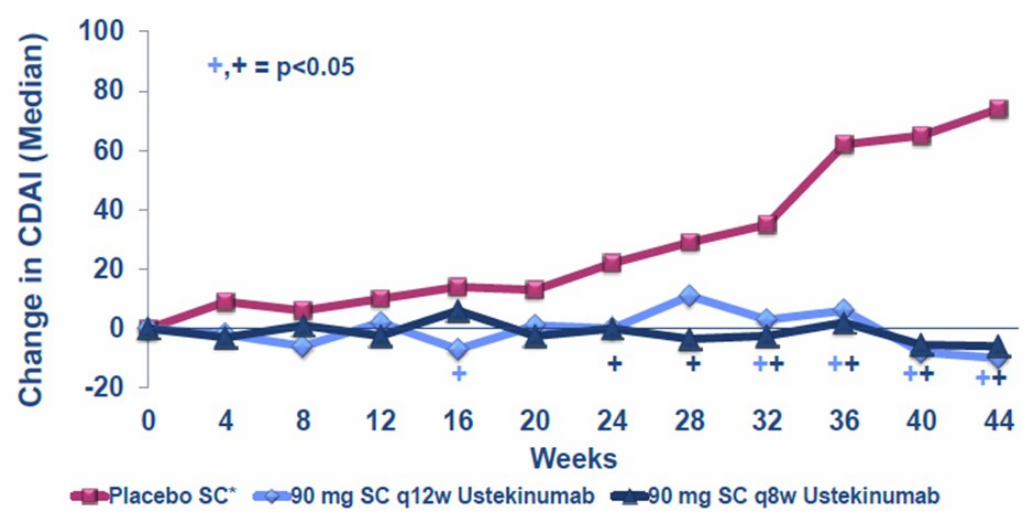
	Arm	Participants who achieved the outcome (%)
Clinical remission at week 44	Placebo	47/131 (35.9%)
	UST 90mg q8w	68/128 (53.1%)
	UST 90mg q12w	63/129 (48.8%)
CDAI-100 response at Week 44	Placebo	58/131 (44.3%)
	UST 90mg q8w	76/128 (59.4%)
	UST 90mg q12w	75/129 (58.1%)
Corticosteroid-free clinical remission at Week 44	Placebo	39/131 (29.8%)
	UST 90mg q8w	60/128 (46.9%)
	UST 90mg q12w	55/129 (42.6%)
Clinical remission at Week 44 in patients who were refractory or intolerant to anti-TNFα therapy	Placebo	16/61 (26.2%)
	UST 90mg q8w	24/56 (41.1%)
	UST 90mg q12w	22/57 (38.6%)
Clinical remission at week 0 (of maintenance study) and Week 44	Placebo	36/79 (45.6%)
	UST 90mg q8w	52/78 (66.7%)
	UST 90mg q12w	44/78 (56.4%)

Key: q8w, every 8 weeks; q12w, every 12 weeks

The results show that whilst all patients were ustekinumab responders (CDAI-100) at week 8 (start of maintenance) only around 50% of responders who remain on ustekinumab were in remission at Week 44 and around 60% were in clinical response. The results also indicate that higher proportions of patients randomised to the two ustekinumab dosages retained their responder status and a higher proportion were in remission at Week 44 than those randomised to placebo

This loss of responders on active treatment is not reflected in the change in median CDAI over time; see Figure 1 below taken from Figure 14 Page 93 of the CS. The graph shows that CDAI scores appeared to increase for the participants who were switched to placebo after the induction period, while the scores seem to decrease or stabilise for those who continued on the two ustekinumab dosages. These results indicate that who have responded to ustekinumab will have a greater probability of maintaining their response if they continue active treatment rather than stopping.

Figure 1 Change of CDAI through Week 44 in IM-UNITI population



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 21 Patients in clinical remission over time from Week 44 through to Week 92 in the IM-UNITI trial

	Ustekinumab 90mg SC q12w[a]	Ustekinumab 90mg SC q8w				Placebo[a]
		q8w[a]	Prior dose adjustment[b]	Combined	All ustekinumab	
Randomised patients who were in clinical response at Week 44[c] and entered a long-term extension	**	**	**	***	***	**
Week 44	**********	*********	*********	*********	*********	*********
Week 56	**********	**********	**********	**********	**********	**********
Week 68	**********	**********	**********	**********	**********	**********
Week 80	**********	**********	**********	**********	**********	**********
Week 92	**********	**********	**********	**********	**********	**********

Key: IV, intravenous; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous.
Notes: [a], Subjects who were in clinical response to ustekinumab IV induction dosing, were randomised to receive study drugs on entry into the maintenance study,
and did not meet loss of response criteria from Week 8 through to Week 32;
[b], Subjects who were in clinical response to ustekinumab induction dosing, were randomised, met loss of clinical response criteria from Week 8 through Week
32, and initiated ustekinumab 90 mg SC q8w (for subjects randomised to receive placebo SC or ustekinumab 90 mg SC q12w on entry into the maintenance
study) or continue ustekinumab 90 mg SC q8w (for subjects randomised to receive ustekinumab 90 mg SC q8w on entry into the maintenance study) in this
maintenance study;
[c], Based on calculated CDAI without treatment failure rules applied.
Source: IM-UNITI CSR Addendum.

Other outcomes

The CS (pages 101-104) and CSR (page 101-103, and pages 105-107) presented additional longitudinal data about inflammatory biomarkers and patients reported outcomes which are summarised below.

Inflammatory biomarkers

The patterns of the CDAI scores above (Figure 1) are also reflected in the CRP results of IM-UNITI. The median CRP changes from baseline appear to be stabilised for the participants who received ustekinumab over time, while in participants who received placebo the changes appeared to consistently increase over time. Results for faecal calprotectin and faecal lactoferrin are also consistent with these findings, with increases over time for placebo patients, and stabilised results for those patients treated with ustekinumab.

Patient reported outcomes

Reported health related quality of outcomes for the IM-UNITI trial using patient-reported questionnaires (i.e. SF-36 and IBDQ scores) reflect the response outcomes (see Table 18 page 103-104 of the CS)

Endoscopic response

Endoscopic response results indicate that participants in the ustekinumab 90mg q8w dosage group appear to have responded better than those participants from the ustekinumab 90mg q12w and placebo groups, see Table 22 below.

Table 22 Summary of endoscopic outcomes in the IM-UNITI trial at week 44

	Placebo	Ustekinumab q8w	Ustekinumab q12w
Patients with eligible SES-CD score at baseline, combined UNITI-1 and UNITI-2 studies	24	29	12
Change from baseline in SES-CD, mean (SD)	-1.9 (4.1)	-3.1 (4.1)	-1.6 (2.8)
Patients with ≥3 point reduction from baseline in SES-CD score, n (%)	6 (25.0)	12 (41.4)	5 (29.4)
Patients in mucosal healing, n (%)	1 (4.2)	5 (17.2)	1 (5.9)
Patients in endoscopic response, %	1 (4.2)	7 (24.1)	1 (5.9)
Patients in endoscopic remission, %	1 (4.2)	NR	NR

Key: NR,not reported; q8w, every 8 weeks; q12w, every 12 weeks.

4.2.5 Efficacy endpoints from the non-randomised component of IM-UNITI

Delayed responders

Across UNITI-1 and UNITI-2, a total of 476 patients did not achieve clinical response (CDAI-100) with ustekinumab IV induction infusion. These patients were treated with ustekinumab 90mg subcutaneous at Week 0 of the maintenance trial (8 weeks after IV ustekinumab). After a further 8 weeks treatment, 50.5% of these patients achieved clinical response (CDAI-100), and 28.9% achieved clinical remission at Week 8 (16 weeks post induction treatment initiation).

Maintenance ustekinumab 90mg SC q8w was continued in 251 patients from Week 8 of the IM-UNITI trial (16 weeks post treatment initiation). Of these patients, 68.1% were in clinical response (CDAI-100) at Week 44 (1-year post treatment initiation), and 50.2% were in clinical remission.

These results suggest that patients who do not achieve clinical response (CDAI-100) following an IV induction dose of ustekinumab but receive a further ustekinumab 90mg subcutaneous dose at Week 8 achieve similar outcomes to patients who do achieve clinical response (CDAI-100) to ustekinumab

after the single IV induction dose (see Figure 2 below). However as this analysis pools non-responders to the very low 130 mg dose with non-responders to the licensed ~6mg/kg dose, it is not clear whether such results would be seen in clinical practice.

Figure 2 Clinical remission and clinical response for patients receiving ustekinumab 90mg SC at Week 8 regardless of response to IV induction

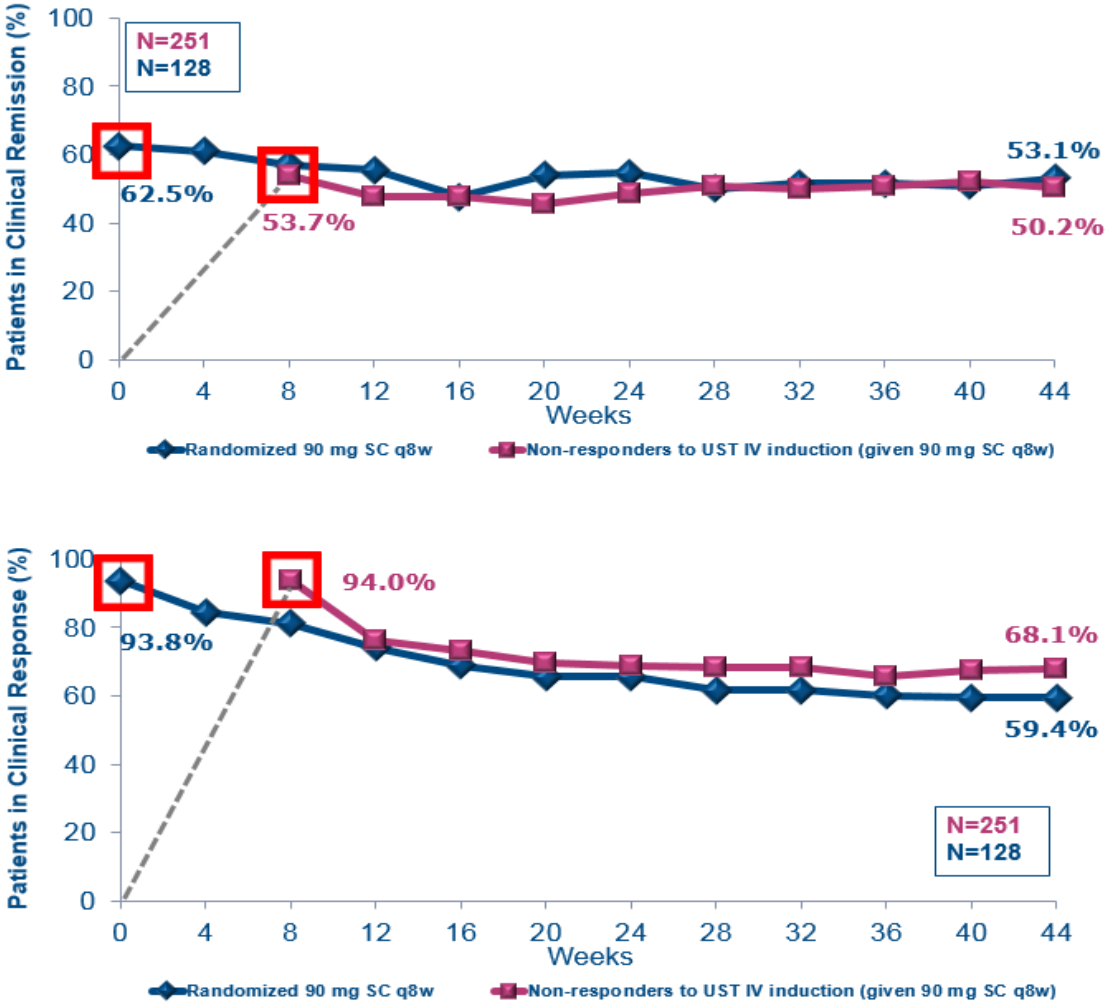


Figure adopted from figure 15 of the CS.

Placebo responders

A total of 120 patients in the placebo groups of UNITI-1 and UNITI-2 who achieved clinical response (CDAI-100) continued to receive placebo (i.e. including non-biologic conventional care) in the maintenance trial. At Week 8 of the maintenance phase, 74.2% of these patients achieved clinical response (CDAI-100) and 53.3% achieved clinical remission. At Week 44 (1-year after treatment initiation), of the 118 patients who continued to receive placebo after the Week 8 assessment in IM-

UNITI (16 weeks post treatment initiation), 55.9% achieved clinical response (CDAI-100) and 47.5% achieved clinical remission.

4.2.6 The CERTIFI trial

The CERTIFI trial details are summarised in Table 6. CERTIFI was a Phase-IIb study which investigated the clinical effectiveness of ustekinumab in 526 patients with moderately to severely active CD, 524 of whom had previously failed one or more TNF-α inhibitor therapies; the study population was therefore comparable to that of UNITI-1. The CS did not provide detailed information on this study in the sections on clinical effectiveness. The CS did include CERTIFI in their cost-effectiveness scenario analyses but it was excluded from the base case analysis and does not appear in the final induction phase NMA. There was little information on this study presented in the main submission, which the ERG obtained from publicly available sources.

The CERTIFI study was double-blinded and placebo controlled, conducted at 153 centres in 12 countries; it comprised both an induction phase of 8 weeks, followed by a maintenance phase of 28 weeks. During induction, patients were randomised to one of four study arms; these were to receive IV ustekinumab at a dose of 1, 3, or 6 mg/kg of body weight, or placebo at week 0. One hundred and forty five patients who reached the primary endpoint of a clinical response to ustekinumab at 6 weeks (≥100-point decrease in CDAI score from baseline) were re-randomised to receive SC ustekinumab (90mg) or placebo at weeks 8 and 16. Those who responded to placebo during induction received SC placebo at weeks 8 and 16, while those who did not respond received SC ustekinumab (270mg) at 8 weeks, followed by 90mg at 16 weeks.

The induction phase of the trial was conducted in a similar manner to UNITI-1 and UNITI-2, and as such the same criticisms apply. CERTIFI is generally a good-quality Phase-II study containing a significant number of CD patients, and has an appropriately constructed and similar comparator group. However, it should be noted that none of the doses administered to patients in the ustekinumab arms of the induction phase are licensed in the UK: one arm of the trial was of exactly 6 mg/kg, whereas the licenced states the dose is to be composed of two to four 130mg vials of ustekinumab according to patients' weight categories, approximating to a 6mg/kg dose. The ERG deems 6mg/kg to be sufficiently similar to the licensed ~6mg/kg dose (which was used in the UNITI trials) to be included in the CS analyses, particularly as the results of the unlicensed dose of 130mg were included in many of the CS analyses.

The ERG does not accept that the explanation provided in the CS for the exclusion of this evidence was satisfactory, and that the results from the 131 patients randomised to receive 6mg/kg IV ustekinumab during induction should be included in the anti-TNFα failure induction phase NMA. As

in the UNITI-1 and -2 trials all patients who responded to ustekinumab at Week 6, irrespective of induction dose (1 mg/kg, 3mg/kg and 6mg/kg) were re-randomised at Week 8 to ustekinumab 90 mg SC or placebo. Results were not presented separately by induction phase dose of ustekinumab. The maintenance phase results from CERTIFI, therefore, include many patients who were given induction doses much lower than permitted under UK license terms so should be interpreted with caution. . Participants who were not in clinical response to placebo at week 6 also received a much higher non-licenced SC dose of 270mg at week 8.

4.2.6.1 Participant flow in the CERTIFI trial

There were 526 participants randomised into the induction phase of the CERTIFI trial, 132 were randomised to placebo, 131 to the 1mg/kg and 6mg/kg study arms, and 132 into the 3mg/kg arm. During the induction phase, 19 placebo patients withdrew from the study, as did 30 ustekinumab patients, balanced approximately equally across the different dosages. 145 of the 364 participants randomised to ustekinumab during induction were responders, and at week 8 were re-randomised to receive placebo SC (n=73) or 90mg ustekinumab SC (n=72) during the maintenance phase. The remaining 219 non-responders were randomised separately to placebo SC (110) or 90mg ustekinumab SC (n=109). There were 28 responders to placebo during induction, who went on to receive placebo SC at weeks 8 and 16, the 85 placebo non-responders received 270mg ustekinumab SC at week 8 and 90mg at week 16. A breakdown of participant flow during the maintenance phase of the study is presented in Table 23 below. There was a generally higher rate of completion in induction phase responders, particularly those re-randomised to ustekinumab. Those who did not respond to ustekinumab during induction had a higher rate of study withdrawal during maintenance due to treatment discontinuation compared to ustekinumab responders. Reasons for treatment discontinuation included adverse events, worsening of symptoms, and lack of efficacy.

Table 23 Participant flow during CERTIFI maintenance phase

Treatment arm	Total	Completed study (%)	Discontinued treatment (%)
Placebo	113	77 (68.1)	9 (8.0)
Responders (Placebo)	28	20 (71.4)	2 (7.1)
Non-responders (UST)	85	57 (67.1)	7 (8.2)
Ustekinumab responders	145	108 (74.5)	15 (10.3)
Placebo SC	73	53 (72.6)	10 (13.7)
Ustekinumab SC	72	55 76.4)	5 (6.9)
Ustekinumab non-responders	219	151 (68.9)	39 (17.8)
Placebo SC	110	77 (70.0)	22 (20.0)
Ustekinumab SC	109	74 (67.9)	17 (15.6)

Key: UST, Ustekinumab; SC, subcutaneous

4.2.6.2 Baseline characteristics of the CERTIFI trial population

The population baseline characteristics are summarised in Table 7. Detailed information on patient baseline characteristics was taken by the ERG from the appendices of Sandborn *et al.* [44]. Baseline data was provided on demographics, CD characteristics, disease site, medication use, and history of conventional and biologic medication use for CD. The authors concluded that demographic and baseline disease characteristics were balanced across each treatment arm, pointing out some noticeable but not statistically significant differences in baseline CDAI and median CRP between arms. The baseline characteristics were broadly similar to those of the UNITI-1 population, including a higher proportion of males in the placebo arm relative to the treatment groups (48.5% vs 36.6% for placebo and 6mg/kg UST respectively). This similarity would suggest that data from the induction phase of this trial should be included in analysis alongside the UNITI-1 data.

4.2.6.3 Study quality of the CERTIFI trial

The ERG assessed the quality of the CERTIFI study using the Cochrane risk of bias assessment tool in **Table 24** below. The ERG considers that the overall risk of bias was low; as the induction phase of the trial was conducted and reported in a similar manner to UNITI-1 and UNITI-2, there is the same possibility of bias as in those trials due to the way in which missing data was handled.

Table 24 Quality assessment of CERTIFI trial using Cochrane risk of bias tool

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	Patients randomised using adaptive randomisation procedure stratified by prognostic factors.
Allocation concealment	Low	Randomisation performed centrally via an IVRS.
Baseline comparability	Low	Patient characteristics were balanced across treatment groups, although the placebo arm had a considerably higher proportion of males than the treatment groups.
Blinding of participants and personnel	Low	Blinding of patients and investigators maintained until the conclusion of the study using identical placebos for each study arm.
Blinding of outcome assessment	Low	Investigators remained blinded throughout.
Incomplete outcome data	Unclear	All participants accounted for in results. Drop-outs generally balanced across treatment groups with reasons for withdrawal proportionally similar. Non-response assumed for missing data
Selective reporting	Low	Outcome measures reported are those stated in the study protocol.

4.2.6.4 Summary results of CERTIFI trial

Clinical effectiveness

The induction phase of the CERTIFI trial comprised three ustekinumab arms and a placebo arm. Key outcomes with associated RRs and 95% CIs calculated by the ERG for the 6mg/kg and placebo arms of the induction phase are summarised in Table 25. The UNITI-1 results are also presented for ease of comparison.

The induction phase efficacy results indicate that those randomised to receive 6mg/kg ustekinumab at week 0 were significantly more likely to achieve clinical response at week 6 than those randomised to placebo. Six-week CDAI-100 response in the 6mg/kg treatment arm of the CERTIFI trial (39.7%) is similar to that seen in the ~6mg/kg arm of the UNITI-1 trial at 33.7%.

Rates of clinical remission during induction did not differ significantly between the placebo group and ustekinumab group at week 6. This is likely to be due to the relatively high baseline CDAI scores in the patient population compared to UNITI-2 (CDAI of 302.2), particularly in the 6mg/kg group, which had a median baseline CDAI score of 333, similar to the mean CDAI of 327 seen in the UNITI-1 trial. This meant that a decrease in CDAI score of over 180 points was required for the majority of these patients to achieve remission by the 6 week endpoint. More severe disease in these trials' populations may be due to the more extensive treatment history required to have failed one or more biologics. The ERG concludes that participants randomised to the ustekinumab trial arm had a better chance of achieving improvement in their disease than those on placebo. As with UNITI-1, the ERG believes the follow-up period was potentially too short to properly assess ustekinumab induction treatment: in particular the 6 week primary endpoint is too soon, as is the 8 week assessment, and there is a suggestion that the proportion of patients achieving response and remission continues to increase between these time points.

Among patients with an induction response, reductions in mean CDAI scores and CRP levels were sustained in those who continued to receive ustekinumab maintenance therapy but were not sustained in those receiving placebo.

Table 25 Key induction phase outcomes

Outcome	Arm	Number of participants* (%)	Relative Risk and 95% CI*	UNITI-1 no. participants	Relative Risk and 95% CI*
CDAI-100 response at week 6[a]	Placebo	31/132 (23.5)		53/247 (21.5)	
	UST 6mg/kg	52/131 (39.7)	1.69 (1.16 to 2.46)	84/249 (33.7)	1.57 (1.17 to 2.11)
Clinical remission (CDAI <150) at week 6[b]	Placebo	14/132 (10.6)		22/247 (8.9)	Ref
	UST 6mg/kg	16/131 (12.2)	1.15 (0.59 to 2.26)	46/249 (18.5)	2.07 (1.29 to 3.34)
CDAI-70 response at week 6[b]	Placebo	38/132 (28.8)		75/247 (30.4)	
	UST 6mg/kg	62/131 (47.3)	1.64 (1.19 to 2.27)	109/249 (43.8)	1.44 (1.14 to 1.82)
CDAI-100 response at week 8[b]	Placebo	23/132 (17.4)			
	UST 6mg/kg	57/131 (43.5)	2.50 (1.64 to 3.80)		
Clinical remission (CDAI <150) at week 8[b]	Placebo	14/132 (10.6)		18/247 (7.3)	
	UST 6mg/kg	24/131 (18.3)	1.73 (0.94 to 3.19)	52/249 (20.9)	2.87 (1.72 to 4.75)

Key: *, calculated by ERG; [a] primary outcome; [b] secondary outcome; CDAI, CD activity index; UST, ustekinumab; NR, not reported.

Induction phase responders were pooled and re-randomised regardless of their induction dose of ustekinumab, and no maintenance phase results split by induction dose were made available; therefore the following results may not be as representative of what might be seen in patients given the licensed induction dose, as many received 1mg/kg and 3mg/kg induction doses.

Among those patients exhibiting a response to ustekinumab in the induction phase, a greater proportion of those re-randomised to 90mg SC ustekinumab maintained clinical response at each follow-up point up to week 22 of the maintenance phase than those re-randomised to placebo (55.6% vs 32.9%). Patients in clinical remission at week 6 were more likely to remain in remission until week 22 of the study if they were re-randomised to the 90mg ustekinumab group than when given placebo throughout the maintenance phase. Clinical response and clinical remission rates were significantly higher at 22 weeks in those patients treated with ustekinumab over placebo. There was a greater number of patients in glucocorticoid-free remission at week 22: the ERG calculated relative risk is 1.72 (95% CI 0.94 to 3.14). Further details of maintenance phase outcomes can be found in Table 26 below.

All participants who failed to achieve clinical response to ustekinumab during the induction phase had a similar rate of clinical response at week 22, regardless of whether they were re-randomised to placebo or ustekinumab (20.2% and 18.2% respectively).

Table 26 Key maintenance phase outcomes

	Arm	Number of participants (%)	Relative Risk and 95% CI*
CDAI-100 response at week 22	Placebo	31/73 (42.5)	
	UST 90mg SC	50/72 (69.4)	1.64 (1.20 to 2.22)
Sustained CDAI-100 response at week 22	Placebo	24/73 (32.9)	
	UST 90mg SC	40/72 (55.6)	1.69 (1.15 to 2.49)
Clinical remission (CDAI <150) at week 22	Placebo	20/73 (27.4)	
	UST 90mg SC	30/72 (41.7)	1.52 (0.96 to 2.42)
Sustained remission from week 6 to 22	Placebo	16/30 (53.3)	
	UST 90mg SC	22/28 (78.6)	1.47 (1.00 to 2.17)
Glucocorticoid-free clinical remission at week 22	Placebo	13/73 (17.8)	
	UST 90mg SC	22/72 (30.6)	1.72 (0.94 to 3.14)

Key: *, calculated by ERG; CDAI, CD activity index; UST, ustekinumab

4.2.7 Pairwise Meta-analysis

The CS stated that the trials that compared ustekinumab and placebo used different types of patients. Therefore, they decided against performing a pairwise meta-analysis. Although the ERG agrees with the CS's assumption that the UNITI-1 and UNITI-2 trial populations were too heterogeneous to be aggregated, it believes that data from the ~6mg/kg and 6mg/kg arms of UNITI-1 and CERTIFI trials could have been combined, as both had the same anti-TNFα failure populations and very similar designs. The ERG therefore conducted a meta-analysis of data from the two trials using a fixed effect model. Based on the aggregate results, those patients randomised to ustekinumab ~6mg/kg dosage achieved better outcomes than the placebo group, see Table 27 below. The I-squared (i^2) values for all the CDAI based outcomes were between 0 and 20% which suggests that the response rates in the UNITI-1 and CERTIFI trials were almost identical; see Table 27 below.

Table 27 Summary results of key outcomes in UNITI-1 and CERTIFI trials

		UNITI-1	CERTIFI	RR and 95% CI	X^2(p-value); i^2
Clinical (CDAI-100) response at week 6	Placebo	53/247(21.5)	31/132 (23.4)		
	UST ~6mg/kg	84/249 (33.7)	52/131 (39.7)	1.62 (1.28 to 2.04)	0.09 (0.77), 0%
Clinical (CDAI-100) response at week 8	Placebo	50/247 (20.2)	23/132 (17.4)		
	UST ~6mg/kg	94/249 (37.8)	57/131 (43.5)	2.05 (1.61 to 2.61)	1.25 (0.26); 20%
Clinical remission at week 8	Placebo	18/247 (7.3)	14/132 (10.6)		
	UST ~6mg/kg	52/249 (20.9)	23/131 (18.3)	1.68 (1.15 to 2.48)	0.01 (0.94); 0%
CDAI-70 response at week 6	Placebo	75/247 (30.4)	38/132 (28.8)		
	UST ~6mg/kg	109/249 (43.8)	62/131 (47.3)	1.56 (1.29 to 1.88)	0.16 (0.69); 0%

Key: CDAI , CD activity index; CI, confidence intervals; RR, relative risk; UST, ustekinumab

4.2.8 Adverse events of ustekinumab

Adverse events from UNITI-1

Based on the CSR's reported safety results (page 81-88 of the CSR), the proportions of subjects who had at least 1 adverse event were very similar across the treatment groups: 64.9% (159/245), 64.6% (159/246) and 65.9% (164/249) of participants in the placebo, 130 mg ustekinumab, and 6 mg/kg ustekinumab groups, respectively. The proportion of participants who had one or more serious adverse events was also not significantly different: 6.1% (15/245) in the placebo group compared with 4.9% (12/246) in the 130 mg ustekinumab group and 7.2% (18/249) in the 6 mg/kg ustekinumab group. There were no reported deaths during the follow-up period, see Table 28 below.

Table 28 Reported safety results of UNITI-1 trial at week 8

	AEs	SAEs	Infections	Serious infections	Withdrawal due adverse events	Malignancies	Death
Placebo (N=245)	159 (64.9%)	15 (6.1%)	58 (23.7%)	3 (1.2%)	14 (5.7%)	1 (0.8%)	0 (0.0%)
UST ~6mg/kg (N=249)	164 (65.9%)	18 (7.2%)	64 (25.7%	7 (2.8%)	7 (2.8%)	0 (0.0%)	0 (0.0%)

Adverse events from UNITI-2

Based on the CSR's reported safety results (page 81-88 of the CSR), the proportions of subjects who had at least one adverse event were very similar across the treatment groups: 54.3% (113/208), 50.5% (106/212) and 55.6% (115/207) of participants in the placebo, 130 mg ustekinumab, and 6 mg/kg ustekinumab groups, respectively. The proportion of participants who had one or more serious adverse events was also not significantly different: 5.8% (11/208) in the placebo group compared with

4.7% (10/212) in the 130 mg ustekinumab group and 2.9% (6/207) in the ~6 mg/kg ustekinumab group. There were no reported deaths during the follow-up period.

Table 29 Reported safety results of UNITI-2 trial at week 8

	AEs	SAEs	Infections	Serious infections	Withdrawal due to adverse events	Malignancies	Death
Placebo (N=208)	113 (54.3%)	12 (5.8%)	48 (23.1%)	3 (1.4%)	5 (2.4%)	0 (0.0%)	0 (0.0%)
UST ~6mg/kg (N=207)	115 (55.6%)	6 (2.9%)	45 (21.7%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)

Adverse events from CERTIFI

The CERTIFI trial reported safety results for the induction and maintenance phases separately. Based on the results, ustekinumab appears to have similar risk of adverse events during the follow up. For example, 11/132 (8.3%) and 9/131 (6.9%) of those who were randomised to placebo and ustekinumab ~6mg/kg, respectively, had at least one serious adverse event at the end of Week 8. See Table 30 for details.

Table 30 Reported safety results of CERTIFI trial

	AEs	SAEs	Infections	Serious infections	Malignancy
Induction phase (0-8 weeks)					
Placebo (N=132)	94 (71.2%)	11 (8.3%)	32 (24.2%)	1 (0.8%)	
UST 6mg/kg (N=131)	80 (61.1%)	9 (6.9%)	29 (22.1%)	5 (3.8%)	
Maintenance phase (8-36 weeks)*					
Placebo (N=183)	151 (71.2%)	33 (18.0%)	73 (39.9%)	7 (3.8%)	0 (0.0%)
UST 90mg (N=181)	140 (77.3%)	31 (17.1%)	71 (39.2%)	4 (2.2%)	1 (0.6)

Notes: patients came from three ustekinumab dosages (i.e. 1mg/kg, 3mg/kg, and 6mg/kg).

Adverse events from IM-UNITI trial

Based on the CSR's reported safety results (page 118-129 of the CSR), the proportions of subjects who had at least one adverse event were identical across the three groups. Two malignancies were reported. No death occurred during the 44 weeks of follow-up period, see Table 31.

.

Table 31 Reported safety results of IM-UNITI trial

	AEs	SAEs	Infections	Serious infections	Withdrawal due to adverse events	Malignancies	Death
Placebo (N=133)	111 (83.5%)	20 (15.0%)	66 (49.6%)	3 (2.3%)	8 (6.0%)	1 (0.8%)	0 (0.0%)
UST 90mg q8w(N=131)	107 (81.7%)	13 (9.9%)	63 (48.1%)	3 (2.3%)	4 (3.1%)	1 (0.8%)	0 (0.0%)
UST 90mg q12w (N=132)	106 (80.3%)	16 (12.1%)	61 (46.2%)	7 (5.3%)	10 (7.6%)	0 (0.0%)	0 (0.0%)

Summary of adverse events for ustekinumab

Results of the four trials show that the adverse event profile of ustekinumab is similar to that of placebo during the induction and maintenance phase follow-up.

4.2.9 Summary of trial evidence of the clinical effectiveness of ustekinumab for CD

Four well conducted placebo-controlled, double-blind RCTs provided data on the licensed dose of ustekinumab in CD. Three trials were of induction therapy (single dose of ~6mg/kg followed for 8 weeks (dose in CERTIFI was exactly 6mg/kg)): two trials were of a population who had failed anti-TNFαs (UNITI-1 and CERTIFI), one was of patients who had failed conventional care (UNITI-2). One trial was of maintenance therapy treatment (up to one year) and investigated the effect of treatment withdrawal in those who had responded to ustekinumab induction (conventional care and anti-TNFα failures combined)(IM-UNITI).

Based on the short term clinical effectiveness results, ustekinumab appears to be more effective than placebo in terms of clinical response and remission in both the conventional care failure and anti-TNFα failure populations. The ERG calculated Relative Risks and 95% CI for Clinical (CDAI-100) response at week 6 were: UNITI-1 1.57 (1.17 to 2.11); UNITI-2 1.93 (1.51 to 2.47); and CERTFI 1.69 (1.16 to 2.46). The Relative Risks and 95% CI for clinical remission (CDAI <150) at week 6 were: UNITI-1 2.07 (1.29 to 3.34); UNITI-2 1.97 (1.40 to 2.79); and CERTIFI 1.15 (0.59 to 2.26). Endoscopic response outcomes were also more likely to be achieved by those patients randomised to ustekinumab over placebo in UNITI-1 and -2, with a greater change in SES-CD score from baseline, and a higher chance of endoscopic remission at week 8. Differences in inflammatory biomarker levels between ustekinumab and placebo weresignificant; patients randomised to ~6mg/kg ustekinumab in the UNITI-1 and UNITI-2 trials had a greater reduction of CRP levels at 8 weeks (UNITI-1: PLA +3.30 vs UST -5.55; UNITI-2: PLA -0.14 vs UST -8.56).

The results of IM-UNITI indicate that around half of patients who respond to ustekinumab are in clinical remission at Week 44. A higher proportion of patients randomised to the two ustekinumab dosages (UST 90mg every 8 weeks or 12 weeks) retained their responder status and a higher proportion were in remission at Week 44 than those randomised to placebo (53%, 49% and 36% respectively). Further long-term data demonstrate that 45% of ustekinumab responders were in clinical remission on ustekinumab q8w or q12w at week 92. In comparison only 16.5% of those ustekinumab responders withdrawn from treatment were in remission at week 92, demonstrating the need for retreatment in most patients. IM-UNITI patients on ustekinumab q8w at week 44 appear to have improved endoscopic outcomes over both placebo and the q12w group, whose outcomes were comparable to placebo. Given the chronic progressive nature of CD, further, longer-term data on response are required.

The data indicate that the placebo response in CD is substantial. The proportion of placebo responders to induction was high (22% in anti-TNFα failure patients and 29% conventional care failure patients). The results of the follow-up of placebo responders from UNITI-1 and -2 also indicate that placebo response can be sustained. Of the placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% achieved clinical response (CDAI-100) and 48% achieved clinical remission at one year. At 44 weeks 12% of all those randomised to placebo were in remission.

The results of the four trials show that the adverse event profile of ustekinumab is similar to that of placebo during the induction and maintenance phase follow-up. Data on adverse effects in long term are lacking.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1 Search strategy

The CS's literature search for the indirect multiple treatment comparison/network meta-analyses (NMA) section was part of the overall search strategy which is described in Section 4.1.

4.3.2 Study selection

The study selection criteria were presented in Table 9, page 56 of the CS. In brief, studies that investigated short-term (induction phase) and long-term (maintenance phase) effectiveness of biologics in moderate to severe CD patients were included. All biologic therapies licensed by the EMA for CD were considered. A total of 13 studies were found eligible for inclusion in the NMA analysis presented in the CS, with 9 studies included in the induction stage analysis and all 13 studies in a longer term analysis including the induction and maintenance phase data. The CERTIFI trial

discussed earlier was not used consistently in the NMA. This is discussed further in Section 4.4.1. Further discussion and critique of the trials included in the NMA analyses presented in the CS are presented in Section 4.4.

4.3.3 Quality of the studies included in the NMA

The company conducted a quality assessment of the studies (Table 9 on Page 54 of CS Appendices) although it is not clear which risk of bias assessment tool was used, the quality assessment included non-relevant studies and did not include the trials identified in the updated searches. The ERG therefore conducted its own assessment of the studies included in the NMA using the Cochrane risk of bias assessment tool. These are presented in Appendix 10.1. Note that risk of bias assessments for UNITI-1, UNITI-2, IM-UNITI and CERTIFI are reported in Section 4.2.

Based on the assessment results, the ERG considers that the induction phase studies included were, on average, good quality trials. The only significant issue raised by the risk of bias assessment relates to the handling of missing data which was not well reported: in three trials it was not clear, in the GAIN trial (adalimumab) missing assessments were classed as non-response.

In the CS the Targan 1997 trial of infliximab is particularly criticised for this issue (as well as it being a 'small and relatively old phase II study'(CS page 121); this is based on a FDA memorandum.

The CS also criticises the Targan 1997 trials for reporting a lower treatment effect with the higher doses of infliximab: this would suggest the lack of a dose response effect at the doses investigated (which is reflected to some extent in the ustekinumab results). The CS also states that the induction results reported in Targan 1997 were not corroborated by the induction phase of ACCENT-1. The ERG found from the published papers the CDAI-70 response rates in the two studies to be 81% and 58%, i.e. statistically different.

The maintenance trials (or phases of trials) were randomised withdrawal studies, i.e. they all addressed the question of how responders to active treatment fare if treatment is withdrawn (or not). As such they were all good quality trials, although the ERG has identified some issues in the risk of bias assessment. Firstly, in the ACCENT (infliximab), and CHARM (adalimumab) studies, blinding of patients, personnel, and assessors was broken as the trials allowed for some participants to be switched over to alternative treatment if they lost response during the follow-up period. However, this was not the case in the IM-UNITI (ustekinumab) study, where blinding was preserved in the event of dose adjustment upon loss of response. Secondly, in the CHARM study, patients without CDAI assessments at weeks 26 or 56 were classified as remission failures, and in the ACCENT study it was unclear how missing data was handled, as no information was presented in the trial's publication.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Two sets of NMA analyses were conducted: one of induction phase data, and one combining induction phase and maintenance phase data (the treatment sequence analysis). In line with the scope, separate analyses were conducted for the conventional care failure and anti-TNFα failure subpopulations. NMAs were conducted for three outcomes (CDAI-70, 100 and <150). The CDAI -70 and CDAI<150 were reported in all the studies. Some studies did not report CDAI-100 and were not included in NMA for this outcome. Standard analyses were conducted within a Bayesian framework, preserving the randomisation of each trial. The relative goodness of fit of the models was assessed using the Deviance Information Criterion (DIC). All analyses were performed in WinBUGS V1.4 using the MCMC (Markov Chain Monte Carlo) simulation method. The details of the methods adopted in this evidence synthesis by the company were presented in the CS (Appendix 5 page 73-93). The ERG believes appropriate methods were implemented.

4.4.1 Induction phase

The induction phase analysis used data from the relevant induction trials identified in the systematic literature review. These are summarised in Table 28.

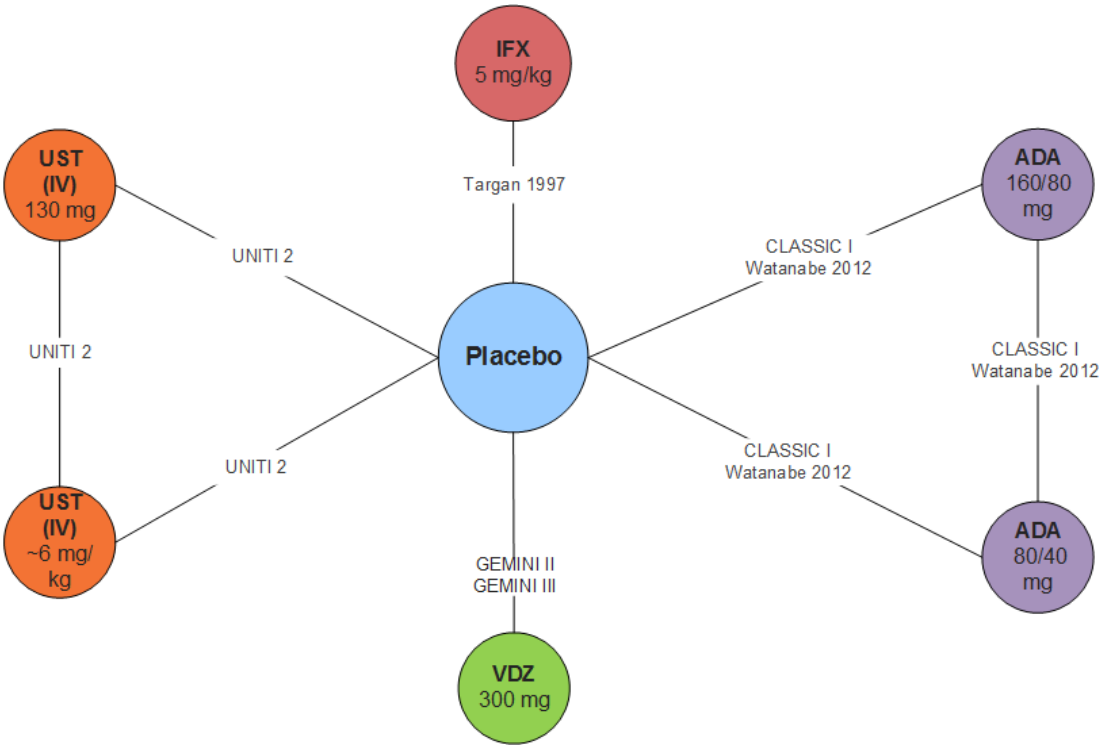
Table 32 List of included studies in induction phase NMA

Trial	Subpopulation	Intervention	Trial length	BCA time point selected (weeks)	Included in BCA
Targan 1997 [14]	Conventional care failure	Infliximab	Week 4	4	Yes
CLASSIC I[15]	Conventional care failure	Adalimumab	Week 4	4	Yes
Watanabe 2012[16]	Conventional care failure and TNF failure	Adalimumab	Week 4	4	Yes
GAIN [17]	TNF failure	Adalimumab	Week 4	4	Yes
GEMINI II[10]	Conventional care failure and TNF failure	Vedolizumab	Week 6	6	Yes
GEMINI III [18]	Conventional care failure and TNF failure	Vedolizumab	Week 10	6	Yes
UNITI-1[19]	TNF failure	Ustekinumab	Week 8	6	Yes
UNITI-2[20]	Conventional care failure	Ustekinumab	Week 8	6	Yes
CERTIFI [21]	TNF failure	Ustekinumab	Week 8	6	No
Key: BCA, base case analysis; TNF, tumour necrosis factor.					

The network used in the NMA analysis for the conventional care failure population is presented in Figure 3 and for the anti-TNFα failure group in Figure 4. There were no head-to-head comparisons of

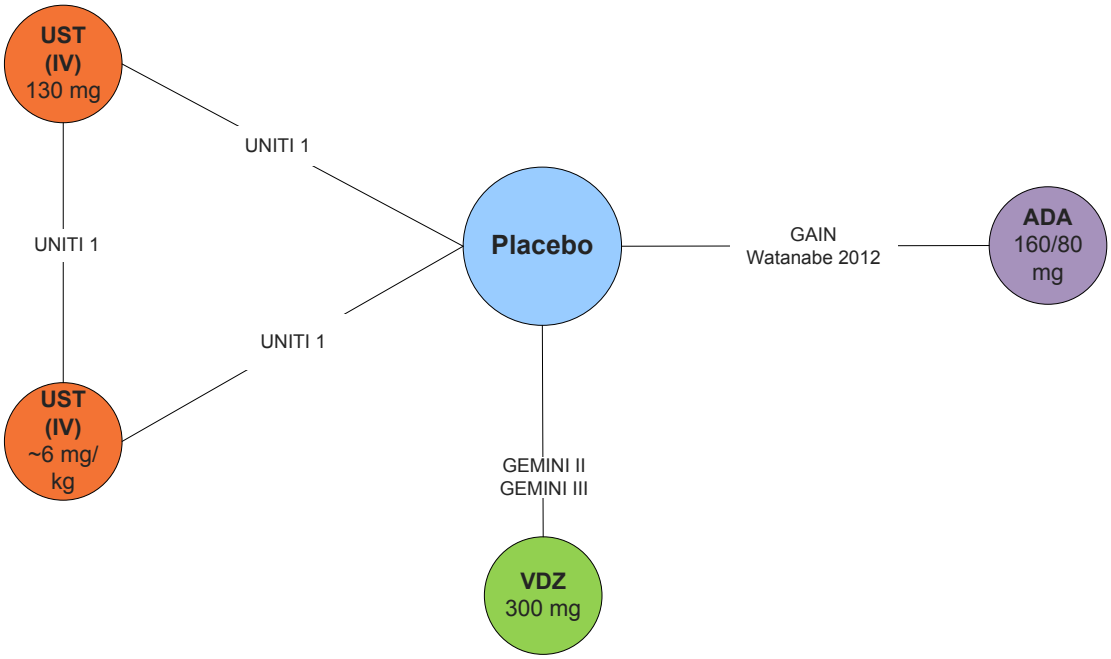
biologic therapies and therefore the network was established via the placebo arm of each of the induction trials. The feasibility of pooling data was evaluated by considering the comparability of the following potential treatment effect modifiers: duration of disease, CDAI score at baseline, CRP concentration and fistula at baseline, and administration of concomitant/allowed therapies.

Figure 3: Network for the induction NMA – conventional care failure



Key: ADA, adalimumab; IFX, infliximab; IV, intravenous; UST, ustekinumab; VDZ, vedolizumab.

Figure 4: Network for the induction NMA – anti-TNFα failure



Key: ADA, adalimumab; IV, intravenous; UST, ustekinumab; VDZ, vedolizumab.

ERG Comments on induction phase NMA

The ERG has a number of concerns regarding the NMA analysis carried out for the induction phase, these included concerns regarding the comparability of the included trials, and the trials included in the analysis.

Comparability of trials in induction phase NMA

The ERG is largely satisfied that the trials included in the NMA are comparable in terms of the baseline treatment effect modifiers. However, the ERG is concerned about the variability in the time at which clinical outcomes were assessed, being 4 weeks for infliximab and adalimumab, and 6 weeks for vedolizumab and ustekinumab. Assessing response at a later time point in vedolizumab and ustekinumab may make these treatments appear more effective than if they had been assessed at the earlier time point. Also, the response in infliximab and adalimumab may have continued to increase over those two weeks. This difference is assessment time is unlikely to reflect clinical practice, where assessment of response is actually unlikely to differ substantially between biologic treatments. The ERG, however, acknowledge that there are limited data available and consider the analysis carried out by the company to the most appropriate.

With respect to the conventional care failure population the ERG is concerned that there are differences in previous anti-TNFα treatment history across the trials: a significant proportion of participants in the UNITI-2 trial had a history of anti-TNFα treatment [22] whilst in the other

conventional care failure trials all patents were truly anti-TNFα naïve (see table 12 of the appendices part of the CS).

With respect to the anti-TNFα failure population there are also differences in the treatment history of the patients recruited. In the GAIN trial [17] only secondary anti-TNFα failure patients were recruited i.e. patients who had failed anti-TNFα following initial response. In at least four of the other trials included in the NMA both primary and secondary anti-TNFα failure patients were included[10, 17, 19, 21]. The composition of the patient population in terms of primary and secondary anti-TNFα failures was unclear in the GEMINI III trial [18].The anti-TNFα failure population from the adalimumab Watanabe trial[16] comprised anti-TNFα experienced patients but who had not necessarily failed an anti-TNFα.

Trials included in NMA

The ERG notes that although the CERTIFI Phase II trial was listed in the table of included trials it was not included in the base-case induction phase NMA. The CS justified the decision to exclude this trial because the company considered that the fixed 6 mg/kg dose adopted in the CERTIFI trial was not comparable to licensed induction dose of approximately 6mg/kg, as adopted in UNITI-1 and UNITI-2. The ERG however considers that this minor difference is not substantial enough to warrant its exclusion from the NMA, as all trials included patients receiving a dose of approximately 6mg/kg. The ERG also note that the exclusion of the CERTIFI trial is somewhat inconstant with the long term NMA (treatment sequence analysis) which included the CERTIFI trial. The ERG therefore reran the NMA in which CERTIFI is included in Section 4.6. We also include the results of this re-analysis in to the economic model to consider it impact on the cost-effectiveness of ustekinumab (Section 6).

The ERG notes that the data for vedolizumab are included in the conventional care failure analysis despite this treatment not being recommended by NICE in this population. However, in terms of the methods for conducting a NMA, this is methodologically appropriate.

Table 33 Studies included in the induction phase NMA

Study name	Treatment	Clinical effectiveness outcome reported
Conventional care failure		
Targan 1997 [14]	Infliximab	CDAI-70 & CDAI<150
CLASSIC I [15]	Adalimumab	CDAI-70, CDAI-100 & CDAI<150
Watanabe 2012 [16]	Adalimumab	CDAI-70, CDAI-100 & CDAI<150
GEMINI II [10]	Vedolizumab	CDAI-70, CDAI-100 & CDAI<150
GEMINI III [18]	Vedolizumab	CDAI-70, CDAI-100 & CDAI<150
UNITI-2 [22]	Ustekinumab	CDAI-70, CDAI-100 & CDAI<150
Anti-TNFα failure		
GAIN [17]	Adalimumab	CDAI-70, CDAI-100 & CDAI<150
Watanabe 2012 [16]	Adalimumab	CDAI-70, CDAI-100 & CDAI<150
GEMINI II [10]	Vedolizumab	CDAI-70, CDAI-100 & CDAI<150
GEMINI III [18]	Vedolizumab	CDAI-70, CDAI-100 & CDAI<150
UNITI-1 [19]	Ustekinumab	CDAI-70, CDAI-100 & CDAI<150
CERTIFI [21]	Ustekinumab	CDAI-70, CDAI-100 & CDAI<150

Key: BCA, base case analysis; CDAI, CD activity index; TNF, tumour necrosis factor.

4.4.2 Long-term (Treatment Sequence) analysis

The CS notes that the analysis of the long-term effectiveness of biologic therapies in CD is subject to a number of methodologic challenges as the trial data available do not directly address the research question, nor are they directly comparable across trials. This issue primarily stems from the fact that the patients enrolled in the maintenance phases (or trials) were responders to active treatment and furthermore, had responded to different active treatments (ustekinumab, adalimumab, infliximab or vedolizumab). Furthermore, the placebo arm in the maintenance phase is a 'withdrawal' arm to investigate the effect of active treatment withdrawal from induction responders. Given this problem, the company argue in the CS that a standard NMA would not be appropriate to analyse the long-term effectiveness of biologic therapy, and presented supporting evidence on the substantial heterogeneity between maintenance trials as justification for this. The ERG considers this argument reasonable and accepts that a traditional NMA of the maintenance phase trials would be inappropriate given their design.

As an alternative to a standard NMA the company proposed the use of what it termed a 'treatment sequence' analysis. The purpose of the treatment sequence analysis is to combine the induction phase

and the maintenance phase whilst addressing the issue that different induction treatments regimens were received by patients enrolled in the maintenance trials (i.e. that patients had responded to different biologics) and the lack of comparability of the placebo arms. The central concept of the treatment sequence analysis is that outcomes in the maintenance phase are not considered in absolute terms, but rather are considered conditional on response to treatment in the induction phase. The treatment sequence analysis also makes use of a number of adjustments to the placebo data to make it more comparable and therefore to reduce heterogeneity. Details of how the inputs for the treatment sequence analysis are calculated are described below.

Active treatment inputs

The treatment sequence analysis focuses on the outcomes remission (defined as patients achieving a CDAI<150) and response (defined as patients achieving a drop in CDAI <100 or more). To calculate the rate of remission in the treatment sequence analysis the % responders at the end of the induction phase was multiplied by the % remitters (CDAI<150) at the end of the maintenance phase. To calculate the rate of response the % responders at the end of the induction phase was multiplied by the % responders (CDAI-100) at the end of the maintenance phase. It should be noted that the induction response rate used in this calculation was defined with respect to a 70 points drop rather than a 100 point drop, as CDAI-100 was not reported for infliximab.

Placebo treatment inputs

Placebo treatment inputs were calculated in a similar fashion to those from the active treatment arms by multiplying the response rate at induction by the response/remission rate at the end of maintenance. There are however, two important points to note. Firstly, the placebo maintenance data for all biologic therapies used to perform the adjustment (A and C in the formula below) is sourced from the non-randomised placebo patients from IM-UNITI, i.e. the patients who were randomised to placebo in UNITI-1 or -2 trials and had responded to placebo, and therefore remained on placebo throughout follow-up. They are **not** the placebo patients in the randomised comparison with ustekinumab. Secondly, this data is adjusted for the proportion of responders who achieve remission based on the response and remission rates in the relevant induction trials. Table 34 gives details of the formula used to generate the response and remission rates in the treatment sequence together with an example.

Table 34 Simplified form of the manufacturer's formula for generating placebo response rate for the maintenance phase – Weighted Maintenance Placebo response rate

Weighted Maintenance Placebo response rate	=	$\frac{\mathbf{(A \times B) + (C \times D)}}{\mathbf{(B+D)}}$

Where

A is the placebo response rate at the end of 1 year follow-up for those who were placebo responder non-remitters at the end of induction (originated from UNITI-1 or UNITI-2 trials);

B is the proportion of placebo responder non-remitters in the induction phase from each of the active comparator NMA trials;

C is the placebo response rate at the end of 1 year follow-up for those who were placebo remitters at the end of induction phase (originated from UNITI-1 or UNITI-2 trials);

D is the proportion of remitters in the induction phase from each of the active comparator NMA trials.

Note: **Responders rate** =proportion of participants with CDAI ≥100

Remitters rate= proportion of participants with CDAI<150

Responder non-remitters rate= responders rate – remitters rate

Key: †, conventional care failure and anti-TNFα failure response rate are calculated separately.

Table 35 lists the data sources for the treatment sequence analysis (adapted from table 3 of company clarification document).

Table 35 Treatment Sequence analysis data sources

Treatment	Induction phase data source	Maintenance phase data source	Subpopulation
Placebo-Placebo	CLASSIC I and Watanabe pooled data	IM-UNITI adjusted using CLASSIC I and Watanabe	Conventional care failure
Adalimumab 160 80 - adalimumab 40 eow	CLASSIC I and Watanabe pooled data	CHARM	Conventional care failure
Adalimumab 160 80 - adalimumab 40 weekly	CLASSIC I and Watanabe pooled data	CHARM	Conventional care failure
Placebo-placebo	Targan 1997	IM-UNITI adjusted using Targan 1997	Conventional care failure
Infliximab 5	Targan 1997	ACCENT I	Conventional care failure
Infliximab 5 & 10	Targan 1997	ACCENT I	Conventional care failure
Placebo-placebo	UNITI II	IM-UNITI adjusted using UNITI II	Conventional care failure
Ustekinumab 6 - ustekinumab 90 q12w	UNITI II	IM-UNITI	Conventional care failure
Ustekinumab 6 - ustekinumab 90 q8w	UNITI II	IM-UNITI	Conventional care failure
Placebo-placebo	GEMINI II and GEMINI III pooled data	IM-UNITI adjusted using GEMINI II and GEMINI III	Conventional care failure
Vedolizumab 300 - vedolizumab 300 q8w	GEMINI II and GEMINI III pooled data	GEMINI II	Conventional care failure
Vedolizumab 300 - vedolizumab 300 q4w	GEMINI II and GEMINI III pooled data	GEMINI II	Conventional care failure
Placebo-placebo	GEMINI II and GEMINI III pooled data	IM-UNITI adjusted using GEMINI II and GEMINI III	TNF failure
Vedolizumab 300 - vedolizumab 300 q8w	GEMINI II and GEMINI III pooled data	GEMINI II	TNF failure
Vedolizumab 300 - vedolizumab 300 q4w	GEMINI II and GEMINI III pooled data	GEMINI II	TNF failure
Placebo-placebo	UNITI I and CERTITI pooled data	IM-UNITI adjusted using UNITI I and CERTIFI	TNF failure
Ustekinumab 6 - ustekinumab 90 q12w	UNITI I and CERTITI pooled data	IM-UNITI	TNF failure
Ustekinumab 6 - ustekinumab 90 q8w	UNITI I and CERTITI pooled data	IM-UNITI	TNF failure
Placebo-placebo	GAIN and Watanabe pooled data	IM-UNITI adjusted using GAIN and Watanabe	TNF failure
Adalimumab 160 80 - adalimumab 40 eow	GAIN and Watanabe pooled data	CHARM	TNF failure
Adalimumab 160 80 - adalimumab 40 weekly	GAIN and Watanabe pooled data	CHARM	TNF failure

ERG Comment

The ERG has identified a large number of issues with the treatment sequence analysis presented by the company. These issues concern the comparability of the included trials; the methods used to generate a control arm used for infliximab, adalimumab and vedolizumab; the response rate data used;

quality assurance and validity of presented analyses; and interpretation of the treatment sequence analyses by the company. These issues are discussed in turn below.

Comparability of the included trials

The ERG has several concerns regarding the comparability of the trials include in the treatment sequence NMA. Most of these are those of the induction phase trials detailed earlier in Section 4.4.1: the length of induction phase follow-up period and the types of anti-TNFα patients they enrolled. In addition, the maintenance trials varied in terms of re-randomisation criteria: the adalimumab (CHARM [23]), infliximab (ACCENT I [24]) and vedolizumab (GEMINI II [10]) trials used a CDAI-70 response whilst ustekinumab IM-UNITI [25] trial used CDAI-100 as an inclusion criterion.

Methods used to generate a control arm

A key part of the treatment sequence analysis presented by the company is the reliance on the placebo-placebo UNITI-1, UNITI-2 and IM-UNITI data to provide a control arm for all biologics. The use of the UNITI trials' data in this way has substantial implications. Primarily, it removes the randomised placebo from the maintenance trials of infliximab, adalimumab and vedolizumab and replaces them with an historical control. Therefore the analysis is not based on randomised comparisons and there is a risk of confounding due to differences in setting, treatments received and severity of disease. The extent that these differences are prognostic will influence the corresponding performance of the placebo arm and undermine the reliability of the presented treatment sequence analysis. It is very difficult to quantify these differences, but no attempt was made to adjust for them. The ERG considers that caution should be taken in interpreting the present analyses due to the potential for unobserved confounding. Note this issue does not affect the comparison of ustekinumab and placebo which relies on the randomisation in the relevant induction trial.

In addition, the ERG notes that the placebo response rate was higher in ustekinumab trials than in the trials of anti-TNFαs, particularly infliximab and adalimumab (see Figure 18 page 58, appendices of the CS). Therefore, after adjustment, the placebo rates of the other biologics will be higher than the ustekinumab trials' comparators. This means that in the treatment sequence analysis the effectiveness of the other biologics relative to placebo will be diminished and the relative effectiveness of ustekinumab will be increased.

Response rate data

The ERG note that in the treatment sequence analysis, the type of active treatment response rates utilised in the model were inconsistent (a mixture of CDAI-70) and CDAI-100 (Figure 30 page 131 of the CS): the CS stated that the induction data were based on the CDAI-70 and the maintenance data were based on CDAI-100 and CDAI≤150. These two data were then aggregated (i.e. response rates

multiplied) during the treatment sequence analysis. In addition, when the maintenance placebo response rates for each of the trials were imputed, the induction CDAI scores used were not consistent across the trials (e.g. CDAI-70 for infliximab and CDAI-100 for ustekinumab).

The ERG noted that in the treatment sequence analysis, the type of active treatment response rates utilised in the model were consistent across the trials (see figure 30 page 131 of the CS). ITT response rates were used for all trials, including ustekinumab trials.

In the generation of inputs for the treatment sequence NMA, multiple trials of a single biologic were aggregated by simply adding the numbers or proportions of responses of the trials (e.g. simple pooling of UNITI-1 and CERTIFI induction data) prior to doing the NMA. The ERG notes that this approach ignores any heterogeneity between the trials of the same biologic and is methodologically incorrect; data from each of the trials should have been input separately and the overall response rate (or treatment effect) for each of the biologics should have been estimated by the model.

Quality assurance and validity issues

The resources and time available to the ERG did not permit the ERG to carry a thorough and complete assessment of all of the inputs included in the treatment sequence analysis, but the ERG were able to carry out a limited check on some of the inputs used. This limited quality assurance exercise identified a number of inputs for treatment sequence analysis for TNF failure population which the ERG could not replicate. The ERG found some differences in the rates of response and remission for vedolizumab, ustekinumab and placebo-placebo. Details of all differences between the ERG and company inputs are provided in appendix 10.2. Given these differences, the ERG considers that the analysis presented by the company may be unreliable. Unfortunately, given the time and resource required to do a complete validation of the NMA inputs, the ERG could not provide an alternative version of the treatment sequence analyses.

Interpretation of the treatment sequence analyses

The ERG has some concerns about how the company interpret the treatment sequence analysis. Specifically, the ERG wants to make it clear what the treatment sequence analysis does and does not represent. The treatment sequence analysis is not a maintenance phase analysis because the outcomes are conditional on response in induction, and therefore relative effectiveness is dependent upon effectiveness during both induction and maintenance. Furthermore, the analysis also does not represent relative effectiveness of the compared treatments over one year i.e. a trial where patients are randomised to either treatment or placebo at initiation of treatment and then followed up for the

period of year regardless of response at induction. This is because no data on non-responders to induction therapy are included in the analysis. What the treatment sequence does do is compare the outcomes of patients over the maintenance period conditional on the likelihood of achieving response. This gives a sense of the relative effectiveness of the compared treatments over the period of one year, but as stated does not give the true relative effectiveness of the compared treatments over a year. This distinction is not necessarily important when considering the relative performance of the alternative therapies from a clinical perspective as we are interested in how often patients achieve response at induction and how responders perform during maintenance therapy, both of which are accounted for in the presented treatment sequence analysis. This distinction, however, has much greater significance when attempting to utilise this analysis to populate an economic model. This issue is therefore discussed further in Section 5.2.7, but is raised here to ensure it is clear what the treatment sequence analysis is actually representing.

In summary, due to the reasons that have been highlighted above, the ERG considers that the results based on the treatment sequence analysis to be potentially unreliable and the ERG have significant concerns about how they have been interpreted particularly with respect to the economic model (see section 5.2.6 for further discussion).

4.4.3 Results of NMA of included studies

Induction phase

The company presented an overall summary of all NMA analyses it conducted for the conventional care failure and anti-TNFα failure populations based on different outcomes categories (Figure 32-33 page 135-136 of the main CS, and Figure 28-29, page 77-78 of the appendices of the CS).

The results presented in the CS are presented in Table 32, which also includes the vs placebo results which the company provided in their clarification response letter. The ERG re-ran a fixed effects model for these conventional care failure data and the results agreed with the CS. The company also included a sensitivity analysis excluding the infliximab data; this had little effect on the results for the other comparators. The ERG compared the vs placebo results for ustekinumab generated by the NMA and these reflect well the actual direct results from the trials of the biologics (See Table 37 below) and support the reliability of the induction phase NMA.

In the conventional care failure population, the clinical effectiveness of the ustekinumab ~6mg/kg was comparable with the other biologics across the response/remission outcomes (CDAI-70, CDAI-100 and CDAI<150 scores). Infliximab appeared the most effective, although the results for infliximab are based on only a single small trial. Vedolizumab was the least effective biologic in the conventional care failure population (Note NICE Guidance does not recommend its use in this population). The

SUCRA plots submitted by the company after request by the ERG also strongly support the results (see figure 4 page 29 of Janssen's points for clarification).

Table 36 Summary of NMA (relative treatment effects) results of biologics in the conventional care failure population—CS results

	CDAI-70	CDAI-100	CDAI<150
	Median OR (95 % CrI)	Median OR (95 % CrI)	Median OR (95 % CrI)
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	1.58 (0.85 to 2.94)	1.85 (0.96 to 3.51)	0.93 (0.39 to 2.08)
Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.92 (0.43 to 1.91)	1.03 (0.47 to 2.20)	0.64 (0.25 to 1.53)
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	0.98 (0.46 to 2.05)	1.39 (0.64 to 2.97)	1.14 (0.44 to 2.82)
Ustekinumab 6 mg/kg vs. Infliximab 5 mg/kg	0.11(0.02 to 0.48)	NA	0.08(0.01 to 0.59)
Ustekinumab 6 mg/kg vs. Placebo	2.89 (1.95 to 4.32)	3.12(2.08 to 4.68)	2.50 (1.60 to 3.98)
Vedolizumab 300 mg vs. Placebo	1.83(1.14 to 2.95)	1.69(1.02 to 2.84)	2.69 (1.38 to 5.59)
Adalimumab 160/80 mg vs. Placebo	3.15 (1.70 to 5.94)	3.03 (1.60 to 5.89)	3.92 (1.86 to 8.95)
Adalimumab 80/40 mg vs Placebo	2.94 (1.59 to 5.55)	2.25 (1.18 to 4.34)	2.2 (1.00 to 5.17)
Infliximab 5 mg/kg vs. Placebo	25.8 (6.50 to 136.10)	NA	31.34 (4.50 to 963.60)

Key: CDAI, CD Activity Index; CrI, credible interval; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; TNF, tumour necrosis factor; vs. versus

Table 37 Summary of ustekinumab induction trial results – Direct trial results and NMA results

	Treatment	CDAI-70 Median OR (95% CrI)	CDAI-100 Median OR (95% CrI)	CDAI<150 Median OR (95% CrI)
CCF				
NMA induction ADA	ADA 160/80	3.15 (1.70 to 5.94)	3.03 (1.60 to 5.89)	3.92 (1.86 to 8.95)
CLASSIC I*	ADA 160/80	2.52 (1.31 to 4.89)	2.89 (1.45 to 5.76)	3.98 (1.72 to 9.22)
Wanatabe 2012*	ADA 160/80	14.67 (1.97 to 109.21)	4.00 (0.62 to 25.97)	3.00 (0.46 to 19.59)
NMA induction ADA	ADA 80/40	2.94 (1.59 to 5.55)	2.25 (1.18 to 4.34)	2.2 (1.00 to 5.17)
CLASSIC I*	ADA 80/40	2.47 (1.28 to 4.78)	1.93 (0.96 to 3.87)	2.28 (0.95 to 5.47)
Wanatabe 2012*	ADA 80/40	10.00 (1.44 to 69.26)	5.33 (0.82 to 34.83)	1.6 (0.23 to 11.08)
NMA induction INF	INF 5	25.8 (6.50 to 136.10)	NR	31.34 (4.50 to 963.60)
Targan 1997*	INF 5	22 (5.17 to 93.56)	NR	21.36 (2.51 to 181.48)
NMA induction UST	UST 6	2.89 (1.95 to 4.32)	3.12 (2.08 to 4.68)	2.50 (1.60 to 3.98)
UNITI-2*	UST 6	2.89 (1.94 to 4.29)	3.10 (2.07 to 4.65)	2.50 (1.58 to 2.93)
NMA induction VDZ	VDZ 300	1.83(1.14 to 2.95)	1.69(1.02 to 2.84)	2.69 (1.38 to 5.59)
GEMINI II*	VDZ 300	1.87 (1.04 to 3.38)	1.50 (0.80 to 2.80)	2.17 (0.87 to 5.43)
GEMINI III*	VDZ 300	1.71 (0.77 to 3.80)	2.04 (0.87 to 4.82)	3.35 (1.19 to 9.47)

Anti-TNFαα failure				
NMA induction ADA	ADA 160/80	2.16 (1.41 to 3.32)	2.02 (1.28 to 3.20)	3.65 (1.90 to 7.38)
GAIN*	ADA 160/80	2.09 (1.34 to 3.27)	1.90 (1.18 to 3.05)	3.49 (1.73 to 7.02)
Wanatabe 2012*	ADA 160/80	2.74 (0.64 to 11.75)	4.00 (0.69 to 23.26)	1.47 (0.23 to 9.49)
NMA induction ADA	ADA 80/40	1.29 (0.38 to 4.40)	0.66 (0.18 to 2.34)	2.24 (0.36 to 20.32)
Wanatabe 2012*	ADA 80/40	1.60 (0.39 to 6.62)	4.50 (0.79 to 25.78)	1.33 (0.11 to 16.39)
NMA induction UST	UST 6	1.79 (1.24 to 2.60)	1.87 (1.26 to 2.80)	2.34 (1.37 to 4.08)
NMA induction UST (ERG + CERTIFI)	UST 6	1.93 (1.43 to 2.61)	1.96 (1.43 to 2.71)	1.86 (1.21 to 2.92)
UNITI-1*	UST 6	1.79 (1.23 to 2.58)	1.86 (1.25 to 2.79)	2.32 (1.35 to 3.99)
CERTIFI*	UST 6	2.22 (1.34 to 3.70)	2.14 (1.26 to 3.66)	1.17 (0.54 to 2.51)
NMA induction VDZ	VDZ 300	1.86 (1.29 to 2.72	1.79 (1.20 to 2.70)	1.53 (0.87 to 2.76)
GEMINI II*	VDZ 300	1.36 (0.71 to 2.62)	1.05 (0.52 to 2.16)	2.61 (0.70 to 9.73)
GEMINI III*	VDZ 300	2.14 (1.35 to 3.38)	2.25 (1.37 to 3.69)	1.30 (0.68 to 2.48)

*ERG calculated ORs

The NMA results for the anti-TNFα failure population were also re-run by the ERG and these agree with those in the CS (Table 34).

Table 38 Summary of NMA (relative treatment effects) results of biologics in the anti-TNFα failure population—CS results without CERTIFI trial

	CDAI-70	**CDAI-100**	**CDAI<150**
	Median OR (95 % CrI)	**Median OR (95 % CrI)**	**Median OR (95 % CrI)**
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	0.96 (0.57 to 1.62)	1.05 (0.59 to 1.85)	1.53 (0.69 to 3.39)
Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.83 (0.47 to 1.46)	0.93 (0.51 to 1.70)	0.64 (0.26 to 1.51)
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	1.29 (0.38 to 4.40)	0.66 (0.18 to 2.34)	2.24 (0.36 to 20.32)
Ustekinumab 6 mg/kg vs. Placebo	1.79 (1.24 to 2.60)	1.87 (1.26 to 2.80)	2.34 (1.37 to 4.08)
Vedolizumab 300 mg vs. Placebo	1.86 (1.29 to 2.72)	1.79 (1.20 to 2.70)	1.53 (0.87 to 2.76)
Adalimumab 160/80 mg vs. Placebo	2.16 (1.41 to 3.32)	2.02 (1.28 to 3.20)	3.65 (1.90 to 7.38)
Adalimumab 80/40 mg vs Placebo	1.38 (0.43 to 4.49)	2.84 (0.85 to 9.90)	1.05 (0.12 to 6.16)

Key: CDAI, CD Activity Index; CrI, credible interval; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; Pr, probability; TNF, tumour necrosis factor; vs. versus

Based on the findings, ustekinumab ~6mg/kg was the second best in all the outcomes (CDAI-70, CDAI-100 and CDAI <150 scores) – note that infliximab was not included in this analysis due to a lack of data.

As discussed earlier the ERG was of the opinion that the CERTIFI trial should not have been excluded from this analysis. The ERG reran a fixed model including the CERTIFI [21] so the results were slightly different due to the inclusion of this trial (Table 39).

Table 39 Summary of NMA (relative treatment effects) results of biologics in the anti-TNFα failure population—ERG results after CERTIFI trial is included

	CDAI-70 Median OR (95% CrI)	CDAI-100 Median OR (95% CrI)	CDAI<150 Median OR (95% CrI)
Ustekinumab 6 mg/kg vs. Vedolizumab 300 mg	1.04 (0.64 to 1.68)	1.10 (0.65 to 1.87)	1.23 (0.60 to 2.53)
Ustekinumab 6 mg/kg vs. Adalimumab 160/80 mg	0.89 (0.53 to 1.51)	0.97 (0.55 to 1.70)	0.51 (0.22 to 1.13)
Ustekinumab 6 mg/kg vs. Adalimumab 80/40 mg	1.40 (0.41 to 4.72)	0.68 (0.19 to 2.39)	1.80 (0.29 to 16.98)
Ustekinumab 6 mg/kg vs. Placebo	1.93 (1.43 to 2.61)	1.96 (1.43 to 2.71)	1.86 (1.21 to 2.92)
Vedolizumab 300 mg vs. Placebo	1.86 (1.28 to 2.72)	1.78 (1.19 to 2.71)	1.52 (0.87 to 2.73)
Adalimumab 160/80 mg vs. Placebo	2.16 (1.41 to 3.33)	2.03 (1.28 to 3.23)	3.64 (1.89 to 7.32)
Adalimumab 80/40 mg vs Placebo	1.40 (0.41 to 4.72)	2.88 (0.85 to 9.92)	1.04 (0.11 to 6.15)

Key: CDAI, CD Activity Index; CrI, credible interval; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; TNF, tumour necrosis factor; vs. versus

Treatment sequence analysis

The CS presented treatment sequence NMA results (Figure 36-39, pages 139-142 of the CS). The results found that ustekinumab was comparable in terms of clinical response and remission with the other biologics for both populations. However, the analysis is complex and based on the concerns expressed above about the process of data analysis (see section 4.4), the ERG believes that the results are highly unreliable and not a realistic evaluation of the relative treatment effectiveness over the first year of treatment, and so are not presented here. The ERG did not consider it worthwhile re-running the CS model to correct for all these issues as the ERG do not use the NMA results in their economic analysis due to a number of issues with incorporating this data into the economic model, see section 5.2.7 for details.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As stated in Section 4.4.2, the ERG conducted its own NMA of the biologic for the anti-TNFα failure population including the CERTIFI trial [21] and the results are summarised in Table 39.

4.6 Conclusions of the clinical effectiveness section

The manufacturer had conducted a comprehensive systematic literature review and presented its evidence based on 13 RCTs. The studies included in the clinical evidence were generally good quality trials.

The clinical evidence covers four biologics (ustekinumab, adalimumab, infliximab and vedolizumab) which were used to treat moderate-to-severe CDs patients over short-term (induction phase) and long-term (maintenance phase) periods. It included two types of patient subpopulations: conventional care failure and anti-TNFα failure patients.

Four well conducted placebo-controlled, double-blind RCTs provided data on the licensed dose of ustekinumab in CD. Three trials were of induction therapy (single dose of ~6mg/kg followed for 8 weeks (Dose in CERTIFI was exactly 6mg/kg)): two trials were of a population who had failed anti-TNFαs (UNITI-1 and CERTIFI), one was of patients who had failed conventional care (UNITI-2). One trial was of maintenance therapy treatment (follow-up to two years) and investigated the effect of treatment withdrawal in those who had responded to ustekinumab induction (conventional care and anti-TNFα failures combined)(IM-UNITI).

Based on the short term clinical effectiveness results, ustekinumab appears to be more effective than placebo in terms of clinical response and remission in both the conventional care failure and anti-TNFα failure populations. The ERG calculated Relative Risks and 95% CI for Clinical (CDAI-100) response at week 6 were: UNITI-1 1.57 (1.17 to 2.11); UNITI-2 1.93 (1.51 to 2.47); and CERTFI 1.69 (1.16 to 2.46). The Relative Risks and 95% CI for clinical remission (CDAI <150) at week 6 were: UNITI-1 2.07 (1.29 to 3.34); UNITI-2 1.97 (1.40 to 2.79); and CERTIFI 1.15 (0.59 to 2.26). Endoscopic response outcomes were also more likely to be achieved by those patients randomised to ustekinumab over placebo in UNITI-1 and -2, and a higher chance of endoscopic remission at week 8. Patients randomised to the ustekinumab achieved higher inflammatory biomarker reduction during the same follow-up period.

The results of IM-UNITI indicate that around half of patients who respond to ustekinumab are in clinical remission at week 44. A higher proportion of patients randomised to the two ustekinumab dosages (UST 90mg every 8 weeks or 12 weeks) retained their responder status and a higher proportion were in remission at Week 44 than those randomised to placebo (53%, 49% and 36%

respectively). Further long-term data demonstrate that 45% of ustekinumab responders were in clinical remission on ustekinumab q8w or q12w at week 92. In comparison only 16.5% of those ustekinumab responders withdrawn from treatment were in remission at week 92, demonstrating the need for retreatment in most patients. Given the chronic progressive nature of CD, further, longer-term data on response are required.

The data indicate that the placebo response in CD is substantial. The proportion of placebo responders to induction was high (22% in anti-TNFα failure patients and 29% conventional care failure patients). The results of the follow-up of placebo responders from UNITI-1 and -2 also indicate that placebo response can be sustained. Of the placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% achieved clinical response (CDAI-100) and 48% achieved clinical remission at one year. At 44 weeks 12% of all those randomised to placebo were in remission.

The results of the four trials show that the adverse event profile of ustekinumab is similar to that of placebo during the induction and maintenance phase follow-up. Data on adverse effects in long term are lacking.

Since there were no head-to-head comparative analyses carried out in the past to allow a direct comparison of ustekinumab with its comparators in CD, a NMA was conducted. The methods of analyses for the analysis of response to treatment induction were clearly presented and were generally appropriate and the results appear reliable. However, the methods adopted for the NMA of the one year treatment (induction plus maintenance) are not based on a randomised comparison and so are subject to confounding. The relative and absolute treatment effects of the biologics were presented in the CS. The results of the induction phase NMA indicates that ustekinumab is not the most clinically effective biologic both in the conventional care failure and anti-TNFα failure subpopulations in terms of achieving an initial clinical response to or achieving remission). For the maintenance phase, however, the clinical evidence presented by the company is highly unreliable. No evaluation of the relative effectiveness of the biologics beyond one year was possible as data are lacking.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided to the ERG at the points for clarification stage. (PFC) The submission was subject to a critical review on the basis of the company's report and direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key

assumptions and possible limitations. Section 6 presents additional work undertaken by the ERG to explore identified uncertainties and alternative assumptions.

The company's initial economic submission included:

- A description of the search strategy and databases used in the literature review of cost-effectiveness studies (CS appendix, pg. 152 to 155), resource use studies (CS appendix, pg. 259 to 262) and quality-of-life studies (CS appendix, pg.205 to 208);
- A report on the de novo economic evaluation conducted by the company. The report outlined the cost-effectiveness review carried out by the company, the intervention, comparators and patient population considered in the economic model; the modelling methodology used; the data input sources and assumptions used to populate the model; and, the base-case and sensitivity analysis carried out by the company (CS, pg. 163 to 254, additional information was also provided in the CS appendix);
- The company's electronic Excel-based de novo model.

A Patient Access Scheme (PAS) for the comparator therapy vedolizumab was also made available to ERG by the National Institute for Health and care Excellence (NICE) alongside the CS. All results contained in the main body of this report do **not** apply the vedolizumab PAS scheme. Results for the company's base-case and all analysis carried out by the ERG with the PAS applied are instead presented in a confidential appendix.

Following the PFC raised by the ERG, a number of addenda were submitted by the company. These included:

- A descriptive reply to the ERG's PFC questions.
- An updated Excel based model, which corrects for a number of minor errors identified in the executable model and presents a number of additional scenario analysis requested by the ERG.

5.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify relevant economic evidence associated with Crohn's Disease. The ERG's critique of the systematic review presented by company is given below.

5.1.1 Searches

The company provided the methods and search strategies used to identify economic evaluations relating to moderate to severe active Crohn's disease in Appendix 7.

The searches were carried out on 21st July 2015 and updated on 12th October 2016. The following electronic databases were searched: MEDLINE, MEDLINE In Process, EMBASE and the NHS Economic Evaluation Database. To supplement the electronic database searches, the company hand searched the proceedings of five conferences, from 2012-2015: European Crohn's and Colitis Organisation, American College of Gastroenterology, United European Gastroenterology Week, Digestive Disease Week and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Ongoing trials were sought from ClinicalTrials.gov, the EU Clinical Trials Register and the WHO International Clinical Trials Registry Platform Search Portal. In addition, several UK, European and International HTA agency websites were searched.

The methods and sources used to identify cost-effectiveness studies were mostly appropriate. However, the search strategies for MEDLINE and EMBASE contain a search line to remove clinical trials from the search results. This seems an unnecessary restriction for a systematic review and may have caused relevant trials with a cost analysis to be missed. Retrieval was also limited to English language studies, therefore any foreign language papers would not have been identified by the searches.

5.1.2 Inclusion/exclusion criteria used for study selection

Details of the inclusion and exclusion criteria in the selection of cost-effectiveness studies are listed below.

- **Population:** Patients with active moderate to severe CD;
- **Intervention/comparators:** No restriction applied;
- **Outcomes:** Costs including direct and indirect costs, resource use, health gains (including QALYs), ICERs;
- **Study designs:** Health Economic evaluations including: cost-effectiveness, cost utility, cost-benefit, and budget impact analyses;
- **Date restriction:** A data restriction of 2012 to 2015 was applied to conference abstracts, no restriction was applied for other publication formats.
- **Other restrictions:** Studies published in English.

The ERG considers that the inclusion/exclusion criteria used were largely reasonable. The exclusion of non-English language studies may, however, have led to some studies being missed, though the ERG considers this unlikely. Furthermore, the inclusion criteria were described in very general terms allowing for considerable interpretation by reviewers. There is therefore is some uncertainty regarding the actual criteria applied. The ERG also note that the focus on patients with active moderate to severe

disease means the cost-effectiveness model developed as part of the NICE clinical guidance on Crohn's disease (CG152)[26] was not eligible for inclusion.

5.1.3 Studies included and excluded in the cost effectiveness review

A total of 21 studies were identified in the company's cost-effectiveness review, 16 of these were non-UK economic evaluations and 5 were UK economic evaluations. Selected details of the 5 UK economic evaluations are presented in Table 40 below. Full details of all 21 studies can be found in Table 31, Table 32 and Table 36 of the CS Appendix pg. 132 to 161. A number of points are worth highlighting from the available cost-effectiveness evidence. Firstly, all of the identified UK based economic evaluations were of one or more anti-TNF therapies, but none evaluated the cost-effectiveness of ustekinumab, with all of studies. The de novo model presented by the company therefore presents the best available evidence regarding the cost-effectiveness of ustekinumab. Secondly, there is considerable variation in the time horizon used in the models and only few used a life-time time horizon. Further as, noted by the company, shorter time horizons are associated with higher ICERs and over a short time-horizon anti-TNF treatments are generally not cost-effective. Thirdly, the SMC evaluation of vedolizumab estimated an ICER of £6,922 per QALY compared with standard care. This contrasts significantly with the estimated ICER from the present company model of £91,779 per QALY and the ICER reported by NICE following TA352. This issue is explored further in Section 5.2.11 in which the external validity of the company model is explored. Table 40 below.

Table 40 Overview of UK economic evaluations

Study	Treatment and comparator	Model description	Estimated ICER
Lindsay (2008)[27]	Infliximab	Markov model with 5 year time horizon.	Severe active luminal CD: £26,128 per QALY Fistulising CD £29,128 per QALY
Bodger (2009)[28]	Infliximab, adalimumab vs SOC	Markov model with lifetime time horizon	Infliximab: £19,050 per QALY Adalimumab: £7,190 per QALY
Saito (2013)[29]	Infliximab vs infliximab + azathioprine	Decision tree, 1 year time horizon,	£24,917 per QALY
Loftus (2009)[30]	Adalimumab vs SOC	Regression model, 1 year time horizon	£33,731 per QALY
SMC Drug ID1064/16 (2015)[31]	Vedolizumab vs SOC	Markov model with lifetime time horizon	£6,922 per QALY
SOC, standard care			

The ERG also notes that the cost-effectiveness analysis carried out as part of NICE's appraisal of vedolizumab TA 352 was not included in the cost-effectiveness review. Inclusion of this model may have been helpful for externally validating the company's model as it adopts a very similar model structure and makes a number of similar assumptions. The company, however, appear to be aware of this economic evaluation referencing comments made by the assessing ERG group with respect to assumptions made in the companies de novo model.

5.1.4 Conclusions of the cost effectiveness review

The company's cost-effectiveness review did not identify any relevant economic assessments of ustekinumab. The company's review, however, identified a number of economic evaluations of other biologic therapies for CD including a number of UK based economic evaluations. These economic evaluations provide a useful insight into assumptions made in previous economic models and provide an external validity check on the results of the de novo model presented by the company.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach and signposts to the relevant sections in the company's submission is reported in Table 41 below:

Table 41 Summary of the company's economic evaluation (and signposts to CS)

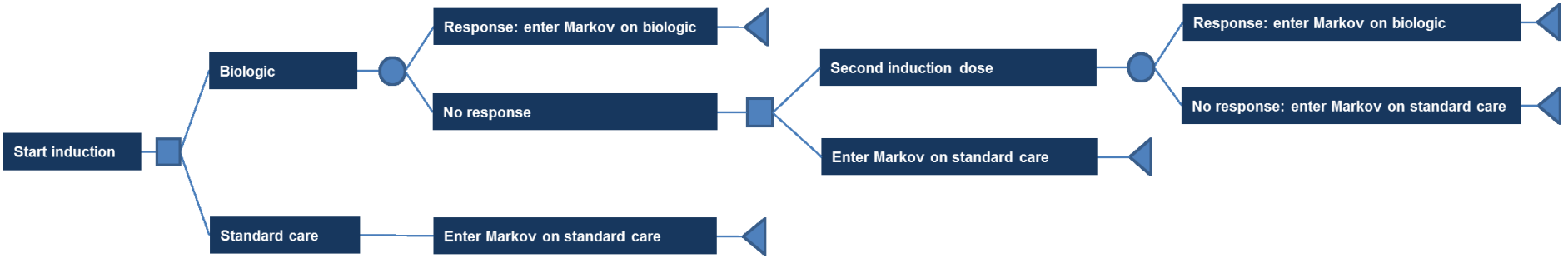
	Approach	Source / Justification	Signpost (location in company submission)
Model	Cost-effectiveness (cost-utility) analysis using a decision tree and Markov model.		Section 5.2.2 pg. 165
States and events	The mode had 5 health states, Remission, mild, moderate to server, surgery and death.	The model structure was based on previous economic model developed by Bodger et al.[28], with a number of modification accounting for comments made by the ERG in TA352.	Section 5.2.2 to 5.2.3 pg. 165 to 169
Comparators	Ustekinumab was compared with adalimumab and conventional care in the conventional care failure population. A scenario analysis was also presented comparing ustekinumab with infliximab. Ustekinumab was compared with vedolizumab and convention care in the anti-TNF failure population.	Infliximab and adalimumab are the primary anti-TNF therapies used in the NHS. Since 2015 vedolizumab has been available for the treatment of CD patients who have failed treatment with anti-TNF treatment or for who anti-TNF treatment is unsuitable.	Section 5.2.4 pg. 170
Subgroups	No subgroup analysis was undertaken.	Analysis is presented for conventional care failure (including patients who exposed to TNFs but didn't failed the treatment) and TNF failure patients separately. During clarification process a further subgroup analysis is presented for TNF naïve patients.	Section 5.9 pg. 246
Treatment effectiveness	Health states were defined with respect to CDAI score and treatment effectiveness data sourced from two separate NMA of induction phase and treatment sequence analysis of the and maintenance phases	Treatment effectiveness data was sourced from the relevant RCT for the induction phase and estimated using NMA. Treatment effectiveness in the maintenance phase was estimated using data from the treatment arms relevant RCTs for the biologic therapies. This was compared to a constructed placebo group generated from data IM-UNITI (non-randomised placebo arm data) and adjusted for the proportion of remitters and responders in the induction phase. Relative effectiveness of biologic therapies was estimated using NMA.	Section 5.3 pg. 175 to 194
Adverse events	Adverse events were included based on expert clinical opinion and included serious infection (defined as septicaemia, pneumonia, urinary tract infections, respiratory infections and bronchitis), tuberculosis, hypersensitivity, injection site reactions and lymphoma.	Adverse events were sourced from relevant RCTs for all biologic therapies. Adverse event rates for convention care were calculated a weighted average of AE event rates in the placebo arm.	Section 5.3.5 pg. 191
Health related quality of life	Utilities were generated using a published mapping tool to map IBDQ to EQ5D.	Utility values are derived by mapping IBDQ scores to EQ5D using an algorithm presented in Buxton et al.[32]	Section 5.4 pg. 193 to 201

	Adverse even disutility's were	Disutilities were applied for adviser event based on values taken from published sources.	
Resource utilisation and costs	Cost categories were as follows: drug acquisition, drug administration, monitoring and management costs, treatment of adverse events, cost associated with surgery and recovery.	Drug acquisition costs for all biologic therapies were sourced from MIMS. Drug acquisition costs for convention care were based on audit data from the UK[33] with unit costs drawn from the BNF. Resource use was estimated using a Delphi exercise of 12 clinical experts with unit costs based on NHS reference costs. Adverse event costs were based on NHS reference costs. Surgery costs were based on NHS reference costs and data from m Hospital episode statistics.	Section 5.5 pg. 203 to 213
Discount rates	Costs and benefits were discounted at 3.5% per annum	In accordance with the NICE reference case.	Section 5.2.2 pg. 169
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic univariate probabilistic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 5.8 pg. 232 to 246

5.2.1 Model structure

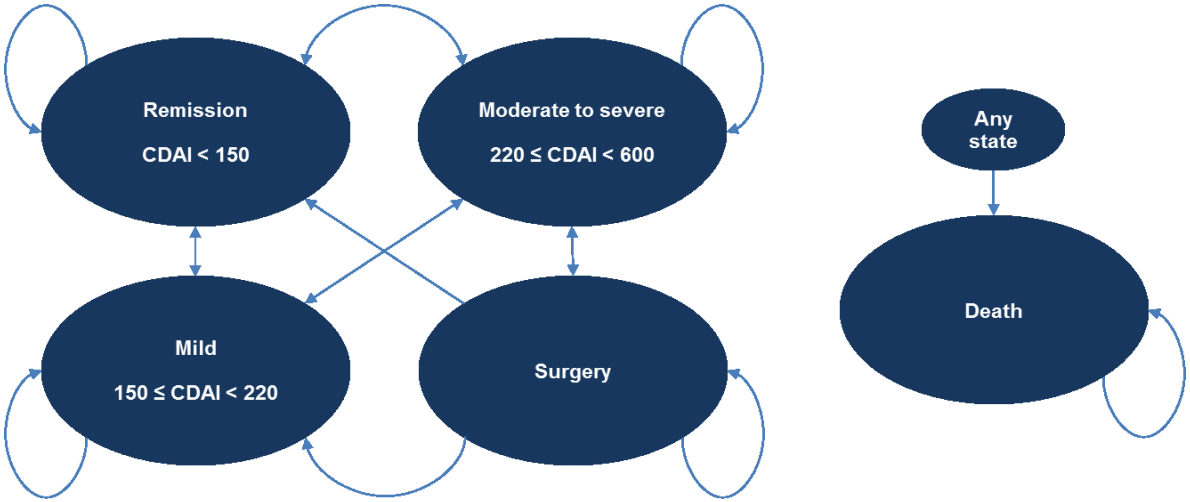
The *de novo* analysis presented by the company consists of two parts: a short-term induction phase, represented by a decision tree (Figure 5), and a long-term maintenance phase, represented by a Markov model (Figure 6).

Figure 5 Induction phase (decision tree)



Note: 'No response' in the induction phase is defined as not achieving a reduction in Crohn's Disease Activity Index score of >100 points.

Figure 6 Maintenance phase (Markov model)



Key: CDAI, Crohn's Disease Activity Index.

Patients enter the model at the start of the treatment induction period. The length of the induction period varies by treatment and is based on the market authorisations of the respective treatments (See Section 5.2.4 for further details). At the end of the induction period, patients are assessed for response to treatment. Response is defined as a decrease in CDAI score of greater than 100 points (CDAI-100). A scenario analysis is presented using the alterative response definition of a decrease in CDAI score of greater than 70 points (CDAI-70). Patients receiving ustekinumab, vedolizumab or adalimumab who fail to respond to the initial induction dose(s) are assumed to receive a further induction dose to allow for a delayed response to treatment. This is in-line with the marketing authorisations for the respective drugs. At the end of the induction phase all patients move into the Markov model. Patients initiating on biologics who have responded to treatment either at first or second induction continue on therapy for a maximum of one year. After this point, biologic therapy is stopped and all patients move to conventional care. Alternative maximum treatment durations of two and three years are explored in scenario analysis presented by the company. Patients who fail to respond to induction and where allowed second induction are assumed to move directly to conventional care. Patients who initiate conventional care from the beginning are assumed to continue to receive conventional care regardless of response in the induction phase.

At any point during the maintenance phase of the model patients in the moderate to severe health state can receive surgery. Patients in the moderate to severe health state are at a constant risk of surgery in the model and therefore can effectively receive multiple surgeries throughout their lifetime. The memoryless nature of the Markov model, however, means that surgery does not influence the likelihood of future surgeries or effect future prognosis.

Utilities for all health states are the same regardless of whether a patient is receiving biologic therapy or conventional care. Monitoring and management costs are associated with each health state and increase with disease severity. Differential costs are applied for monitoring and management depending on whether a patient is receiving a biologic therapy or conventional care.

The model structure adopted by the company is based on a previous economic model developed by Bodger et al.[28], a variant of which was used in the NICE appraisal of the comparator therapy vedolizumab (TA 352). This model, while capturing a number of important aspects of the CD, has a number of significant weaknesses that significantly undermine the credibility of the results produced by the model. These weaknesses are discussed in turn below.

Representation of CD

A key weakness of the presented model is that it fails to capture the progressive and chronic nature of CD. Specifically, the model does not account for the fact that CD is a relapsing condition. Biologic

therapies do not represent a cure for CD and it is not thought that they fundamentally alter the course of the disease. As such, the aim of treatment with biologic therapies including ustekinumab is to induce and ideally maintain remission. If patients discontinue treatment, loss of remission is, however, considered to be inevitable and follow up therapy will be necessary at some time for all patients. Also even on treatment eventual loss of response is likely. As such it is common in practice for patients to cycle through multiple biologic therapies as needed to combat relapses in disease. The model fails to capture these dynamics of CD and the need for additional lines of therapy. This failure is a significant problem as it makes meaningful interpretation of the long-term predictions of the model difficult. The impact of this failure to capture the dynamics of CD on cost-effectiveness estimates is also difficult to predict and may serve to either over or under estimate the cost-effectiveness of treatment with biologics including ustekinumab. Unfortunately, as this represents a major structural flaw in the model the ERG has been unable to address or even explore the impact of this.

Surgery

Related to the above issue is the failure to appropriately incorporate surgery into the model. The model structure does not recognise that patients who receive surgery are likely to have a quite different prognosis and treatment pathway to patients receiving drug therapy. Specifically, the model while allowing for multiple surgeries over a patient's life-time does not consider the impact of surgery on the prospect of receiving future surgery or the long-term impact of surgery on HRQoL, for example where surgery involves resection (removal of inflamed area of the intestine). The company do comment that they attempted to incorporate post-surgical remission health states into the model structure, but found that the data available to populate the transition probabilities produced unrealistic results.

Calculation of transition probabilities

The transition probabilities used in the model determine how patients move around the different health states in the model and are determined by the effectiveness data used to populate the economic model TO calculate the transition probabilities used in the model the company makes use of a calibration technique to estimate the transition probabilities of patients in the maintenance phase of the model. This method relies on imposing a series of constraints and selecting a series of starting values. The Excel solver function is then used to estimate transition probabilities that fit with the limited clinical data available. The constraints implied in this process are however, only partially justified, though based on those used in TA352, and the starting values are entirely arbitrary. Both the constraints imposed and starting values have a considerable impact on the estimated transition probabilities and as consequence the estimated cost-effectiveness of ustekinumab. Furthermore, it is not clear that the transition probabilities estimated are clinical plausible given clinical data available

from the IM-UNITI trial on the likelihood of maintaining response to treatment during the maintenance phase. This issue is explored further in Section 5.2.7 and results of exploratory analysis are presented in section 6.

Structural assumptions

The economic model presented by the company makes a number of structural assumptions that are inconsistent with clinical practice in the UK:

- All non-responders are assumed to have moderate to severe disease. However, a proportion of patients who are non-responders will have mild disease (defined as CDAI score between 150 and 220). For instance, a patient with a CDAI score of 250 at baseline with a drop in CDAI of 60 would be classified as a non-responder, but at the end of the induction phase will be in the mild health state (CDAI 150 to 220).
- No distinction is made between responders with moderate to severe CD and non-responders (except for continuation on biologic treatment following induction). The ERG believes that the outcomes (HRQoL, management and the probability of surgery) are likely to differ between responders and non-responders.
- Response in the base-case analysis is defined as a drop of 100 points or more in the CDAI score, which is consistent with the definition of response used in the UNITI trials. A scenario analysis was also presented in which the alternative criteria of a 70 point drop in CDAI score. It is not clear which of these is the most appropriate response criteria as in clinical practice CDAI score is rarely used and response is assessed based on symptom relief.
- All patients who are still receiving anti-TNF therapy at one year are assumed to discontinue (and subsequently receive non-biologic treatment), irrespective of whether they are currently responding to treatment. In practice it is, however, unclear to what extent clinicians adhere to the guidance requiring patients to discontinue therapy. This issue is discussed further in Section 5.2.8.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 42 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 42 Features of de novo analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partially	The base-case model compares ustekinumab with conventional care and adalimumab in the conventional care failure population (including patients exposed to TNFs). A comparison with the comparator therapy infliximab is only presented as a scenario analysis due to limited outcome data for infliximab. Ustekinumab is compared with conventional care and vedolizumab in the TNF failure population. This is in line with the NICE scope.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective on outcomes	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model has a time horizon of 60 years equivalent to life-time time horizon.
Synthesis of evidence on outcomes	Systematic review and mixed treatment comparison of relative effects.	Yes	Clinical effectiveness data is informed by a network meta-analysis
Measure of health effects	QALYs	Yes	HRQoL data was sourced by mapping IBDQ score on to EQ-5D using a published algorithm presented in Buxton et al.[32] No directly reported HRQoL were collected as part of the UNITI clinical trials.
Source of data for measurement of HRQoL	Reported directly by patients and/or caregivers	No	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes	
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes	Costs and benefits have been discounted at 3.5% per annum.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

5.2.3 Population

The economic mode analysis presented by the company is carried out for two population groups, conventional care failure patients and TNF failure patients. Clinical data to populate the economic model for the convention car failure subpopulation is sourced from the UNITI-2 trial for the TNF failure subpopulation are sourced from the UNITI-1 trial. The population included in the economic model is therefore representative of the patients included in the UNITI trials. The eligibility criteria for the UNITI-1 and UNITI-2 trials are discussed in more detail in Section 4.2.

The population recruited to the trials raises three issues.

Firstly, both the UNITI trials were international multicentre trials and as such the patients recruited were not necessarily reflective of the patient population in the UK. This is particularly an issue with respect to whether the non-biologic treatments received by both ustekinumab and placebo patients are representative of the care they would receive in UK practice. This issue is considered further in Section 5.2.10 below.

Secondly, the UNITI trials included patients with a CDAI score between 220 and 450; and therefore excluded patients at the higher end of the CDAI spectrum (CDAI > 450). Advice from the clinical advisor to the ERG suggests that the number of patients with a CDAI score in excess of 450 is likely to be small and therefore the exclusion of patients is likely to have only a limited impact on the representativeness of the UNITI trials. It is however, uncertain whether patients with a CDAI score of 450 or greater would benefit to the same degree as patients will less severe disease.

Thirdly, the inclusion criteria for the UNITI-2 trial did not recruit an entirely anti-TNF naive population, but allowed patients who had previously received anti-TNF therapy to be recruited as long as they had not failed anti-TNF therapy. As such, approximately 30% of UNITI-2 patients had previous experience of using an anti-TNF therapy. This population group is likely to include patients who have been responsive to anti-TNF treatment and as such may be more likely to respond to other biologic therapies such as ustekinumab than a truly naive patient group. The company do present some limited clinical evidence analysing response and remission rates for both the truly naive patient group and the patients with anti-TNF experience. However, this data was not included in the economic model.

At the PFC stage the ERG request that scenario analysis be carried out which uses clinical data from truly TNF naive patients there by excluding the data from patients who have previously received TNF therapy. This was supplied by the company as part of their response and is presented in Section 5.11. The company however, also outline in their response that they consider the mixed population of truly

TNF naïve and TNF experienced patients to be better reflective of the conventional care failure population. In support of this position the company cite the example of patients who are given TNF therapy at diagnosis to bring symptoms under control before commencing conventional care. These patients would not be TNF failures as they have not failed treatment, but are not truly TNF naïve either. They also comment that selecting this sub-population breaks the randomisation in the trial and results in a smaller sample size which increases uncertainty. The ERG put this reasoning to the clinical advisor to the ERG who suggested that instances of using biologic therapy in this way would be very rare in UK practice and that the truly TNF naïve population is more representative of the conventional care failure population. The ERG therefore have a preference for the truly TNF naïve population over the mixed population used in the company base-case.

5.2.4 Interventions and comparators

The intervention comparators considered in the economic model are dependent on the population considered. In the convention care failure patient group ustekinumab is compared with conventional care and adalimumab. A scenario analysis using the CDAI 70 response criteria is also presented in which infliximab is included as a comparator (data for the CDAI 100 response criteria are unavailable for infliximab). In this scenario analysis comparison of two biosimilar remsima and inflectra are also considered assuming equal effectiveness to remicade (infliximab). In the TNF failure patient group ustekinumab is compared with conventional care and vedolizumab.

The company's analysis within the TNF failure subgroup excludes the biologic therapies infliximab and adalimumab. The ERG questions the exclusion of these biologic therapies, as the use of a second anti-TNF agent following the failure of a first anti-TNF agent may be possible particularly where loss of response has occurred due to development of antibodies to the first anti-TNF therapy. The ERG, however recognises the limited efficacy evidence available. To the ERG's knowledge, no data are available on the efficacy of infliximab in patients in TNF failure subgroup. In contrast, the ERG note that the treatment sequence NMA presented by the company in the anti –TNF population included adalimumab as comparator. Adalimumab was the second TNFα antagonist approved and was used in one trial in patients with secondary failure to infliximab.[152] This trial excludes patients with primary failure to infliximab (i.e. patients that initially did not respond; see Section 5.2.1), including only secondary non-responders to infliximab (i.e. patients who initially responded but subsequently lost response; see Section 5.2.1) and may therefore reflect a population of patients who are likely to respond to adalimumab, as both treatments have the same mode of action. Therefore, anti-TNFs are only considered as comparators in conventional care failure population.

Reflecting differences in the marketing authorisation of the different biologic therapies the dosing regimens for the different biologic therapies differed with respect to the length of induction. Further

for ustekinumab, adalimumab and vedolizumab it was permitted that patients be assessed for response following a second induction dose. Table 43 details the dosing regimens for the treatment and comparator therapies used in the company model.

Table 43 Dosing Regimens –biologic therapies

Treatment	Induction duration (weeks)	Response assessed (weeks)	Induction dosing		Second induction dose?	Second induction details	Second induction end (weeks)	Maintenance dosing	Dose escalated maintenance dosing	Population
Ustekinumab	8	6 and 8	Weight based:	<55kg: 260mg at Week 0	Yes	Additional dose at Week 8; response assessed at Week 16	16	90mg 12 weeks	90 mg every 8 weeks	Conventional care failure, TNF failure
				>55kg and <85kg: 390mg at Week 0						
				>85kg: 520mg at Week 0						
			130mg at Week 0							
Adalimumab	4	4	160mg at Week 0, 80mg at Week 2 (dose used in UK practice, base case)		Yes	Continued 40mg dose through Week 12	12	40mg on alternate weeks	40mg every week	Conventional care failure
			80mg at Week 0, 40mg at Week 2 (licensed dose, scenario analysis)							
Vedolizumab	10	6 and 10	300mg at Weeks 0, 2 and 6		Yes	Additional dose at Week 10; Response assessed at Week 14	14	300mg every 8 weeks	300mg every 4 weeks	TNF failure
Infliximab and biosimilars	6	2	5mg/kg at Weeks 0 and 2. Dose at Week 6 for responders		No	N/A	N/A	5mg/kg every 8 weeks	10mg/kg every 8 weeks	Conventional care failure

Key: N/A, not applicable; TNF, tumour necrosis factor.
Notes: *infliximab included as scenario analysis only.

While the dosing regimens used by the company are reflective of the respective marketing authorisation, the ERG notes that there are significant difference in when response is assessed for infliximab patients (4 weeks) and other biologic therapies. The ERG is concerned that these differences are not reflective of current practice in the UK and advice for the clinical advisor to the UK suggests that patients initiating on biologic therapy will usually be assessed for response 6 to 10 weeks after initiating therapy regardless of the biologic therapy being used.

Within the company's model, the effectiveness of conventional care reflect the effectiveness of the concomitant therapies used in the placebo arm of the UNITI trials. These are summarised in Table 44 and are made up of combination of therapies including corticosteroids and immunomodulators. A significant proportion of patients (18.7% to 30.1%) also received no concomitant therapies.

Table 44 Summary of Concomitant Medications

Treatment	UNITI -1			UNITI -2		
	Placebo	**Ustekinumab 130mg**	**Ustekinumab 6mg/kg**	**Placebo**	**Ustekinumab 130mg**	**Ustekinumab 6mg/kg**
Subjects with 1 or more concomitant medications	74.9%	72.7%	69.9%	75.2%	77.0%	81.3%
Immunomodulatory drugs	32.8%	30.2%	31.3%	34.8%	35.4%	34.4%
Aminosalicylates	21.9%	20.4%	20.1%	42.4$	42.6%	44.5%
Antibiotics	8.5%	7.8%	9.6%	3.8%	1.9%	4.3%
Corticosteroids (including budesonide)	44.9%	49.4%	43.4%	35.7%	38.3%	44.0%

The ERG is concerned that this mix of therapies is not reflective of current practice in the UK and in particular is concerned that a significant proportion of placebo patients were left untreated. A comparison with IBD Audit data also shows that significantly higher rates of immunomodulators (57% in the IBD- audit data) are used in the UK and lower rates of corticosteroids use (27% in the IBD audit data). These differences mean that the effectiveness of conventional care may not be accurately captured by the UNITI trials as the therapies received are not reflective of current UK practice. In particular the fact that a significant proportion of placebo patients were untreated may lead to the effectiveness of conventional care being underestimated. The ERG also note the costs for conventional care are based on the IBD audit data and therefore there is an inconsistency in the cost and effectiveness data being used in the model, see Section 5.2.10 for details.

5.2.5 Perspective and time horizon

The economic model adopted a National Health Service (NHS) and Personal Social Services (PSS) perspective in accordance with the NICE reference case.

The time horizon used in the economic model was 60 years. The NICE reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The ERG considered the 60 year time horizon to be appropriate, but notes there is considerable uncertainty over the long-term benefits and costs of ustekinumab due to both the short duration of the clinical effectiveness data available (maximum 54 weeks) and the failure of the model structure to incorporate the relapsing remitting nature of CD. Given this uncertainty, the ERG, considers it worth exploring the impact of a shorter time horizon, which effectively imposes the assumption that costs and benefits are the same for the treatment and comparator arms after the time horizon. The ERG therefore presents scenario analysis considering alternative time horizons in Section 6.

5.2.6 Discounting

Costs and benefits in the model were discounted at an annual rate of 3.5% as per the NICE reference case.

5.2.7 Treatment effectiveness and extrapolation

5.2.7.1 Treatment efficacy

Key efficacy parameters used within the CS economic model are either observed, imputed or derived. Table 45 lists the effectiveness parameters used in the economic model, the source of data and whether the parameter was based on observed, imputed or derived data.

Table 45 Key efficacy parameters used within the CS economic model

Parameter	Source	Assumptions
Probability of response and remission in the induction phase	Induction NMA	Observed data
Percentages of responder to the induction phase with moderate to severe CD	IM-UNITI	Observed for ustekinumab and conventional care, assumed same for other biologics
Probabilities of response and remission for patients on active treatments at the end-of- maintenance phase.	Maintenance Trials	Observed data
Probabilities of response and remission for responders to placebo at the end-of-maintenance phase	IM-UNITI adjusted using relevant maintenance trials	Observed data
Transition probabilities maintenance phase	Treatment sequence analysis	Derived using the distribution of patients across the health states at the end-of-induction phase and the distribution of patients across the health states at the end-of-maintenance phase predicted by the treatment sequence analysis
Probabilities of discontinuation	Relevant maintenance trials	Observed data
Post- maintenance phase transitions for biologic therapies	Placebo arm of relevant maintenance trials	Assumes gradual decline in efficacy for first year, derived by weighting reweighting placebo arm remission over maintenance phase
Post-surgery transition probabilities	Bodger et al. (2009)[28]	Observed data
Incidence of AEs	Relevant maintenance trials	Observed data
Mortality	Life tables	Assumed the same as general population

Response – CDAI drop of <100, remission CDAI<150

Efficacy during induction phase

The CS economic model used the induction efficacy data for ustekinumab which come from the ustekinumab induction trials (UNITI-1, TNF failure; UNITI-2, conventional care failure), and efficacy data for all comparators of interest come from the network meta-analysis (NMA) (See section 4.4 for details).[22, 34]

In the economic model, induction transition probabilities are estimated from three parameters:

- Rate of remission (α),
- Rate of response (β), and
- Percentage of responders who remain in the moderate to severe state (γ).

These are used to calculate the proportion of patients in each of the models health states using the formulas shown in Table 46 (see CS, section 5.3.2, pg. 177 for a detailed description).

Table 46 Induction transition probability calculations (CS, table 39, pg. 177)

	Responders (β)			Non-responders
	Remission	**Mild**	**Moderate-severe**	
Probability	A	β - (α + (β * γ))	β * γ	1 - β
α = rate of remission β = Rate of response, and γ = Percentage of responders who remain in the moderate to severe state				

Details of the sources of data and derivation of each parameter are described below.

Rates of response (β) and remission (α) during induction phase

The response and remission rates for ustekinumab are sourced from the relevant induction trial (UNITI 1 and UNITI 2). Probabilities of response and remission for comparator treatments are derived by applying odds ratios calculated in the induction NMA to ustekinumab induction results (See section 4.4 for details). The induction probabilities for all treatments are shown in Table 47. As discussed in section 4.4, the ERG considers that the CERTIFI trial should have been included in the induction NMA for the anti-TNF failure population. The ERG presents a scenario analysis that uses input data from an induction NMA that includes the CERTIFI study in Section 6.

Table 47 Probabilities of response and remission for comparators (CS, table 37, pg. 176)

Comparators	**Probabilities**		
	Response (CDAI-70)	**Response (CDAI-100)**	**Remission**
Conventional care failure population			
Ustekinumab 6mg/kg	64.6%	55.5%	34.9%
Adalimumab 80/40mg	65.1%	47.3%	32.0%
Adalimumab 160/80mg	66.5%	54.8%	45.6%
Conventional care	38.7%	28.6%	17.7%
Infliximab 5mg/kg[a]	94.3%	N/A	87.0%
TNF failure population			
Ustekinumab 6mg/kg	43.8%	33.7%	18.5%
Vedolizumab 300mg	44.8%	*32.7%*	12.90%
Conventional care	30.3%	*21.4%*	8.83%
Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor. **Notes:** [a] Infliximab included as scenario analysis only; numbers provided at PFC as CS numbers were incorrect.			

Percentage of responders who remain in the moderate to severe state (γ) during induction phase

In the model, it is assumed that a proportion of responders to induction therapy will remain in the moderate to severe health state to reflect the fact that not all patients will experience a sufficiently large response to move them to the mild health state. The data available to inform this parameter are however limited, and it is assumed that for all therapies the proportion of moderate to severe responders is the same as in IM-UNITI study data (see Table 48). The ERG accepts the need to make some assumptions, but highlights that data for vedolizumab were available from the TA352 submission and demonstrate quiet different rates of moderate to severe responders (see Table 48); these differences are probably explained by the differential efficacy of the two compounds. The potential influence of this assumption may be quite significant as fewer QALYs and greater costs are associated with the moderate to severe health state. It is, however, uncertain whether the figures used represent an overestimation of the proportion of moderate to severe responders for the comparator therapies.

Table 48 Percentage of moderate to severe responders (γ) [to estimate end-of-induction proportions in each health state] (CS, table 38, pg. 177)

Source	Conventional care failure	TNF failure
CS base-case	***	***
TA352 figures for vedolizumab	17.8%	24.3%
Key: TNF, tumour necrosis factor.		

Efficacy inputs for delayed responders during induction phase

In line with SPC's for number of biologic therapies, the company's economic model allows for the possibility of delayed response. Efficacy inputs for these delayed responders are sourced from best available data for each treatment, see Table 49. It should be noted that this require a number of assumptions to be made including the assumption that the proportion of patients achieving a CDAI-70 response is equal to the proportion of patients achieving a CDAI-100 response for all treatments. This will likely underestimate the proportion of delayed responders and this is a conservative assumption; however, it is not possible to estimate the true proportion. The ERG considers this assumption reasonable given the limited data available.

Table 49 Delayed responder's efficacy inputs (CS, table 40, pg. 178)

	N	Events	%	Source
Ustekinumab (conventional care failure)				

Response (CDAI-70)		N/A: Assumed equal to CDAI-100	*64.9%*	IM-UNITI data
Response (CDAI-100)	185	120	*64.9%*	
Remission	185	83	*44.9%*	
Ustekinumab (TNF failure)				
Response (CDAI-70)		N/A: Assumed equal to CDAI-100	*41.1%*	IM-UNITI data
Response (CDAI-100)	282	116	*41.1%*	
Remission	282	52	*18.4%*	
Vedolizumab (combined conventional care and TNF failure)				
Response (CDAI-70)	86 [b]	N/A: Assumed equal to CDAI-100	*18.6%* [a]	Sandborn *et al*. (2014)[35]
Response (CDAI-100)	86 [b]	16 [b]	16.0%	
Remission	86 [b]	9 [b]	6.8%	
Adalimumab (conventional care failure)				
Response (CDAI-70)	-	N/A: Assumed equal to CDAI-100	43.0%	Adalimumab SPC[36]
Response (CDAI-100)	-	-	43.0%	
Remission	-	-	28.0%	Panaccione *et al.*[37]

Key: CDAI, Crohn's Disease Activity Index; TNF, tumour necrosis factor. *In italics:* The corrected numbers were provided during clarification process and were presented in CS response to clarification table 43 pg. 89-90.
a: proportion does not match with the Sandborn et al (2014).
b: the numbers do not match and are not presented in the Sandborn et al (2014).

Efficacy during maintenance phase

The economic model developed by the company uses the treatment sequence analysis described in detail in Section 4.4 to estimate transition probabilities that are applied in the maintenance phase of model and beyond. For biologic treatments, the model uses the treatment sequence analysis to estimate maintenance phase transition probabilities that are applied for the duration of biologic treatment (assumed to be 1 year in the base-case). After this period a set of transitional probabilities are applied for further a year (see detail in separate section below). For the remaining 58 year time horizon of the base-case model the conventional care maintenance phase transition probabilities are then applied. For conventional care, the treatment sequence analysis is used to generate a set of maintenance phase transition probabilities that are applied for the entire period following induction. The transition probabilities generated by the treatment sequence analysis are fixed and do not vary over time.

The transition probabilities are derived using the distribution of patients across the health states at the end-of-induction (estimated from the induction NMA) and results of treatment sequence analysis. This provides the distribution of patients at the end-of-induction phases and the proportion of patients

at the end-of-maintenance phase in the remission and mild health states, where the proportion of patients in the remission and mild health states at the end-of-maintenance phase is conditional on responding to into induction treatment. The proportion of patients in the moderate to severe state at the end of the maintenance phase is calculated as one minus the proportion of patients in the remission and mild health states.

To calculate the two week transition matrix used in the model, the Microsoft Excel® function solver is used to estimate a set of transition probabilities for the maintenance phase. The solution provided by Excel solver is not unique as there a many possible sets of transition probabilities that will result in the correct distribution of patients at the end of maintenance phase. To ensure the transition probabilities are plausible the company apply a number of constraints. These are detailed in Table 50. The CS stated that the constraints included are consistent with TA352.[38] Additionally, several constraints were added to address previous criticisms of the calibration method in TA352.[39]

Table 50 Description of calibration parameters and constraints (CS Appendix 12, table 57 & 59, pg. 302-303)

Calibration parameters	Transition probability	Value	Constraint	Justification
P1	Remission to remission	Variable	$0 \leq P1 \leq 0.995$	Given the opportunity for the optimisation problem to have many optimal solutions, this constraint avoids the solution of all patients in remission remaining in remission
P2	Remission to mild	Decision variable	$P2 \geq 0$	-
P3	Remission to moderate-severe	Calculated as 1 - (P1 + P2); constrained to equal zero	$P3 = 0$	Based on the assumption that the disease progression/improvement rate is not fast enough to justify a transition between the two extreme states in a 2-week cycle
P4	Mild to remission	Variable	$0 \leq P4 \leq 0.2$	Intended to depict the progressive nature of the disease
P5	Mild to mild	Variable	$P5 \geq 0$ $P5 \geq P6$	This assumes that patients are more likely to remain in their current health state than deteriorate. This is based on observations in currently available clinical data (IM-UNITI transitions; CS, Appendix 11)
P6	Mild to moderate-severe	Calculated as 1 - (P4 + P5)	$P6 \geq 0$	-
P7	Moderate-severe to remission	Variable; constrained to equal zero	$P7 = 0$	Based on the assumption that the disease progression/improvement rate is not fast enough to justify a transition between the two extreme states in a 2-week cycle
P8	Moderate-severe to mild	Variable	$P8 \geq 0$	-

P9	Moderate-severe to moderate-severe	Calculated as 1 - (P7 + P8)	P9 ≥ P8	This assumes that patients are more likely to remain in their current health state than improve. This is based on observations in currently available clinical data (IM-UNITI transitions; CS, Appendix 11)
All transition probabilities must be non-negative, justified as probabilities range between 0 and 1				

The Excel solver method uses an iterative method to find an appropriate solution. This method therefore requires a set of staring values from which to start looking for an appropriate solution. The starting values used by the company in the calculation of the transition probabilities re assumed to be the same for both conventional care and biologics. The starting values used are described in Table 51.

Table 51 Solver solution starting matrix (CS Appendix 12, table 60, pg. 303)

From/to	Remission	Mild
Remission	0.950	0.050
Mild	0.000	0.650
Moderate-severe	0.000	0.100

The ERG has a number of substantial concerns regarding the data, assumptions and methods used to calculate the transition probabilities used in the maintenance phase of the model. These concern: the interpretation of the treatment sequence analysis; clinical plausibility of the transition probabilities; use of the Excel solver to calculate the transition probabilities; reliability of treatment sequence analysis estimates, and, assumptions made regarding the effectiveness of biologic therapies for secondary responders. These issues are discussed in turn below.

Interpretation of the treatment sequence analysis

As described in section 4.4 one of the key issues relating to the treatment sequence analysis and how it is used in the economic model. This problem primarily stems from the interpretation by the company of the treatment sequence analysis. The company in applying the results of the treatment sequence analysis effectively assume that the treatment sequence analysis is an analysis of the relative effectiveness of the compared treatments over one year i.e. a trial where patients are randomised to either treatment or placebo at initiation of treatment and then followed up for the period of year regardless of response at induction. As stated in Section 4.4 however, the treatment sequence analysis cannot represent this comparison because it does not include non-responders to treatment. This misinterpretation has important consequences for the calculated transition probabilities as by interpreting the treatment sequence analysis in this way it makes the implicit assumption that non-

responders to treatment remain in the moderate to severe health state for the entire maintenance period. There is, however, no reason to believe that this is the case as patients will often spontaneously improve even while only receiving conventional care as observed in the placebo arms of the induction trials. The impact of this implicit assumption is that it underestimates the likelihood that patients who are in the moderate to severe health state at the end of induction will move either to mild or remission health states during the course of the maintenance phase. During the maintenance phase this assumption will likely favour conventional care as we may expect that the carry over effects of biological induction therapy would mean relative more moderate to severe patients would achieve response or remission. However, in the long-term the implications of this assumption are likely to favour biologic therapies as the conventional care transition probabilities are applied for the majority of periods in the model. If the conventional care transition probabilities underestimate the likelihood of moderate to severe patients moving to the mild or remission health states it acts to trap for patients who fail to respond to treatment induction ensuring that they are very likely to remain in the moderate to severe health state. This will favour treatments with fewer patients in the moderate to severer health state at the end of the maintenance phase and will overestimate their effectiveness. This would therefore tend to favour biologic therapies over conventional care. The impact of this assumption is potentially very significant and undermines the transition probabilities calculated by the company. Data on the post-treatment outcomes of non-responders is however very limited and there is no way to use the treatment sequence analysis in a way that avoids this issue.

Clinical plausibility of the transition probabilities

The clinical evidence available appears to contradict the predictions made by the transition probabilities. Data for the CS suggest that approximately 60% of ustekinumab patients who achieve remission will retain that remission over the maintenance period. The estimated transition probabilities transition, however predict that over 90% will retain remission. This contradiction was raised with the company at the PFC stage. The company were, however, largely dismissive of this issue arguing that due to the memoryless nature of the Markov model that this contradiction is unimportant as the model predicts the correct distribution of patients at the end of the maintenance phase. This response by the company is only partially correct. The exact transitions used in the model are relatively unimportant up to the end of the first year as long as they predict the correct distribution of patients at that time. However, this ignores the fact that the transition probabilities for conventional care patients are applied for a large proportion of the model time horizon and therefore have a very substantial influence on the results of the model. The calculated transition probabilities tends to overestimate the likelihood of staying in remission and staying in the moderate to severe health state. This tends favour treatments in which patients do better in the first year as it extends the benefits of treatment into the future as patients are assumed to hold remission for a long time following

discontinuation of treatment. This has a very significant impact on the ICER and will mean that the model drastically overestimate the benefits of biologic therapy.

The ERG also note that the maintenance phase transition probabilities used in the maintenance phase of the model imply that conventional care is more effective than adalimumab. This is inconsistent with evidence from the CHARM trial which shows that adalimumab is more effective than placebo during the maintenance phase.

Calculation of transition probabilities using Excel solver

The ERG has quite significant concerns regarding the use of Excel solver to calculate the transition probabilities. Firstly, the model calibration was carried outside the CS executable model and transition matrices are copy-pasted in the CS executable model. Therefore, the transition probabilities remain constant and do not vary if the key assumptions change within the executable model (for example changes in the distribution of responders and remitters). The derivation of these transition probabilities is highly dependent on these structural assumptions and input parameters. Therefore, the model needs to be recalibrated if alternative assumptions are to be used (such as changes in distribution of response and remission, induction phase duration, discontinuation rates, probability of surgery etc.). However, this is not automatic within the CS economic model and transition matrices do not appear to have been recalibrated for the scenario analyses undertaken by the company.

Secondly, the estimated transition probabilities are highly dependent on the constraints imposed and starting values used, both of which are not well justified by the company. To demonstrate the influence of alternative starting values, the ERG carries out additional scenario analyses in Section 6 using a number of alternative sets of staring values to illustrate the significant impact these values have on the estimated ICERs. It should be noted that it is very difficult to justify a set of starting values and the ERG consider that the influence of the starting values is so great that it undermines the Excel solver method used by the company to the point that the ERG consider it unlikely that this method can be used to generate a set of transition probabilities that are properly justified.

Relatability of treatment sequence analysis

As discussed in detail in Section 4.4, the ERG has some concerns regarding the reliability of the estimates provided by the treatment sequence analysis, this uncertainty regarding the reliability of the NMA will impact on the estimated transition probabilities. Some of these issues are addressed in additional analysis carried by the ERG including inclusion of the CERTIFI trial in the induction NMA. It is however, not possible to address all the issues raised and it is uncertain to what degree these may influence the calculated transition probabilities and in turn estimated cost-effectiveness.

Effectiveness for delayed responders

As described above the economic model in line with the SPC's for ustekinumab, adalimumab and vedolizumab allows for delayed response to induction therapy. The maintenance phase transitions for these patients are however, based on data from initial responders. The ERG considers that this assumption is likely to overestimate the effectiveness of these biologic therapies in delayed responders as it is reasonable to expect that delayed responders will not experience the same benefits from maintenance treatment as initial responders, because, by definition, they are less responsive to treatment than initial responders. It is difficult to estimate the influence of this assumption, but the number of secondary responders is quite significant with 34% and 45% of total ustekinumab responders in the conventional care failure and anti-TNF failure populations respectively being delayed responders.

In summary, the ERG considers that there are a number of substantive reasons to believe that the transition probabilities used in the base-case analysis are deeply flawed and unreflective of the relative effectiveness of the compared treatments and should not be relied upon.

The only alternative source of the transition probabilities is a scenario analysis presented by the company, which uses the individual patient data (IPD) from the IM-UNITI trial to calculate transition probabilities. This data does not suffer from the problems relating to the treatment sequence analysis and the Excel solver methods used in the company base-case, though still assumes initial and secondary responders behave in the same way. It also has the advantage that it allows for dynamic transition probabilities that change over time.

The IM-UNITI IPD, however, also has some additional disadvantages Firstly, the transition probabilities for conventional care patients are based upon patients who were randomised to placebo following induction response to ustekinumab and therefore includes any carry over effects from ustekinumab induction therapy. This may lead to the overestimation of the effectiveness of conventional care in the maintenance phase. It is, however, unlikely to effect the long-term transitions as there is substantial washout period and the post maintenance phase transition makes use of only the last two periods of data. The ERG did request that the company provide a scenario based on IM-UNITI IPD data for all patients (placebo responders and non-responders) randomised to placebo at induction, but this was not provided by the company in its response as it was unavailable. Secondly, it assumes that all biologic therapies are equally effective in the maintenance phase. Evidence from the induction phase and treatment sequence analysis suggest this unlikely to be the true.

On consideration of the extensive issues with estimated transition probabilities used in the company base-case, the ERG consider the IM-UNITI IPD data to represent the only plausible estimates of relative effectiveness of biologic therapies to conventional care. The IM-UNITI IPD transition probabilities are therefore included in the ERG's base-case analysis presented in Section 6.

Long-term effectiveness of biologics

While the base-case analysis assumes a maximum duration of biologic treatment of one year there is considerable evidence to suggest that in practice patients receive biologic treatment for a longer period of time. Acknowledging this issue the company present scenario analysis considering longer maximum durations of treatment. There is, however, no clinical data supporting the long-term effectiveness of biologic therapies. The company's model therefore assumes that patients transition using the same transition probabilities as were used in the maintenance period. This is likely to overestimate the effectiveness of biologic therapies as it is common for patients to lose response to therapy over time, for example due to the development anti-bodies that prevent the drugs from working properly. These scenario analyses are therefore likely to overestimate the benefits of biologic therapy relative to conventional care.

Discontinuation due to lack of efficacy

The CS incorporated discontinuation due to lack of efficacy in the model during the maintenance phase. The percentage of patients discontinued is calculated using the number of patients who discontinued the trial due to lack of efficacy over the total number that entered the maintenance phase. The percentage is then converted into an instantaneous rate followed by a per-cycle probability of discontinuation occurring using the exponential formula (details are presented CS, equation 1, pg. 183). Combined cycle probabilities for ustekinumab and vedolizumab are calculated using the proportion of the patients on the higher or lower dose of the treatment. The rate for infliximab is taken directly from the ACCENT I trial and the rate for adalimumab is assumed to be same as infliximab.

Table 52 presents the percentage of discontinuation, instantaneous rate and cycle probability for all active treatments.

Table 52 Discontinuation due to lack of efficacy (CS, table 41, pg. 184)

	Number of patients	Number discontinued	% discontinued	Instantaneous rate	Cycle probability	Reference
Ustekinumab q12w	***	***	***	***	***	IM-UNITI CSR
Ustekinumab q8w	***	***	***	***	***	IM-UNITI CSR
					***	Calculated

Infliximab combined*	385	31	8.05%	0.16%	0.32%	ACCENT I
Adalimumab	385	31	8.05%	0.16%	0.32%	Assumed equal to Infliximab
Vedolizumab 8 week	154	58	37.66%	1.03%	2.03%	GEMINI II
Vedolizumab 4 week	154	48	31.17%	0.81%	1.61%	GEMINI II
Vedolizumab combined					2.03%	Calculated

Key: CSR; clinical study report; q8w, every 8 weeks; q12w, every 12 weeks.
Note: *Infliximab included as scenario analysis only. *In italics*: The corrected number was provided during clarification process and was presented in CS response to clarification table 44 pg. 90.

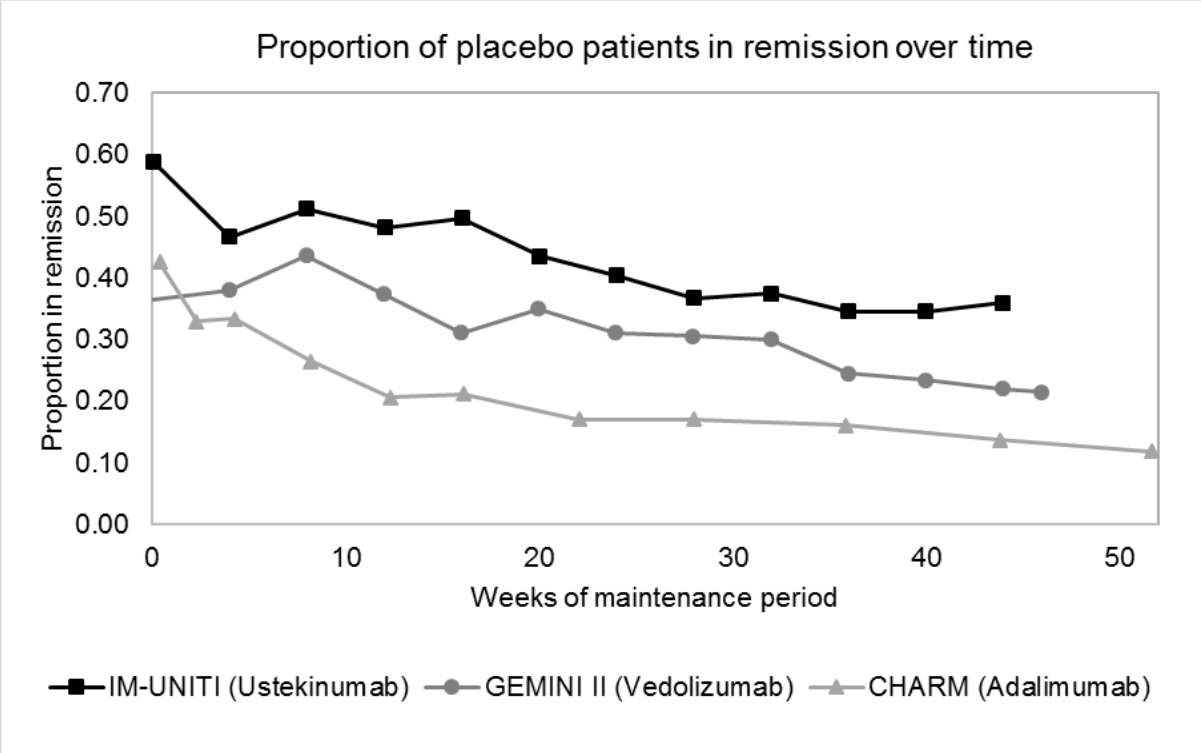
The cycle probabilities of discontinuation are applied to the proportion of patients in the moderate to severe health state, as it is assumed that patients will be in this state if there is loss of response. It should be noted that patients once discontinued move onto conventional care for the remainder of the time horizon or until death. The CS noted that this assumption may underestimate the true proportion of patients discontinuing as the rate is applied to only patients in the moderate to severe state, and also mentioned that it is not possible to know the percentage of patients in the moderate to severe state over time from the study data.

Post maintenance transition probabilities

In the CS base-case model, the biologic maintenance phase ends following the treatment period of one year and patients are switched to conventional care, on which they continue for the duration of the model (60 years in the base case) unless death occurs. However, a gradual decline in efficacy (post treatment) was assumed over a period of time rather than a sharp decline due to immediately discontinuing a biologic. The CS noted that this accounts for an expected carryover effect caused by the recently stopped biologic treatment.

The CS used the placebo arms of the maintenance trials to model this decline. Figure 7 presents the proportion of placebo patients in remission over the maintenance phase of ustekinumab, vedolizumab and adalimumab.[23, 40, 41] Due to a lack of available data, infliximab is assumed to be equal to adalimumab when included in scenario analysis.

Figure 7 Proportion of placebo patients in remission during maintenance phase (CS, figure 46, pg. 186)



Sources: Ustekinumab, IM-UNITI CSR[42]; Vedolizumab, Sandborn *et al.* 2013[40]; Adalimumab, Colombel *et al.* 2007[23]

It should be noted that the change in the proportion of patients in remission over the maintenance phase was calculated for the placebo arm of each study, assuming that this either decreases or remains constant over time. These data were reweighted between 0% and 100% to estimate a percentage of patients who were in remission at the beginning of maintenance and who remained in remission at each time-point out of the percentage of patients who remained in remission at the end of maintenance for each cycle. This was used to weight matrices between conventional care and biologic treatment over time, reflecting the gradual decline in efficacy. All treatments begin the post-maintenance period with a weighting of 100% biologic and 0% conventional care, but have fully transitioned to a weighting of 0% biologic and 100% conventional care by Week 52. Table 53 presents the resulting data.

The ERG is concerned that the modelled estimated decline in the benefits of biologic therapy might not be realised in real life. The estimated values do not represent the population who have had a year long exposure to biologics then stopped. Further, a number of studies have sought to address to investigate the prognosis of patients who discontinue anti-TNF treatment including a systematic review. The results of the systematic review suggest that the approximately 40% of in remission will relapse within one year.[20] This very much contradicts the prediction of the model which predicts that greater than 90% of all patients will hold their remission over 12 months. This contradiction is

however, as a consequence of problems with the methods used to calculate the maintenance phase transition probabilities rather than as a consequence of the assumption that patients will have a gradual transition following discontinuation of biologic therapy. The ERG therefore does not address this issue further in its scenario analysis.

Table 53 Biologic transitions post-maintenance phase (CS, table 42, pg. 188)

Week	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	
Ustekinumab	100%	100%	50%	50%	50%	50%	50%	50%	50%	50%	37%	37%	24%	
Vedolizumab	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	64%	64%	
Adalimumab	100%	100%	100%	69%	69%	69%	48%	48%	28%	28%	28%	28%	28%	
Infliximab*	100%	100%	100%	69%	69%	69%	48%	48%	28%	28%	28%	28%	28%	
Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Ustekinumab	24%	9%	9%	9%	9%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Vedolizumab	64%	64%	64%	64%	61%	61%	57%	57%	21%	21%	13%	13%	4%	0%
Adalimumab	17%	17%	17%	17%	17%	17%	17%	14%	14%	14%	14%	6%	6%	0%
Infliximab*	17%	17%	17%	17%	17%	17%	17%	14%	14%	14%	14%	6%	6%	0%
Note: *Infliximab included as scenario analysis only														

5.2.7.2 Surgery

The CS economic model used an annual rate of surgery of 7%, taken from NHS Hospital Episode Statistics (HES) data.[44] The annual rate of surgery is converted into a 2-week cycle rate using the exponential formula, and the resulting probability for surgery is 0.28% per cycle.[45]

The CS noted due to lack of data in UNITI trials the post-surgery transitions were used from Bodger et al.[28] and methodology was similar with the TA352.[38] The transitions were given for 8-week cycles. Therefore, an identity matrix is applied for three consecutive cycles, followed by application of the post-surgery transitions. Table 54 presents post-surgery transitions used in the CS model. The cost of surgery was only applied in the cycle in which transition to surgery (by which double-counting of costs were avoided).

Table 54 Post-surgery transitions (CS, table 43, pg. 189)

	Remission	Mild	Moderate-severe	Surgery
Conventional care failure				
Patient numbers	105	15	12	67
Transition probabilities	0.528	0.075	0.060	0.337
TNF failure				
Patient numbers	41	6	5	26
Transition probabilities	0.526	0.077	0.064	0.333
Key: TNF, tumour necrosis factor.				

The ERG considers the data sources used in the modelling appropriate, but note that other plausible sources of the frequency of surgery are available that suggest somewhat different rates of surgery amongst CD patients. For example, a population-based cohort study by Ramadas et al. (2010)[46] reported that 1-year cumulative probability of surgery were 32%, 25% and 19% for the cohort of people diagnosed in 1986-1991, 1992-1997 and 1998-2003, respectively. The ERG, however, note that the data available from the Ramadas study are old and mostly predate the widespread use biologic therapy in the UK. In the opinion of the ERG he figures used by the company are therefore more likely to represent current rates of surgery amongst CD patients in UK practice. For completeness the ERG explored the impact of the different surgery rates using plausible maximum and minimum rates of surgery based on this alternative source of data as a scenario analysis presented in Section 6.

5.2.7.3 Adverse events of treatment and surgical complications

In the CS model, AEs of treatment and surgical complications were sourced using the same criteria as used in the NICE submission of vedolizumab.[45] It should be noted, the NICE submission of vedolizumab, AEs for inclusion were based on the opinion of two clinical experts and estimates of the incidence of adverse events were derived through a simple (unadjusted) pooling of adverse event data reported in the publications of the pivotal clinical trials of the biologics identified in the MTC. The incidence of AEs was calculated as number of AEs divided by the total number of patients.[39]

In the CS model then the rates were converted into a cycle rate using the exponential formula, taking into account the duration of each study. The cycle rates used in the base case are given in Table 55, and a scenario is tested assessing the impact of not including AEs.

The ERG is largely satisfied with the approach taken to estimating the AE rates used in the model.

Table 55 Cycle rates of AEs (CS, table 44, pg. 191)

Treatment	Serious infection	Tuberculosis	Lymphoma	Hypersensitivity	Skin reactions	Source
Ustekinumab	0.34%	0.00%	0.00%	0.01%	0.75%	UNITI-1, UNITI-2 and IM-UNITI[19, 22, 34]
Vedolizumab	0.32%	0.00%	0.00%	0.00%	*0.59%*	GEMINI I & GEMINI II[40]
Adalimumab	0.32%	0.00 %	0.00%	0.00%	10.37%	Colombel *et al.*[23], Hanauer *et al.*[15], Rutgeerts *et al.*[47], Sandborn *et al.*[48], and Watanabe *et al.*[16]
Conventional care	0.37%	0.00%	0.00%	0.00%	1.45%	Pooled placebo data from above trials
Infliximab*	0.20%	0.00%	0.00%	0.00%	0.72%	Hanauer *et al.*[24] and Colombel *et al.*[49]

Note: *Infliximab included as scenario analysis only. *In italics:* The corrected numbers were provided during clarification process and were presented in CS response to clarification table 45 pg. 91.

Surgical complications are also considered within the economic analysis and are presented in Table 56. It is assumed that surgical complications have an effect on costs only, and not on HRQoL, this is consistent with TA352.[45] The ERG is satisfied with the approach.

Table 56 Cycle rate of surgical complications (CS, table 45, pg. 192)

Adverse event	Proportion
Wound infection	2.10%
Prolonged ileus/bowel obstruction	1.15%
Intra-abdominal abscess	0.40%
Anastomotic leak	1.02%
Sources: Pooled estimates from the following studies: McLeod *et al.*[50], Milsom *et al.*[51], Zurbuchen *et al.*[52], Kusunoki *et al.*[53], Fazio *et al.*[54], Irvin *et al.*[55], Eshuis *et al.*[56], Maartenese *et al.*[57], Ikeuchi *et al.*[58], Cameron *et al.*[59], Stocchi *et al.*[60] and Funayama *et al.*[61]	

5.2.7.4 Mortality

The CS economic model included rates of all-cause mortality which were taken from the Office for National Statistics (ONS) life tables for England and Wales, 2012–2014 (the most recent available data).[62] Mortality was weighted by sex to account for differences in mortality between men and women. The ratio of male and female patients within the treated population of UNITI-1 and UNITI-2 trials was used to estimate the mix of CD patients. The ERG considers this approach reasonable given the available evidence on the mortality risk associated with CD.

5.2.8 Duration of treatment

In the base-case analysis presented by the company the maximum duration of treatment with biologic therapy is assumed to be one year. This one year stopping rule is aligned to the NICE recommendation on duration of treatment for currently available biologics,[26] and as discussed earlier, if biologic therapy is stopped, CD is highly likely to require retreatment. Furthermore, as noted in the CS, evidence from the annual IBD audit[63] suggest that a significant proportion (~90%) of patients receiving currently available biologic therapies remain on treatment for longer than one year. In an acknowledgement of this uncertainty regarding the duration of treatment the impact of longer maximum treatment durations was explored in two scenario analysis carried out by the company. These two scenarios consider the maximum treatment duration periods of two years and three years. The results of these analyses show that the impact of maximum duration of biologic treatment on the cost-effectiveness of biologic therapies is quite significant, reducing the cost-effectiveness of all biologic treatments including ustekinumab relative to conventional care. Given the sensitivity of the model to this input the ERG sought to identify any further evidence. The ERG was unable to identify any further evidence on the duration of treatment for currently available biologic therapies in the UK evidence on duration of treatment in other European countries suggest that duration of treatment with biologic therapies can be long. In a Belgian cohort study of 261 CD patients the cumulative probability of remaining treatment for 1, 5 and 10 years was 93.7%, 65.9% and 58.2% respectively.[64]

In another French and Belgian study enrolling 350 patients the cumulative probability of remaining on treatment was 90.6% and 57.6% at 1 and 5 years, respectively.[65] Similar evidence of the long-term use of biologics was also found in a number of other studies.[66, 67] While it is uncertain how generalizable these studies are to UK practice they do show that patients can remain on biologic treatment for an extended period of time and potentially far longer that maximum one year treatment duration assumed in the company's base-case analysis. To explore this issue further the ERG presents additional scenarios considering longer maximum durations of treatment in Section 6.

5.2.9 Health related quality of life/ Measurement and valuation of health effects

A systematic literature search was undertaken by the company to identify all published observational studies reporting HRQoL data in patients with CD (see appendix 10.3 for a critique of the search strategy). This search identified 45 studies that measured observational HRQoL data in patients with CD. Among those 29 longitudinal studies were included. The included studies reported HRQoL according to a variety of preference-based tools and reported various CD health states, from deep remission to severe CD (see details in CS appendix 8, pg. 171-238. However, these studies were not used in the CS model. The details of the utility estimates used in the CS model are described next.

In the CS model, the main health benefit assessed is quality-adjusted life-years (QALYs). The utility values for four health states i.e. remission, mild, moderate to severe and surgery, were estimated by mapping from a disease specific measure of HRQoL or SF36 to EQ-5D. In the model, decrements in utilities were assumed for adverse events and also disutility decrements are applied to reflect general-population age-related utility decrements over time. The CS considers different sources of evidence for utilities associated with health states, and disutility decrements.

The UNITI-1, UNITI-2 and IM-UNITI trials collected HRQoL data using generic and disease specific measures of HRQoL, specifically, the 36-Item Short Form Health Survey (SF-36), the Inflammatory Bowel Disease Questionnaire (IBDQ), and the Crohn's Disease Activity Index (CDAI). In order to estimate utilities for the economic model, the CS used three published mapping algorithms to map the measures collected in the trials (SF-36, IBDQ and CDAI) onto EQ-5D values. [32, 68 69] A summary of the methods and mapping algorithm used to estimate utility scores is presented in Table 57. The ERG considers that the use of the mapping algorithm is appropriate.

Table 57 Summary of the methods and mapping algorithm used to estimate utility scores

Measures Mapped	Methods	Equations	Sources
SF-36 mapped to EQ-5D	Generalised least squares (GLS) regression analysis	$EQ-5D = 0.0071 + 0.332 \times PF - 0.060 \times RP + 0.303 \times BP + 0.169 \times GH - 0.039 \times VIT + 0.115 \times SF + 0.010 \times RE + 0.237 \times MH$	Rowen et al.[68]
IBDQ mapped to EQ-5D	Regression using mixed procedure to account for the repeated observation in individual patients	$EQ-5D = 0.03043 + 0.0043 \times IBDQ$	Buxton et al.[32]
CDAI mapped to EQ-5D	Regression using mixed procedure to account for the repeated observation in individual patients	$EQ-5D = 0.9168 - 0.0012 \times CDAI$	Buxton et al.[32]
Key: BP, bodily pain; CDAI, Crohn's Disease Activity Index; EQ-5D, EuroQol five dimensions questionnaire; GH, general health; IBDQ, Inflammatory Bowel Disease Questionnaire; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role physical; SF, social functioning; VIT, vitality.			

The CS reported that utilities by health state showed ustekinumab treatment arms with statistically significantly better utility compared with placebo patients in some cases for SF-36 and IBDQ mappings, and also noted that no difference between treatment arms was observed with CDAI scores. In the CS model, pooled utility values (pooling induction and maintenance studies and pooling all treatment arms) are preferred and justified as they give an increased sample size and also presents a conservative assumption that there is no difference in the utility for each health state for patients receiving ustekinumab or placebo. There is also no covariate adjustments for the pooled analysis. The ERG agrees that these are conservative though plausible assumptions while estimating utilities using the published mapping algorithm. The utility estimates in the total population by health state are presented in Table 58. These utilities are applied in both the induction and maintenance phases of the model.

Table 58 Utility values by health state and mapping algorithm (total population - pooling induction and maintenance studies and pooling all treatment arms) (CS, table 46, pg. 195)

	Statistic	SF-36 mapped to EQ-5D	IBDQ mapped to EQ-5D	CDAI mapped to EQ-5D
Remission (CDAI < 150)	N	[redacted]	[redacted]	[redacted]
	Mean (SD)	0.540 (0.070)	0.680 (0.130)	0.820 (0.050)
Mild (150 ≤ CDAI < 220)	N	[redacted]	[redacted]	[redacted]
	Mean (SD)	0.480 (0.070)	0.680 (0.130)	0.700 (0.020)
Moderate to severe (220 ≤ CDAI < 600)	N	[redacted]	[redacted]	[redacted]
	Mean (SD)	0.420 (0.070)	0.550 (0.130)	0.540 (0.070)

Key: CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

The EQ-5D utility values mapped from SF-36 were much lower than the EQ-5D utility values mapped from IBDQ and CDAI scores, (Table 58) and those published in the work by Bodger et al.[28] (Table 5). The EQ-5D utility values mapped from SF-36 further lack face validity compared with the UK population norms; the CS notes that the utility for patients in remission (0.54) is much lower than the for those age 75+ (0.73). This does not seem reasonable when the mean baseline age of patients in the UNITI-1 and UNITI-2 trials (37 and 39) was considered.[22, 34] Therefore, the EQ-5D utility values mapped from SF-36 were not considered appropriate for use within the economic model. The ERG agrees with CS reasoning that the EQ-5D utility values mapped from SF-36 do not reflect UK population norms and are not appropriate to include within the executable model.

The EQ-5D utility values mapped from IBDQ and CDAI scores gave similar results to each other and both sets of results appear reasonable compared with the utility values presented by Bodger et al.[28] (Table 5). Despite the similarity of results between using IBDQ and CDAI scores to map EQ-5D, the mapping from IBDQ to EQ-5D is preferred for the CS base-case analysis. This was justified on the basis of that the fit of the mapping algorithm is superior for IBDQ compared with CDAI (R-squared of 0.45 versus 0.29) in the Buxton et al.[32] study. The ERG agrees with CS.

The CS reported that no trial-based utility values were available for the surgery health state. To be able to incorporate a utility for the surgery health state in the base case, the same assumptions were used as in Bodger et al.[28] whereby for 8 weeks in the surgery health state, it is assumed the first 2 weeks are spent with a utility equal to that of the moderate to severe health state, followed by 6 weeks of utility equal to the remission health state. To estimates QALYs for the 2-week cycle in the CS

model, it was assumed that the 2-week surgery QALY is equal to the 2-week moderate to severe disease QALY.

Table 59 summarises the health state utility values assumed within the company's model. Scenario analyses are conducted to assess the impact of using SF36 and CDAI mapping and of using health state utility values taken from Bodger *et al.* (Table 59).[28]

Table 59 Summary of health state utility values used in the company's model

Health state	IBDQ mapped to EQ-5D (base-case analysis)	SF36 mapped to EQ-5D (Scenario analysis)	CDAI mapped to EQ-5D (Scenario analysis)	Bodger et al. 2009 [28] (Scenario analysis)
Remission	0.80	0.54	0.82	0.82
Mild	0.68	0.48	0.70	0.70
Moderate-severe	0.55	0.42	0.54	0.55
Surgery *	0.55	0.42	0.54	0.55
Key: CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; SF-36, 36-Item Short Form Health Survey; * Utility values were assumed equal to moderate to severe				

The CS model considered decrements in QALYs due to adverse events which were taken from the TA352[45] (Table 60). The weekly probabilities of each adverse event (Table 55, section 5.2.7.3) were multiplied by decrements to give the expected QALY decrement. Finally, these decrements were summed and subtracted from one to give an AE-adjusted weighting factor per cycle for each treatment, as presented in Table 61. The weight factor was incorrectly presented in the main submission, however, at the point for clarification it was corrected by the company. To explore the impact of adverse events the company carried out a scenario analysis excluding adverse events from the model.

Table 60 Utility decrements for adverse events (CS, table 48, pg. 198)

Adverse event	QALY decrement	Source
Serious infection	-0.52	Brown *et al.* (taken as 1 − 0.48)[70]
Tuberculosis	-0.55	Porco *et al.*, (taken as 1 − 0.45)[71]
Malignancy (including lymphoma)	-0.195	Hornberger *et al.* (taken as 1 − 0.805)[72]
Acute hypersensitivity reactions	-0.11	Beusterien *et al.*[73]
Skin site reactions	-0.03	Beusterien *et al.*[74]
Key: QALY, quality-adjusted life year.		

Table 61: Weighting factors applied to health states utility values (CS response to clarification, table 48, pg. 93)

Treatment	Weighting factor
Ustekinumab	99.60%
Vedolizumab	99.04%
Adalimumab	99.75%
Conventional care	99.63%
Infliximab[a]	99.53%
Note: [a] Infliximab included as scenario analysis only.	

In addition to the above, the CS included scenario analysis using adverse event disutlities sourced from a study conducted by Janssen in 2016. The study sought to obtain values specific to Crohn's disease for disutilities occurring as a result of adverse events and surgical complications. In the study members of the general public were given vignettes describing the moderate to severe health state (which was used as the reference state) and vignettes describing the moderate to severe state plus one of the adverse events or complications. The results are presented in Table 62. The CS reported that the results lack face value for some values, namely the mean utility for moderate to severe disease and the disutility or hypersensitivity. Hence why it was not included in the base-case.

Table 62 Results of disutility study that used in scenario analysis (CS, table 50, pg. 199)

Health States	Disutility from reference state (SD)
Moderate – severe CD TTO score (reference state)	0.70 (-)
Hypersensitivity	+0.06 (0.18)
Injection site reactions	-0.00 (0.22)
Serious infection	-0.07 (0.16)
Tuberculosis	-0.23 (0.80)
Lymphoma	-0.26 (0.29)
Bowel surgery TTO score (reference state)	0.69 (-)
Wound infection	-0.02 (0.27)
Prolonged ileus bowel obstruction	-0.11 (0.29)
Intra-abdominal abscess	-0.13 (0.25)
Anastomotic leak	-0.21 (0.27)
Key: CD, Crohn's disease; SD, standard deviation; TTO, time trade-off.	

In the CS economic model, a decrement in utility was assumed over time in line with general-population age-related utility decrements.[75] The CS model used coefficients for age and age-squared from the study by Ara and Brazier 2010 (Table 63).

Table 63 Age-related utility decrements (CS, table 51, pg. 200)

Item	Coefficient	95% CI		Source
Age	-0.0001728	-0.0009053	0.0005597	Ara and Brazier 2010 [75]
age^2	-0.0000340	-0.0000418	-0.0000263	
Key: CI, confidence interval; SE, standard error.				

The ERG is largely satisfied with the approach used by the company to estimate utility scores for the different health states of the company's model. The ERG, however is unclear why the company did not make use of the utilities used in TA352 which were based on EQ-5D data from GEMINI studies; [40, 76, 77] the ERG note the GEMINI studies were not identified in the company's systematic review of utilities probably due to the exclusion of clinical trials in the strategy (see Appendix 10.3). The estimated utility values in the GEMINI studies were elicited directly from the EQ5D using pooled data from the GEMINI II and GEMINI III studies and were estimated by health state regardless of study visit or treatment received (similar to the approach as the CS). The ERG considers that these utility values derived from the GEMINI studies are theoretically superior to the values estimated from the mapping algorithm because they are directly elicited. The utility values from GEMINI studies are, however, similar to those used in the company's base-case and therefore it is not expected to impact on estimated QALYs greatly. The effect on estimated cost-effectiveness is, however, explored for completeness in scenario analysis presented in Section 6.

5.2.10 Resources and costs

The economic model included the following costs:

- Drug acquisition costs
- Administration costs
- Health state costs
- Surgical costs
- Costs of treating adverse events

The data and assumptions used for each of these costs is consider in turn below.

Drug acquisition costs

Drug acquisition costs for biologic treatments were sourced from the Monthly Index of Medical specialties (MIMS)[78]. Dosing information was sourced from the relevant SPCs. The induction dose of ustekinumab and induction and maintenance dosing of infliximab are based on the weight of the patient. Data on the distribution of patient's weight was sourced from the UNITI trials. Table 64 summarises number of doses required in the induction and maintenance phase along with the drug acquisitions costs for each biologic treatment.

Table 64 Treatment costs for the induction phase and maintenance phase

Treatment	Induction		Maintenance Year 1		Average maintenance Year 2+	
	No. of administrations	Total cost	No. of administrations	Total cost	No. of administrations	Total cost
Lower dose: all treatments						
Conventional care failure						
Ustekinumab	1	[redacted]	4	£8,588	4.35	£9,339
Adalimumab	2	£2,113	25	£8804	26.09	£9187
Infliximab (Remicade)*	2	£3,357	6	£10,071	6.52	£10,944
Infliximab (Inflectra)*	2	£3,021	6	£9,064	6.52	£9,849
Infliximab (Remsima)*	2	£3,021	6	£9,064	6.52	£9,849
TNF failure						
Ustekinumab	1	[redacted]	4	£8,588	4.35	£9,339
Vedolizumab	3	£6,150	6	£12,300	6.52	£13,366
Higher dose: all treatments						
Conventional care failure						
Ustekinumab	1	[redacted]	6	£12,882	6.52	£13,998
Adalimumab	2	£2,113	49	£17,255	52.18	£18,375
Infliximab (Remicade)*	2	£3,357	6	£20,142	6.52	£21,888
Infliximab (Inflectra)*	2	£3,021	6	£18,128	6.52	£19,699
Infliximab (Remsima)*	2	£3,021	6	£18,128	6.52	£19,699
TNF failure						
Ustekinumab	1	[redacted]	6	£12,882	6.52	£13,998

Treatment	Induction		Maintenance Year 1		Average maintenance Year 2+	
	No. of administrations	Total cost	No. of administrations	Total cost	No. of administrations	Total cost
Vedolizumab	3	£6,150	11	£22,550	13.04	£26.732
Key: TNF, tumour necrosis factor; q8w, every 8 weeks; q12w, every 12 weeks. **Notes:** *Infliximab included as scenario analysis only.						

The unit cost of ustekinumab is £2,147 per unit 90mg or 130 mg dose. A confidential agreement with the CMU, however, means that that induction treatment requiring 2 to 4 90mg vials dependent on the patient's weight will be supplied at [redacted] per vial. The mean cost of induction doses of ustekinumab is therefore [redacted] using the weight distribution of patients recruited into the UNITI trials.

The SPCs for all biologic therapies allow for two alternative dosing regimens. For example, ustekinumab allows for of one 90mg dose every 12 weeks or one 90mg dose every 8 weeks. For patients initiating on ustekinumab it was assumed that remitters would be initiated on 12 week interval dosing and responders who did not achieve remission would be initiated on 8 week interval dosing. All patients initiating other biologic therapies were assumed to start on the lower dose regimen as no data was available to justify alternative mix of doing regimens. For all patients receiving biologic therapy dose escalation was permitted in the model to allow for increased frequency of dosing in patients with inadequate response. Table 65 summarises the starting doses and cycle probability of increasing dosing frequency used in the model. Data are sourced from the relevant maintenance trials where available.

Table 65 Starting doses and dose escalation

	Low dose	High dose	2-week probability	Details	Reference
Ustekinumab (conventional care failure)	86%	14%	2.0%	90mg every 12 weeks to 90mg every 8 weeks	IM-UNITI data[79]
Ustekinumab (TNF failure)	77%	23%			
Adalimumab	100%	0%	3.0%	40mg every 2 weeks to 40mg every week	CHARM data[23]
Vedolizumab	100%	0%	2.0%	300mg every 8 weeks to 300mg every 4 weeks	Assumed equal to ustekinumab
Infliximab – Remicade*	100%	0%	3.0%	5mg/kg every 8 weeks to 10mg/kg every 8 weeks	Assumed equal to adalimumab

	Low dose	High dose	2-week probability	Details	Reference
Infliximab – Inflectra*	100%	0%	3.0%	Assumed equal to Remicade	Assumed equal to Remicade
Infliximab – Remsima*	100%	0%	3.0%	Assumed equal to Remicade	Assumed equal to Remicade
Key: TNF, tumour necrosis factor. **Notes:** *Infliximab included as scenario analysis only.					

The costs of conventional care were calculated using values taken from the TA352 submission which estimated the mix of treatments used based on data reported by the UK IBD Audit Steering Group.[63] Dosing and unit costs used in TA 352 were based on the BNF. Costs used in TA352 were based on data from the years 2011/2012 and therefore we uprated using the HCHS to the 2014/15. This method estimates the he cycle cost of conventional care to be £30.56. It is assumed following TA352 that patients receiving biologic treatment receive 50% of the dose of convention care therapies concomitantly. The ERG is largely satisfied with the dosing and costs of biological therapies used, but has some concerns regarding the conventional care costs used for both biologic patients and conventional care patients.

Biologic patients: As stated above it is assumed that patients receiving biologic treatment receive 50% of the dose of convention care therapies concomitantly. This value is taken from TA352 and is not justified given the limited information on concomitant therapies presented in the CSR of the UNITI trials. The impact of increasing the dosing of concomitant therapies for biologic therapies, however has minimal impact on the ICER due to the relatively low cost of the drugs that make up conventional care.

Conventional care patients: The ERG is unclear why the company did not use the updated IBD audit and why they did not update the costs using the latest costs from the BNF rather than applying an inflation rate. The ERG is also concerned that the costs used do not actually reflect what was received by patients in the conventional care arm of the UNITI trials and there is therefore a mismatch between effectiveness data and cost data used. At the PFC the ERG asked the company for any further data on the concomitant therapies used in the UNITI trials and to include a scenario in the model that costed conventional care based on therapies received in the UNITI trials. The company however, indicted in their response that there was insufficient data available on concomitant therapies to provide such analysis. The ERG consider that the impact of these issues on estimated cost-effectiveness is likely to be minimal due to the relative low costs of conventional care therapies.

Administration costs

Infliximab, vedolizumab and the induction dose of ustekinumab are administered via intravenous infusion. An administration cost of £367.00 was sourced from the NHS Reference costs and are consistent with the values used in TA352.

Maintenance treatment with ustekinumab and all treatments with adalimumab are administered as a subcutaneous injection. This may be administered by a nurse or self-administered. Where needed ustekinumab is provided via home care service provided by Janssen free of charge to the NHS. A similar service is also understood to be in place for adalimumab. The base-case model therefore includes no administration costs for maintenance treatments with ustekinumab and all treatments with adalimumab.

The ERG has no concerns regarding the administration costs used in the model.

Health state costs

The health state costs associated with Crohn's disease included in the model were estimated based on an elicitation exercise of 12 clinicians. Details of the specific process used is presented in the CS on pg. 207 to 208, with full details of the resource item and costs used in Appendix 13 of the CS. The resulting health state costs are summaries in Table 66. Note these differ from those present in the CS which were incorrect. The presented values are corrected values sent to the ERG at the PFC stage. This error did not affect the executable model and therefore does not impact on the cost-effectiveness results presented in the CS.

Table 66 Corrected CDAI health state cycle costs

	Remission		**Mild**		**Moderate to severe**
On/off biologic	**On**	**Off**	**On**	**Off**	
Total costs per patient per year	£1,116	£426	£5,800	£7,764	£14,096
Total costs per patient per cycle	£44.69	£16.32	£222.30	£297.60	£540.29

In addition to the values presented above the company also include scenario analyses based on the values used in TA352. Two sets for values were used in TA352. The base-case analysis in TA352 used values updated for inflation from the Bodger et al.[28] model. Following the ACD response these were updated to included values generated from a survey of clinical experts and nurses. These values are summarised in Table 67.

Table 67 Scenario analysis: Health state costs from TA352

	Remission	Mild	Moderate to severe
Original submission	£1,469	£4,194	£6,551
ACD responses	£1,531	£3,138	£18,964

The ERG has a number of concerns regarding the monitoring costs used in the model. These concern the magnitude of the monitoring costs included in the model; the inclusion of surgery costs in health state costs and the use of differential costs for patients receiving biologics and conventional care in some health states.

Magnitude of health states costs

The ERG is concerned that the health state costs used are very high and significantly greater than the health state costs used in TA352. The company acknowledge this point in the CS, but note that the elicitation of costs though a Delphi process is superior to the methods used generate the monitoring costs in TA 352.

The ERG have no specific concerns about the process used to generate the health state costs, but do not consider them to necessarily be superior those use in the ACD response of TA352 which were based on a survey of clinicians and nurses. Furthermore, the ERG note that they are substantially higher than estimated in number of recent costing studies. For example, a recent costing study looking at the cost associated with care of 100 patients before and after receiving infliximab estimated mean annual non-treatment costs prior to the initiation of infliximab to be £4,965 and post to be £2,214.[85] This compares with estimated mean monitoring costs in the first year of the company's model (conventional care failure population) of £12,226 for convention care patients and £9,742 for infliximab patients. Another UK costing study of 72 matched patients compared the cost-effectiveness of adalimumab and infliximab.[86] This study estimated annual non-treatment costs to be £3,103 for adalimumab and £1,724 for infliximab both substantially lower values than the predicted by the company's economic model.

Differential costs for biologic patients

The ERG has some concerns regarding the justification for the use of differential costs for biologic patients. Differential costs were not used in the previous technology appraisals of biologic therapies for CD. Furthermore, advice from the clinical advisor to the ERG suggests that there was no clear reason to expect costs for patients receiving biologic therapy to be significantly different to those for patients receiving conventional care.

Surgical Costs

The ERG notes that additional surgical costs are included in health state costs such that patients in all health states may undergo surgery independent of the separate surgery health state. The ERG expressed concern at the inclusion of these costs at the clarification stage due the potential for double counting of surgery costs given the separate surgery health state. The company response stated that the clinicians included in the Delphi panel were informed of the separate surgery health state and that they felt that additional surgery costs were appropriate. In an acknowledgement of the ERG's concerns the company also included a scenario analysis in their clarification response which excludes these additional surgery costs. The ERG consider this scenario to be more representative than the company's base-case due to the issue of double counting of surgery costs and because the surgery health state accounts for both the HRQoL impact of surgery as well as the costs and is therefore a superior way of accounting for the impact of surgery.

In summary the ERG considers that the base-case health state costs used are likely to overestimate the management and monitoring costs associated with Crohn's disease. The ERG therefore has a preference for the values used in the in TA352 base-case as these health state costs are more in-line with evidence from published UK costing studies.

Surgical costs

The costs of surgery were based on data from NHS Reference costs using data on the costs of surgery day cases, surgery with stay in hospital of less than 5 days and surgery with stay in hospital of 5 days. The total costs of the surgery were calculated as a weighted average of the cost for each type of surgery. The proportion of patients receiving each type of surgery was estimated in consultation with a UK clinician. The total costs of surgery and the data used in the calculation are summarised in Table 68.

Table 68 Surgery costs

Surgery category	Cost	Proportion	Weighted cost
Surgery day case	£2,767.70	20.00%	£553.54
Surgery <5 days	*£5,734.36*	10.00%	*£573.44*
Surgery >5 days	*£10,992.76*	70.00%	*£7,964.93*
Total cost:			*£8,821.91*
In italics: The corrected numbers were provided during clarification process and were presented in CS response to clarification table 22 pg. 56.			

In addition to the direct costs of surgery, costs were also included for complications resulting from surgery. The rate of surgical complications used in the company's model was based on data used in

TA 352. Costs were sourced from NHS Reference costs 2014/15. These costs were added to the total surgical costs to give a surgical health state costs which is applied on entering the surgical health state. The total surgical health state costs including the costs of complications are summarised in Table 69.

Table 69 Total surgery cost

Costs	Additional hospital days	Outpatient visits	Risk per surgery	Weighted costs
Wound infection	4.0	1.0	2.10%	*£338.58*
Prolonged ileus/small bowel obstruction	4.5	1.0	1.15%	*£211.00*
Abdominal abscess	7.0	2.5	0.40%	*£118.97*
Anastomotic leak	9.5	2.5	1.02%	*£396.31*
Surgery			-	*£8,821.91*
	Total cost of surgery			*£9,886.76*

In italics: The corrected numbers were provided during clarification process and were presented in CS response to clarification table 24 pg. 57.

The ERG has no concerns regarding the surgical costs included in the model beyond the issue raised above regarding the inclusion of surgical costs in the health state costs.

Adverse events costs

Five AEs were included in the model: serious infection (defined as septicaemia, pneumonia, urinary tract infections, respiratory infections and bronchitis), tuberculosis, hypersensitivity, injection site reactions and lymphoma. The costs for all AEs, except for lymphoma, were sourced from NHS Reference Costs 2014/15 and are consistent with values used in TA 352. Following TA 3252 the cost of lymphoma the average of lymphoma costs from three technology appraisals of rituximab for lymphoma.

Table 70 summarises the adverse event costs used in the model.

Table 70 Adverse event costs

Adverse event	Cost	Source
Serious infection	£3,957	NHS Reference Costs 2014/15.[80] Average HRGs of: septicaemia, pneumonia, urinary tract infection, respiratory infection, and bronchitis
Tuberculosis	£2,650	NHS Reference Costs 2014/15.[80] Average of non-elective short and long stay tuberculosis, with CC score 0–1
Hypersensitivity	£3,337	NHS Reference Costs 2014/15.[80] Average of non-elective short-stay and long-stay pyrexia
Injection site reactions	£5,240	NHS Reference Costs 2014/15.[80] Average HRGs of skin disorders with interventions
Lymphoma	£15,399	NICE (2003)[81], NICE (2012)[82], and NICE (2011).[83] Average of lymphoma costs from three technology appraisals for rituximab (TA65, TA243, and TA226). Inflated from 2011/12 values to 2014/15 values using PSSRU 2015[84]
Key: CC, complication and comorbidity; HRG, Healthcare Resource Group; NHS, National Health Service.		

The ERG considers the cost values used for adverse events to be largely appropriate, but is concerned about the value used for injection site reactions. The value used in the CS is far in excess of the £1,363 value used in TA352 and it is the opinion of the ERG that this likely to overestimate the costs associate with treating infection site reactions. This is unlikely to have a significant impact on the total costs associated with delivering ustekinumab, though may have greater impact on comparator costs particularly adalimumab for which skin reaction are more common. The ERG therefore presents an alternative analysis in Section 6 using more appropriate values from NHS reference costs.

5.2.11 Cost effectiveness results

The CS model was updated at the clarification stage and updated results provided to the ERG in the company's response to clarification letter. The results presented in this section are those presented in the company's response letter and therefore differ slightly from those presented in the CS. In this section results are presented for the deterministic base-case analysis; probabilistic sensitivity analysis; one-way deterministic sensitivity analysis (OWSA); and, scenario analysis. All results are presented without the PAS for the comparator therapy vedolizumab which are instead presented in a confidential appendix. The presented results do, however, included a discount agreed with the CMU on the price of induction doses of ustekinumab. The CS also presented additional results on the clinical outcomes from the model such as Markov traces not presented here (see CS response to clarification, section 5.7.2.1, pg. 106-112 and CS appendix 15, pg. 348-350).

Due to their being multiple comparator therapies, the CS conducted an incremental analysis to compare multiple mutually exclusive treatments against each other to find the most cost-effective

treatment option out of all the available interventions. Three steps were included to conduct the analysis and were described as:

1. Treatments are ordered from least to most expensive.
2. Then, checked for strong dominance. Treatments are dominated if they are both costlier and less effective than another treatment included in the analysis.
3. Then, checked for extended dominance. Treatments are extendedly dominated if an alternative treatment can provide more QALYs for a lower cost per QALY.

Base-case results

Base-case incremental cost-effectiveness analysis results excluding infliximab

Base-case results are presented for both the conventional care failure and anti-TNF failure populations. Incremental analyses are shown for the conventional care failure population and the TNF failure population in Table 71 and Table 72, respectively. The results from the incremental analysis indicate that ustekinumab dominates both conventional care and adalimumab in the conventional care failure population, and that ustekinumab dominates both conventional care and vedolizumab in the anti-TNF failure population. The benefit is difficult to interpret due to relatively small QALY gains between the treatments, therefore the results are expressed in net monetary benefit (NMB) using a willingness to pay (WTP) threshold of £30,000 (NMB > £0 indicates cost-effectiveness at the specified threshold). The results indicates that choosing ustekinumab over conventional care has highest monetary benefit in both the conventional care failure population (NMB of £27,499) and in the anti-TNF failure population (NMB of £13,234).

Table 71 Base-case results: conventional care failure population (CS response to clarification, table 65, pg. 103)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)	NMB - active treatment vs. conventional care
Ustekinumab	£263,053	43.0941	13.0799			Dominant		*£27,499*
Conventional care	£278,542	43.0941	12.6796	£15,489	-0.4003	-	Dominated	-
Adalimumab	£283,762	43.0941	12.9406	£20,709	-0.1393	£19,999	Dominated	*£2,610*

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*

Table 72 Base-case results: TNF failure population (CS response to clarification, table 66, pg. 103)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)	NMB - active treatment vs. conventional care
Ustekinumab	£288,088	44.9817	12.9819			Dominant		*£13,234*
Conventional care	£294,600	44.9817	12.7578	£6,512	-0.2241	-	Dominated	-
Vedolizumab	£302,820	44.9817	12.8474	£14,732	-0.1345	£91,779	Dominated	*-£5,533*
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; TNF, tumour necrosis factor; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*								

Base-case incremental cost-effectiveness analysis results including infliximab

In the CS base-case, infliximab is not included due to lack of CDAI-100 induction efficacy data. However, it is included as a scenario analysis in Table 73, using the CDAI-100 outcome and assuming equal efficacy for adalimumab and infliximab, and in Table 74 using the CDAI-70 outcome. In the CDAI-100 scenario ustekinumab remains the most cost-effective treatment option. In the CDAI-70 scenario ustekinumab is no longer the most cost-effective treatment, and Inflectra (infliximab) is most the cost-effective treatment option**.**

Table 73 Base-case results: conventional care failure population including infliximab (CDAI-100) (CS response to clarification, table 67, pg. 104)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)	NMB - active treatment vs. conventional care
Ustekinumab	£263,053	43.0941	13.0799			Dominant		*£27,499*
Conventional care	£278,542	43.0941	12.6796	£15,489	-0.4003	-	Dominated	-
Infliximab - Inflectra	£278,693	43.0941	12.8503	£15,640	-0.2296	£883	Dominated	*£4,971*
Infliximab - Remsima	£278,693	43.0941	12.8503	£15,640	-0.2296	£883	Dominated	*£4,971*
Infliximab - Remicade	£279,698	43.0941	12.8503	£16,645	-0.2296	£6,772	Dominated	*£3,965*
Adalimumab	£283,762	43.0941	12.9406	£20,709	-0.1393	£19,999	Dominated	*£2,610*
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*								

Table 74 Base-case results: Anti-TNF failure population including infliximab (CDAI-70) (CS response to clarification, table 68, pg. 105)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) vs conventional care	ICER (£) incremental (QALYs)	NMB - active treatment vs. conventional care
Ustekinumab	£264,420	43.0941	13.0583			Dominant		*£24,995*
Infliximab - Inflectra	£264,476	43.0941	13.1688	£56	0.1104	Dominant	£504	*£28,252*
Infliximab - Remsima	£264,476	43.0941	13.1688	£0	0.0000	Dominant	Dominated	*£28,252*
Infliximab - Remicade	£265,930	43.0941	13.1688	£1,454	0.0000	Dominant	Dominated	*£26,798*
Conventional care	£278,219	43.0941	12.6851	£13,743	-0.4836	-	Dominated	-
Adalimumab	£286,251	43.0941	12.9153	£21,776	-0.2535	£34,897	Dominated	*-£1,127*

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*

5.2.11.2 Results of sensitivity analysis and scenario analysis

Probabilistic sensitivity analysis results

The probabilistic sensitivity analysis (PSA) was run on the model for both populations, using 5,000 simulations.

The results are presented in Table 75 and Table 76 for the conventional care failure and anti-TNF failure populations, respectively. The conclusions of the probabilistic results indicate that ustekinumab is dominant against conventional care in both populations. Additionally, ustekinumab is dominant against adalimumab in the conventional care population, and against vedolizumab in the anti-TNF failure population.

The results of PSA are very different compared to the deterministic analysis (compare Table 71 and Table 75 with for conventional care failure population, and Table 72 and Table 76 for TNF failure population). There is significant increase in total costs and total QALYs for all treatments in the PSA results comparing with deterministic analysis results. The differences in resulting incremental costs and QALYs are also greater in the PSA, resulting in greater net monetary benefit. These suggest that the model is non-linear in its inputs and therefore the deterministic results should not be relied upon. The ERG therefore carries out all it scenario and sensitivity analysis using a probabilistic ICER.

Table 75 Probabilistic incremental analysis – conventional care failure population (CS response to clarification, table 77, pg. 113)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	NMB - active treatment vs. conventional care
Ustekinumab	£313,612	15.5219				*£37,749*
Adalimumab	£338,497	15.3670	£24,885	-0.1549	Dominated	*£8,219*
Conventional care	£338,505	15.0933	£24,893	-0.4285	Dominated	-
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*						

Table 76 Probabilistic incremental analysis – TNF failure population (CS response to clarification, table 78, pg. 113)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	NMB - active treatment vs. conventional care
Ustekinumab	£347,103	15.5672				*£21,847*
Conventional care	£360,982	15.3017	£13,880	-0.2656	Dominated	-
Vedolizumab	£365,790	15.4153	£18,688	-0.1519	Dominated	*-£1,397*
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TNF, tumour necrosis factor NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*						

Cost-effectiveness acceptability curves (CEACs) are presented in Figure 8 and Figure 9 for the conventional care failure and anti-TNF failure populations, respectively. The results indicate that, in both populations, ustekinumab has a 100% chance of being the most cost-effective treatment available at the £30,000 WTP threshold.

Figure 8 Cost-effectiveness acceptability curve: conventional care failure (CS response to clarification, figure 60, pg. 118)

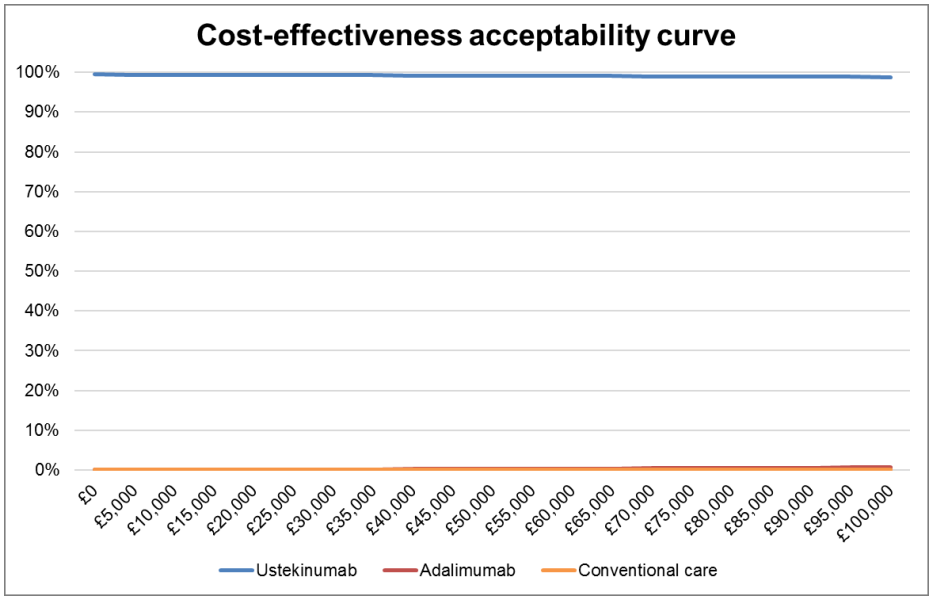
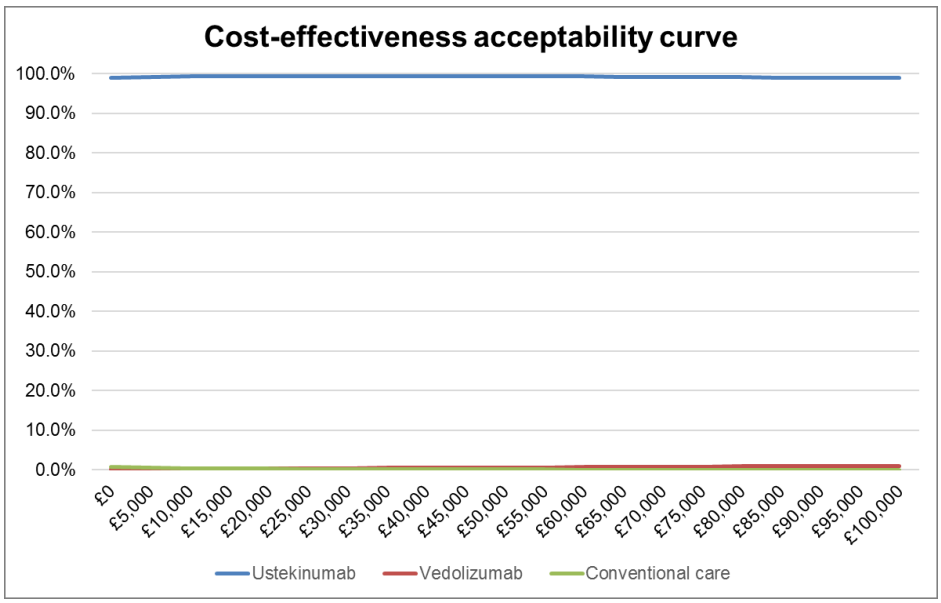


Figure 9 Cost-effectiveness acceptability curve: Anti-TNF failure (CS response to clarification, figure 61, pg. 118)



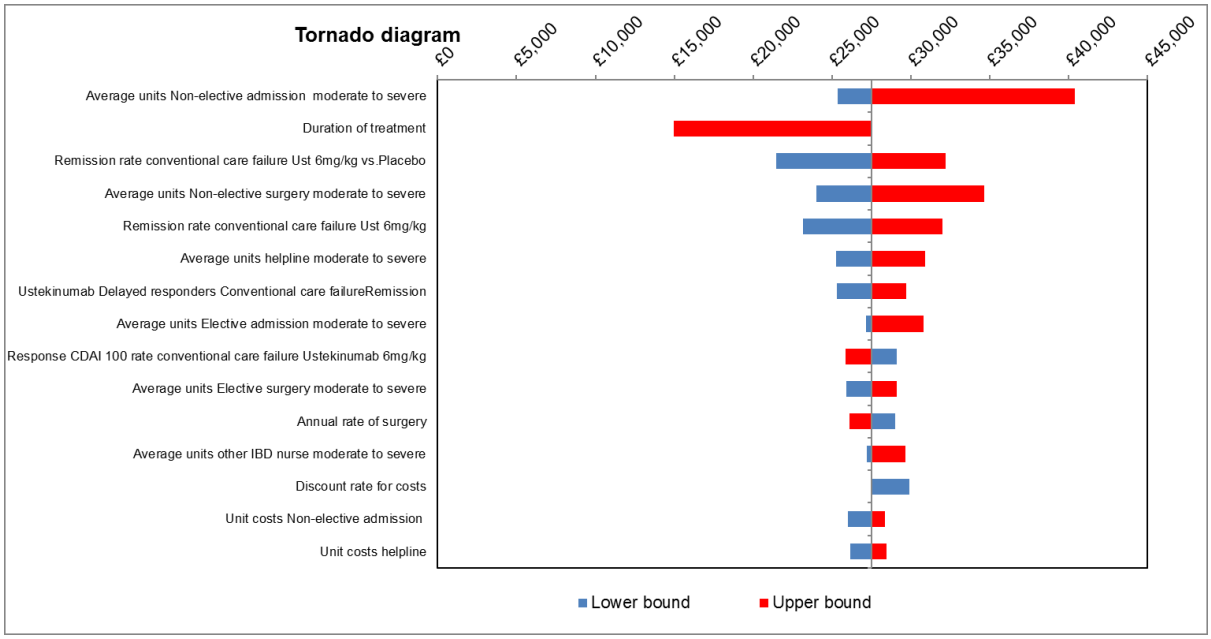
Deterministic sensitivity analysis results

In one-way sensitivity analysis (OWSA), variables were replaced with their upper or lower bounds from PSA. The model was then run with these values. The CS noted that due to relatively small QALY gains between treatments, testing upper and lower bounds may result in ICERs moving between quadrants of the cost-effectiveness plane and can therefore be difficult to interpret. Therefore, the OWSA results are shown in terms of NMB using a WTP threshold of £30,000 as NMB

is easier to interpret where small QALY gains are concerned (NMB > £0 indicates cost-effectiveness at the specified threshold).

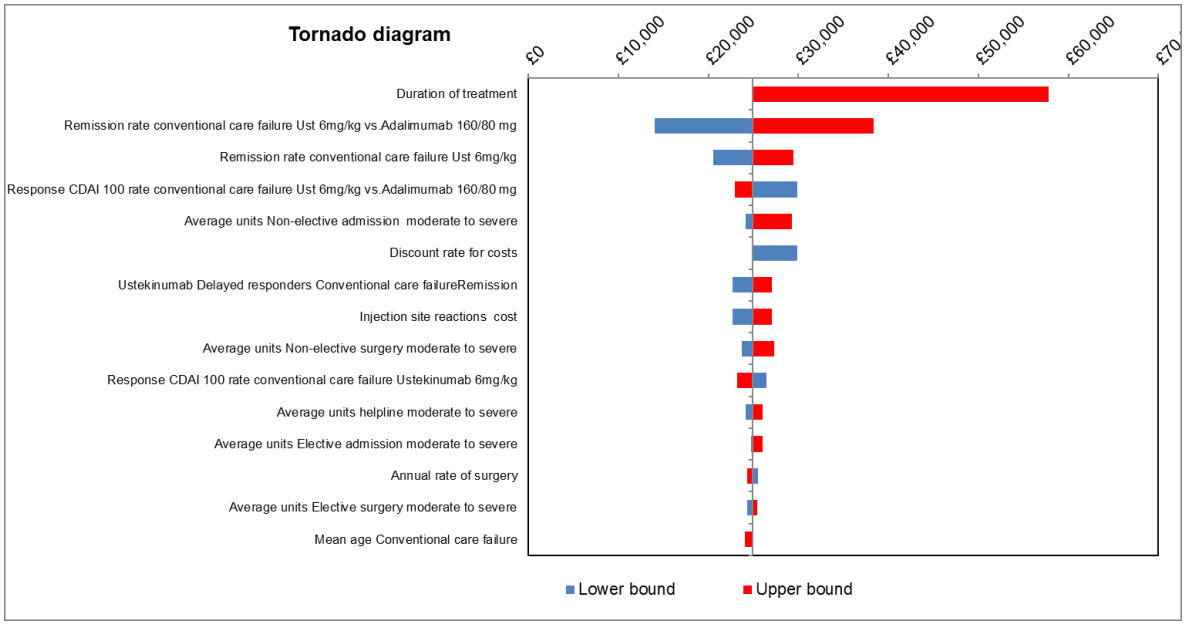
The variables that had the biggest impact on the cost-effectiveness of ustekinumab relative to conventional care were plotted on tornado diagrams and presented for the conventional care failure and anti-TNF failure populations in Figure 10 and Figure 12, respectively. The results indicate that duration of biologic treatment, induction efficacy, and several resource use frequencies for the moderate to severe health state have large effects on the NMB for both populations. Figure 11 and Figure 13 show the results of ustekinumab versus adalimumab and vedolizumab in their respective populations. The results indicate that induction efficacy and resource use units for the moderate to severe health state have an impact on both comparisons. These results demonstrate that the NMB remains above zero (and hence ustekinumab remains cost-effective) under extreme values of all parameters, for all treatments. It should be noted that for duration of treatment the lower bound is equal to the base-case value. The CS noted that the influential parameters versus biologics were in-line with other economic evaluations identified in the cost-effectiveness review (see CS, Section 5.1.2.1, pg. 162-163).

Figure 10 Tornado diagram versus conventional care: conventional care failure population (base case NMB = £27,499) (CS response to clarification, figure 62, pg. 120)



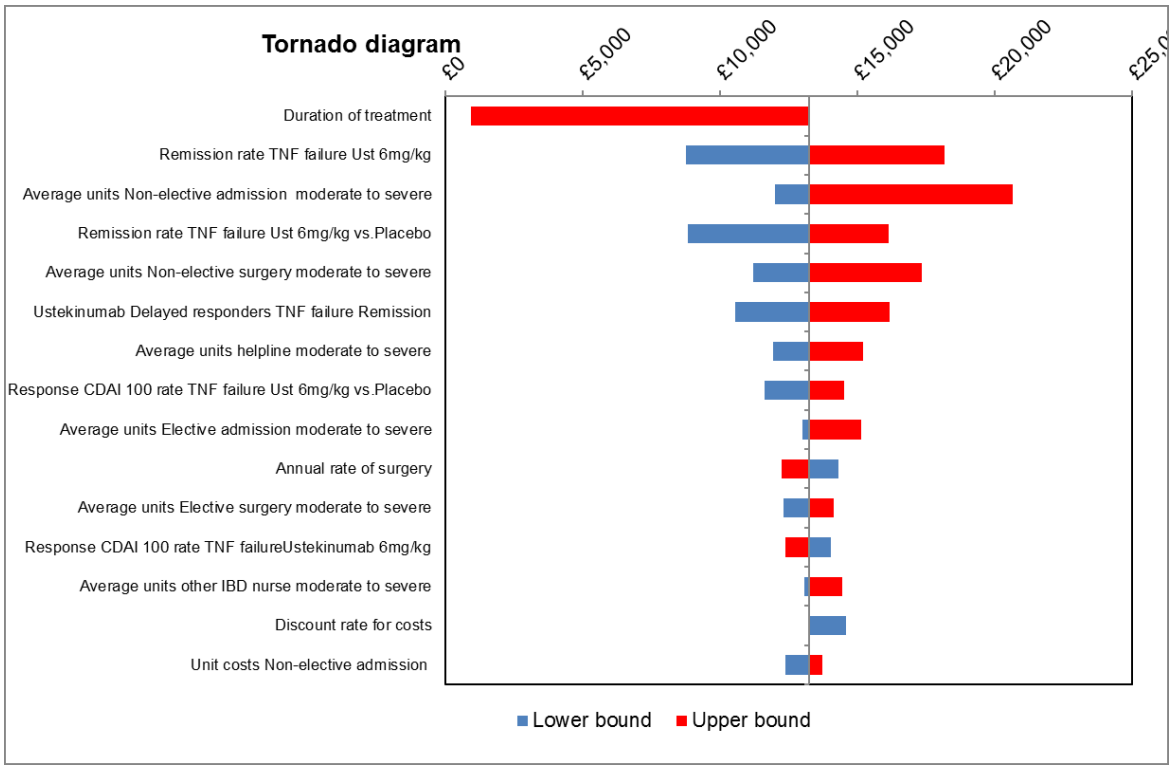
Key: IBD, inflammatory bowel disease; ust, ustekinumab.

Figure 11 Tornado diagram versus adalimumab: conventional care failure population (base case NMB = £24,888) (CS response to clarification, figure 63, pg. 120)



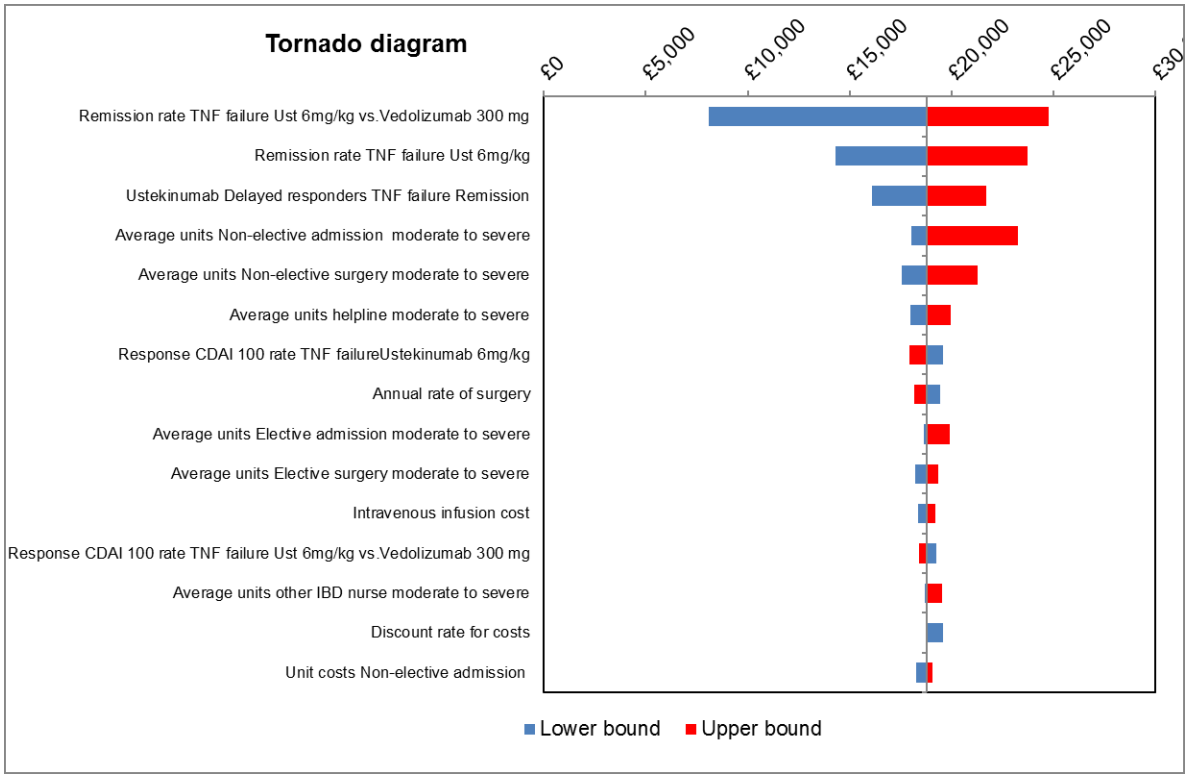
Key: IBD, inflammatory bowel disease; q8w, every 8 weeks; q812, every 12 weeks; ust, ustekinumab.

Figure 12 Tornado diagram versus conventional care: TNF failure population (base case NMB = £10,993) (CS response to clarification, figure 64, pg. 121)



Key: IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ust, ustekinumab.

Figure 13 Tornado diagram versus vedolizumab: TNF failure population (base case NMB = £17,422) (CS response to clarification, figure 65, pg. 122)



Key: IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ust, ustekinumab.

Scenario analyses results

A total of 21 scenarios were tested within the model in the company's main submission. The full list is presented in Table 77.

Table 77 Scenario analyses (CS response to clarification, table 79, pg. 122-125)

	Scenario	Base case setting	Scenario setting	Justification
1	Base case	N/A	N/A	N/A
2	10-year time horizon	60 year time horizon	10-year time horizon	To explore the impact of alternative time horizons on the model results. 10-year time horizon was base case in TA352.
3	1-year time horizon		1-year time horizon	
4	2-year treatment duration	1-year treatment duration	2-year treatment duration	The duration of treatment is uncertain; data are available for comparison with other biologic treatments for 1 year of treatment. These scenarios explore the impact of extending the treatment duration. IBD audit 2015 confirms that in practice patients may remain on biologic treatment beyond 1-year
5	3-year treatment duration		3-year treatment duration	
6	No half cycle correction	Half-cycle correction applied	No half-cycle correction applied	To verify that this does not impact results given the short cycle-length used in the model.

7	Alternative utility source: IMUNITI SF-36	Utility source: IMUNITI IBDQ	Utility source: IMUNITI SF-36	To explore the impact of alternative utility values on the results of the analysis.
8	Alternative utility source: IMUNITI CDAI		Utility source: IMUNITI CDAI	
9	Alternative utility source: Bodger *et al.*		Utility source: Bodger *et al.*	
10	Response criteria: CDAI-70	Response criteria: CDAI-100	Response criteria: CDAI-70	Previous trials defined response using CDAI-70. This analysis explores the impact of assessing initial response to treatment based on CDAI-70.
11	Alternative source for resource use costs: TA352 resource use costs – original	Delphi panel resource use estimates used to derive costs.	Costs used in the original manufacturer's submission for TA352	Resource use costs were identified as a key driver of results. This explores the impact of using costs aligned with the most recent Crohn's disease NICE TA.
12	Alternative source for resource use costs: TA352 resource use costs – ACD responses		Costs used in the manufacturer's ACD response for TA352	
13	Ustekinumab dosing all q12w at start of maintenance phase	Ustekinumab dosing split between q12w and q8w at the start of maintenance based on clinician interpretation of the label	Ustekinumab dosing 100% q12w at the start of maintenance	The label for ustekinumab allows clinicians to use their judgement for dosing of ustekinumab. These scenarios explore the impact of the extreme situations.
14	Ustekinumab dosing all q8w at start of maintenance phase		Ustekinumab dosing 100% q8w at the start of maintenance	
15	No gradual decline in efficacy post-biologic maintenance phase	Gradual decline in efficacy is assumed following the end of the biologic maintenance phase	No gradual decline in efficacy is assumed following the end of the biologic maintenance phase	The true impact on efficacy of biologic treatments following discontinuation at the end of maintenance is uncertain, this reflects the extreme and conservative scenario in which efficacy is lost immediately following cessation of treatment.
16	No dose escalation	Dose escalation is included	No dose escalation is included	To explore the impact of dose escalation on results.
17	Alternative maintenance data source: IMUNITI data	Maintenance data source: NMA transitions (calibrated)	Maintenance data source: IMUNITI transitions	To explore the impact of allowing transition probabilities to vary over time using data observed from the IMUNITI study. It is noted that this assumes that all biologic treatments have equal efficacy during maintenance which is a conservative assumption which is not in line with the results of the treatment sequence NMA.
18	AEs not included	AEs included	AEs not included	To explore the impact of AEs on the results of the analysis.
19	Adalimumab lower induction dose	Adalimumab induction dose 160/80	Adalimumab induction dose 80/40	To explore the impact of assuming the lower dose of adalimumab. It is noted that treatment sequence outcomes are only available for the 160/80 induction dose, and so the

				calibrated transition probabilities for the 80/40 induction dose assume the same treatment sequence outcome as for the 160/80 dose and therefore the efficacy of the 80/40 treatment sequence is likely to be over-estimated.
20	Ustekinumab induction efficacy lower bound	Ustekinumab induction efficacy (responders and remitters) based on mean	Ustekinumab induction efficacy (responders and remitters) based on lower bound	To explore the impact of assuming lower efficacy for ustekinumab during induction.
21	Disutility study included	*Disutilities due to AEs in line with TA352; no disutilities due to surgical complications*	*Disutility study results used for disutilities associated with AEs and surgical complications*	To explore the impact of an alternative source for disutilities due to AEs and the inclusion of disutilities due to surgical complications
Key: ACD, Appraisal Consultation document; AE, adverse event; CDAI, Crohn's Disease Activity Index; N/A, not applicable; q8w, every 8 weeks; q12w, every 12 weeks; SF-36; Short-form 36; TA, technology appraisal. *In italics: the base-case and scenario setting were presented incorrectly in the main submission; the ERG updated with correction.*				

Most scenarios tested did not affect the incremental cost-effectiveness decision (assuming a WTP of £30,000 per QALY). However, a few scenarios did affect the decision in both populations. A 1-year time horizon gave ICERs vs. conventional care of £55,376 and £121,408 in the conventional care failure and anti-TNF failure populations, respectively. This is not considered to be a meaningful scenario given the chronic nature of Crohn's disease.

For both populations, ustekinumab is no longer dominant under the scenario of using the original health state costs from TA352. Although, it remains the most cost-effective treatment at a WTP threshold of £30,000 per QALY gained.

Use of 2-year and 3-year maximum treatment durations did not affect the decision for the conventional care population, but did affect for the TNF failure population. Whilst ustekinumab is no longer dominant under this scenario, it remains the most cost-effective treatment at a WTP threshold of £30,000 per QALY gained.

Using IM-UNITI transition probabilities gave ICERs for ustekinumab versus conventional care of £56,516 and £59,956 for the conventional care and the anti-TNF failure populations, respectively. The result indicates that choosing conventional care over ustekinumab has greater monetary benefit for both conventional care failure and anti-TNF failure populations. The CS noted that IM-UNITI placebo arm, which portrays conventional care in this scenario, is not a true placebo arm as patients had previously received and responded to ustekinumab in the induction phase and were then randomised to placebo in the maintenance phase. The CS mentioned that the effect of ustekinumab induction coupled with longer half-life could potentially explain a smaller difference in efficacy between ustekinumab and conventional care which is reflected in the increased ICERs. As discussed

in Section 5.2.7, the ERG considers that IM-UNITI data to be the best available evidence on the relative effectiveness of ustekinumab with conventional care despite the issues noted by the company. The results of each scenario are shown in Table 78 and Table 79 for the conventional care failure and anti-TNF failure populations, respectively.

Table 78 Scenario analysis: conventional care population (CS response to clarification, submission appendix 16, table 64, pg. 127)

	Ustekinumab			Adalimumab			Conventional care		ICER (full incremental analysis)			NMB
#	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Ustekinumab	Adalimumab	Conventional care	Ustekinumab vs. Conventional care
1	**13.08**	£263,053	£25,805	**12.94**	£283,762	£27,716	12.68	£278,542		Dominated	Dominated	***£27,499***
2	5.53	£101,061	£15,117	5.41	£120,913	£17,029	5.17	£114,496		Dominated	Dominated	*£24,403*
3	0.66	£19,236	£8,913	0.66	£31,363	£10,793	0.59	£15,389	£55,771	Dominated		*-£1,778*
4	13.10	£270,567	£34,813	12.87	£305,618	£37,359	12.68	£278,542		Dominated	Dominated	*£20,552*
5	13.12	£276,684	£42,311	12.81	£325,425	£46,926	12.68	£278,542		Dominated	Dominated	*£14,961*
6	13.08	£262,915	£25,808	12.94	£283,386	£27,720	12.68	£278,395		Dominated	Dominated	*£27,497*
7	8.97	£263,053	£25,805	8.90	£283,762	£27,716	8.78	£278,542		Dominated	Dominated	*£21,261*
8	13.17	£263,053	£25,805	13.01	£283,762	£27,716	12.72	£278,542		Dominated	Dominated	*£28,917*
9	13.22	£263,053	£25,805	13.07	£283,762	£27,716	12.79	£278,542		Dominated	Dominated	*£28,444*
10	*13.06*	*£264,420*	*£25,941*	*12.92*	*£286,251*	*£28,246*	*12.69*	*£278,219*		*Dominated*	*Dominated*	*£24,995*
11	13.08	£138,504	£25,805	12.94	£153,224	£27,716	12.68	£136,731	£4,430	Dominated		*£10,236*
12	13.08	£207,195	£25,805	12.94	£225,129	£27,716	12.68	£214,732		Dominated	Dominated	*£19,546*
13	13.07	£263,073	£25,474	12.94	£283,762	£27,716	12.68	£278,542		Dominated	Dominated	*£27,298*
14	13.11	£263,204	£27,825	12.94	£283,762	£27,716	12.68	£278,542		Dominated	Dominated	*£28,309*
15	13.08	£263,326	£25,805	12.97	£282,187	£27,716	12.68	£278,542		Dominated	Dominated	*£27,087*
16	13.07	£263,009	£25,346	12.91	£283,560	£25,995	12.68	£278,542		Dominated	Dominated	*£27,330*
17	12.72	£284,399	£25,848	12.72	£296,691	£27,757	12.65	£280,455	£56,949	£3,111,715		*-£1,867*
18	13.14	£212,120	£25,805	13.01	£221,737	£27,716	12.74	£226,706		Dominated	Dominated	*£26,638*
19	13.08	£263,053	£25,805	13.01	£278,157	£26,287	12.68	£278,542		Dominated	Dominated	*£27,499*
20	13.05	£264,881	£25,718	12.94	£283,762	£27,716	12.68	£278,542		Dominated	Dominated	*£24,692*
21	13.13	£263,053	£25,805	13.00	£283,762	£27,716	12.73	£278,542		Dominated	Dominated	*£27,542*

In italics: Values extracted from the CS executable model; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALY =quality-adjusted life year

Table 79 Scenario analysis: TNF failure population (CS response to clarification, submission appendix 16, table 65, pg. 128)

	Ustekinumab			Vedolizumab			Conventional care		ICER (full incremental analysis)			NMB
#	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Acquisition costs	QALYs	Total costs	Ustekinumab	Adalimumab	Conventional care	Ustekinumab vs. Conventional care
1	***12.98***	£288,088	£24,713	***12.85***	£302,820	£29,727	12.76	£294,600		Dominated	Dominated	***£13,234***
2	5.25	£117,145	£13,678	5.13	£130,883	£18,693	5.05	£121,992		Dominated	Dominated	*£10,723*
3	0.61	£20,793	£7,518	0.59	£29,127	£12,786	0.58	£16,401	£122,877	Dominated		*-£3,319*
4	12.97	£294,695	£31,214	12.84	£309,662	£35,547	12.76	£294,600	£440	Dominated		*£6,401*
5	12.97	£299,967	£36,400	12.84	£315,649	£40,610	12.76	£294,600	£25,551	Dominated		*£935*
6	12.98	£287,969	£24,717	12.85	£302,711	£29,732	12.76	£294,464		Dominated	Dominated	*£13,221*
7	8.98	£288,088	£24,713	8.91	£302,820	£29,727	8.87	£294,600		Dominated	Dominated	*£9,739*
8	13.02	£288,088	£24,713	12.87	£302,820	£29,727	12.77	£294,600		Dominated	Dominated	*£14,052*
9	13.09	£288,088	£24,713	12.94	£302,820	£29,727	12.85	£294,600		Dominated	Dominated	*£13,779*
10	*12.97*	*£289,274*	*£25,035*	*12.85*	*£303,344*	*£30,446*	*12.78*	*£293,328*		*Dominated*	*Dominated*	*£9,662*
11	12.98	£145,652	£24,713	12.85	£154,554	£29,727	12.76	£142,515	£14,002	Dominated		*£3,584*
12	12.98	£226,474	£24,713	12.85	£238,644	£29,727	12.76	£228,745		Dominated	Dominated	*£8,993*
13	12.98	£287,818	£24,330	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated	*£13,446*
14	12.99	£288,990	£25,998	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated	*£12,526*
15	12.98	£288,078	£24,713	12.85	£302,765	£29,727	12.76	£294,600		Dominated	Dominated	*£13,248*
16	12.98	£287,867	£24,437	12.85	£302,025	£28,972	12.76	£294,600		Dominated	Dominated	*£13,427*
17	12.03	£344,394	£24,751	12.01	£352,781	£29,935	11.98	£341,046	£60,403	Dominated		*-£1,685*
18	13.04	£235,958	£24,713	12.91	£250,696	£29,727	12.82	£241,709		Dominated	Dominated	*£12,493*
19	12.98	£288,088	£24,713	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated	*£13,234*
20	12.94	£290,377	£24,547	12.85	£302,820	£29,727	12.76	£294,600		Dominated	Dominated	*£9,695*
21	13.04	£288,088	£24,713	12.90	£302,820	£29,727	12.81	£294,600		Dominated	Dominated	*£13,255*

In italics: Values extracted from the CS executable model; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALY =quality-adjusted life year

In the company's clarification response the company provided results from two additional scenario analyses:

1. True TNF naïve population in conventional care failure (See section 5.2.1 & 5.2.3)
2. Exclusion of surgery cost from the mild/severe health states in both conventional care failure and TNF failure population (See section 5.2.9)

The results of these additional sensitivity analyses are presented in Table 80. Ustekinumab remains dominant compared with other treatments in both analyses.

Table 80: Additional scenario analyses results (CS response to clarification; table 25-26, pg. 58; table 39, pg. 80)

Conventional care failure										
	Ustekinumab		**Adalimumab**		**Conventional care**		**ICER (full incremental analysis)**			**NMB**
#	**QALYs**	**Total costs**	**QALYs**	**Total costs**	**QALYs**	**Total costs**	**Ustekinumab**	**Adalimumab**	**Conventional care**	**Ustekinumab vs. Conventional care**
CS base-case	***13.08***	£263,053	***12.94***	£283,762	12.68	£278,542	**-**	Dominated	Dominated	***£27,499***
Excluding surgery costs from the mild and moderate/severe health states	13.08	£218,119	12.94	£236,872	12.68	£227,730	-	Dominated	Dominated	*£21,621*
True TNF naïve	12.93	£272,140	12.48	£290,357	12.80	£292,393	-	Dominated	Dominated	*£31,679*
Anti-TNF failure										
	Ustekinumab		**Vedolizumab**		**Conventional care**		**ICER (full incremental analysis)**			**NMB**
#	**QALYs**	**Total costs**	**QALYs**	**Total costs**	**QALYs**	**Total costs**	**Ustekinumab**	**Vedolizumab**	**Conventional care**	**Ustekinumab vs. Conventional care**
CS base-case	***12.98***	£288,088	***12.85***	£302,820	12.76	£294,600	-	Dominated	Dominated	***£13,234***
Excluding surgery costs from the mild and moderate/severe health states	12.98	£239,447	12.85	£252,351	12.76	£242,877	-	Dominated	Dominated	*£10,151*

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; *In italics: Values extracted from the CS executable model*

Conclusions

The results of the probabilistic and deterministic sensitivity analyses, and of pre-defined scenario testing demonstrate that ustekinumab remains dominant over comparator treatments in a range of scenarios. The incremental result is changed in only few circumstances - notably, using IMUNITI data as the alternative source of maintenance data transition probabilities.

5.2.11.3 Cost-minimisation analysis results

The CS notes that the results of sensitivity analysis indicate that a cost-minimisation approach may be more appropriate than a full cost-utility analysis as the ICER is subject to large differences due to the small QALY gains in the base-case results. A cost-minimisation analysis was therefore conducted in the CS, using only the acquisition and administration costs for each biologic treatment (derived directly from the cost-effectiveness model). Costs of health states and adverse events were excluded as the biologic treatments are assumed to have equal efficacy and comparable safety profiles. Conventional care was excluded from this analysis on the basis that it is not reasonable to assume that biologic treatments and conventional care have equal efficacy.

The results of the cost-minimisation analysis are presented in Table 81 and Table 82. They indicate that ustekinumab is cost-saving compared with other biologic treatments for both sub-populations.

Table 81 Cost-minimisation analysis: Conventional care failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
Ustekinumab	[redacted]	£367	[redacted]	
Adalimumab	£13,486	£0	£13,486	[redacted]

Table 82 Cost-minimisation analysis: TNF failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
Ustekinumab	[redacted]	£367	[redacted]	
Vedolizumab	£20,307	£5,138	£25,445	[redacted]

It should be noted that the difference between treatment acquisition costs for ustekinumab in conventional care failure and anti-TNF failure population is due to increased use of every 8 weeks

dosing in the anti-TNF population. This is because these patients are at a more advanced stage of disease and therefore are at greater need of dose escalations.

5.2.12 Model validation and face validity check

The ERG undertook a review of the company's Excel based executable model. This included the use of a check list to carry out a series of black box tests to evaluate the internal validity of the model. These black box test the internal logic of the model as well checking the predictive validity of parameter inputs (e.g. that increasing effectiveness of the treatment lowers cost-effectiveness). Further to this, the code of the model was examined for potential errors, this included tracking how parameters fed into the model and an examination of the main calculation sheets with a view to understanding how QALYs and costs are accumulated in the model. This review identified two minor errors. One affecting a number of the calculation sheets in which the proportion of patients with moderate to severe who were responders, was erroneously calculated using the proportion of responders who had a moderate to severe disease. Also the proportion of delayed vedolizumab responders in the CDAI 70 scenario analysis is incorrectly calculated. These errors have minimal impact on the results of the model. Corrected results are presented in Section 6. At the clarification stage the company also identified an error in the way adverse events had been implemented in the model. This was rectified by the company and a revised model sent to the ERG; this error was again minor and does not significantly impact on the results of the model. The ERG would like to note that the ERG's review of the executable model was made significantly more difficult by the company due to the fact that it used multiple names for the same cell in its executable model. This made tracking of precedent and dependent cells much more difficult than necessary.

The company did not formally validate the external validity of the results of the economic model presented in the CS, but did present a discussion of the differences between the presented model and previous economic analyses in Crohn's disease with an emphasis on how they have addressed a number of concerns raised by the ERG in TA 352[39].

A comparison of the results of the model presented in the CS and those of previous cost-effective analyses is useful check especially given the similarities between the two models. Table 3 presents the cost effectiveness results from the previous Bodger et al.[28] model, the model present in TA352 and the company's model.

Table 83 Comparison of results presented in the company submission and previous cost-effective analyses (compared with conventional care)

Technologies	Company submission ICER/QALY		TA352 ACD (2015) ICER/QALY	Bodger (2009) ICER/QALY
	Conventional care failure population	TNF failure population	TNF failure population	Mixed population
Ustekinumab	Dominant	Dominant	-	-
Infliximab	£6,772	-	-	£19,050
Adalimumab	£19,999	-	-	£7,190
Vedolizumab	-	£91,779	£21,620	-
ICER, Incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

A comparison of the results shows that the company model is in-line with those presented by Bodger et al.[28] for the comparator therapies adalimumab and infliximab. The results presented in the current submission regarding the cost-effectiveness of vedolizumab, however, differ significantly from those present in TA352 with the company's model estimating a pairwise ICER for vedolizumab compared to conventional care well in excess of a £30,000 per QALY WTP threshold. Attempts by the ERG to calibrate the company's model to use assumptions more in-line with those used in TA 352 do not reduce this difference and nor is the difference explained by the application of the PAS discount for vedolizumab. Comparison of the assumption used in the company's model and the model presented in TA 352, however, highlight a number of differences in assumption and inputs data that it is not easy to incorporate in the company's model. It is the opinion of the ERG that these alone explain the difference in results. The ERG note in particular that the treatment sequence analysis used in the generation of the transition probabilities is different to the method used to calculate the transition matrices used in TA352 and as discussed in Section 5.2.7.1 these inputs have a significant impact on estimated cost-effectiveness. The ERG is therefore not concerned that these differences in model predictions are due to internal validity error in the company's model, but rather likely due to differences in assumptions and input data.

5.3 Conclusions of the cost effectiveness section

The cost-effectiveness review carried out by the company did not identify any published evidence on the cost-effectiveness of ustekinumab in CD in the UK. Consequently, the company's model represents the most relevant source of existing evidence. The company's analysis is presented for two patient groups, patients who have failed convention care and, patients who have previously failed anti-TNF-α therapy. The comparator therapies in the conventional care failure subpopulation were adalimumab and conventional care. Conventional care consisted of a mix of non-biologic therapies including 5-ASAs, immunomodulators and corticosteroids In this scenario analysis comparison of two

biosimilar remsima and inflectra are also considered assuming equal effectiveness to remicade (infliximab). In the TNF failure subpopulation the economic model include the comparator therapies vedolizumab and conventional care.

Within the conventional care failure subgroup, the company's model estimates ustekinumab to be dominant (lower costs greater effectiveness) compared with adalimumab and conventional care. In the scenario analysis including infliximab, the biosimilar inflectra is the most cost-effective therapy with an ICER of £504 per QALY compared with ustekinumab and dominating all other therapies. Within the TNF failure subgroup, the company's model estimates ustekinumab to be dominant compared to vedolizumab and conventional care.

In addition to the base-case analysis the company also presented a series of one-way sensitivity analyses and scenario analyses to assess the impact of uncertainty around key input variables and assumptions on the ICER estimates. The results of these indicated that the base-case cost-effectiveness estimates were most sensitive to: (i) duration of therapy; (ii) use of alternative transition probabilities based on IM-UNITI IPD data; (iii) the source of health state costs data; and (iv) the time horizon of model.

The health economic model submitted by the company is subject to a number of issues which limit the credibility of the company's results. The principal issues identified by the ERG are outlined in brief below, with an exhaustive list presented in Table 84.

- Omission of key aspects of CD in the model structure including the relapsing-remitting nature of CD and the role of surgery. The impact of these structural failure is difficult to ascertain and the ERG unclear whether correction of the identified structural issues would lead to increase or decrease in the estimated ICER.
- The clinical effectiveness data used to parametrise the model is subject to a number of significant problems relating to both the interoperation of the NMA results and the methods used to generate the transition matrices used. These issues are likely to significantly overestimate the benefits of the ustekinumab therapy compared with conventional care.
- The maximum duration of treatment biologic therapy was assumed to be 1 year in the base-case analysis. Evidence form the annual IBD audit, however, suggest that the vast majority (~90%) of patients continue on currently used biologic therapies for more than one year. Increasing the maximum duration of ustekinumab treatment has the effect of reducing the cost-effectiveness of ustekinumab relative to conventional care.

- The health state cost used in the model potentially overestimate the costs associated with monitoring and managing patients with CD. Use of alternative values from TA 352 reduces the cost-effectiveness of ustekinumab relative to conventional care.

Table 84 List of key concerns identified by the ERG:

	Section
Concerns relating to the model structure/key structural assumption	
The presented model fails to capture the progressive and chronic nature of CD. Specifically, the model does not account for the fact that CD is a relapsing condition.	5.2.1
The model structure does not recognise that patients who receive surgery are likely to have a quite different prognosis and treatment pathway to patients receiving drug therapy. Specifically, the model while allowing for multiple surgeries over a patient's life-time does not consider the impact of surgery on the prospect of receiving future surgery or the long-term impact of surgery on HRQoL, for example where surgery involves resection (removal of inflamed area of the intestine)	5.2.1
Structural assumptions that are inconsistent with clinical practice in the UK - All non-responders are assumed to have moderate to severe disease. However, a proportion of patients who are non-responders will have mild disease (defined as CDAI score between 150 and 220). For instance, a patient with a CDAI score of 250 at baseline with a drop in CDAI of 60 would be classified as a non-responder, but at the end of the induction phase will be in the mild health state (CDAI 150 to 220). - No distinction is made between responders with moderate to severe CD and non-responders (except for continuation on biologic treatment following induction). The ERG believes that the outcomes (HRQoL, management and the probability of surgery) are likely to differ between responders and non-responders. - Response in the base-case analysis is defined as a drop of 100 points or more in the CDAI score, which is consistent with the definition of response used in the UNITI trials. A scenario analysis was also presented in which the alternative criteria of a 70 point drop in CDAI score. It is not clear which of these is the most appropriate response criteria as in clinical practice CDAI score is rarely used and response is assessed based on symptom relief. Therefore, both criteria are equally plausible to define response. - All patients who are still receiving anti-TNF therapy at one year are assumed to discontinue (and subsequently receive non-biologic treatment), irrespective of whether they are currently responding to treatment. In practice it is, however, unclear to what extent clinicians adhere to the guidance requiring patients to discontinue therapy.	5.2.1
Concerns relating to the population	
Both the UNITI trials were international multicentre trials and as such the patients recruited were not necessarily reflective of the patient population in the UK. This is particularly an issue with respect to whether the non-biologic treatments received by both ustekinumab and placebo patients are representative of the care they would receive in UK practice.	5.2.3
The UNITI trials included patients with a CDAI score between 220 and 450; and therefore excluded patients at the higher end of the CDAI spectrum (CDAI > 450). Advice from the clinical advisor to the ERG suggests that the number of patients with a CDAI score in excess of 450 is likely to be small and therefore the exclusion of patients is likely to have only a limited impact on the representativeness of the UNITI trials. It is however, uncertain whether patients with a CDAI score of 450 or greater would benefit to the same degree as patients will less severe disease.	5.2.3
The inclusion criteria for the UNITI-2 trial did not recruit an entirely TNF naïve population, but allowed patients who had previously received anti-TNF therapy to be recruited as long as they had not failed anti-TNF therapy. As such, approximately 30% of UNITI-2 patients had previous experience of using an anti-TNF therapy. This population group is likely to include patients who have been responsive to anti-TNF therapy and as such may be more likely to respond to other biologic therapies such as ustekinumab than a truly TNF naïve patient group. The company do present some limited clinical evidence analysing response and remission rates for both the truly TNF naïve patient group and the patients with TNF experience. However, this data was not included in the economic model.	5.2.3
Concerns relating to the comparators	

In the CS model, the effectiveness of conventional care reflect the effectiveness of the concomitant therapies used in the placebo arm of the UNITI trials. These are made up of combination of therapies including corticosteroids and immunomodulators. A significant proportion of patients (18.7% to 30.1%) also received no concomitant therapies. The mix of therapies is not reflective of current practice in the UK and in particular is concerned that a significant proportion of placebo patients were left untreated. A comparison with IBD Audit data also shows that significantly higher rates of immunomodulators (57% in the IBD- audit data) are used in the UK and lower rates of corticosteroids use (27% in the IBD audit data). These differences mean that the effectiveness of conventional care may not be accurately captured by the UNITI trials as the therapies received are not reflective of current UK practice. In particular the fact that a significant proportion of placebo patients were untreated may lead to the effectiveness of conventional care being underestimated.	5.2.4
Concerns relating to time horizon	
The time horizon used in the economic model was 60 years. The ERG considered the 60 year time horizon to be appropriate, but notes there is considerable uncertainty over the long-term benefits and costs of ustekinumab due to both the short duration of the clinical effectiveness data available (maximum 54 weeks) and the failure of the model structure to incorporate the relapsing remitting nature of CD.	5.2.5
Concerns relating to effectiveness data used to derive the initial induction vectors/transition matrices	
The derivation of the transition probabilities from the treatment sequence analysis makes the implicit assumption that all non-responders to induction treatment remain the moderate to severe health state for the duration of the maintenance period.	4.4, 5.2.7
Estimating transition probabilities: The model makes use of a calibration technique to estimate the transition probabilities of patients in the maintenance phase of the model. This method relies on imposing a series of constraints and selecting a series of starting values. The Excel solver function is then used to estimate transition probabilities that fit with the limited clinical data available. The constraints implied in this process are however, only partially justified and the starting values are entirely arbitrary. Both the constraints imposed and starting values have a considerable impact on the estimated transition probabilities and as consequence the estimated cost-effectiveness of ustekinumab. Furthermore, it is not clear that the transition probabilities estimated are clinical plausible: they do not match or even approximate to the clinical data available from the IM-UNITI trial on the likelihood of maintaining response to treatment during the maintenance phase.	5.2.1, 5.2.7
The economic model in line with the SPC's for ustekinumab, adalimumab and vedolizumab allows for delayed response to induction therapy. The maintenance phase transitions for these patients are however, based on data from initial responders. This is likely to overestimate the effectiveness of these biologic therapies as secondary responders as it is reasonable to assume that secondary responders will not experience the same benefits of maintenance treatment as initial responders, because by definition are less responsive to treatment than initial responders.	5.2.7
Relatability of treatment sequence analysis	4.4, 5.2.7
Long term effectiveness and duration of treatment	
The CS base-case analysis assumes a maximum duration of biologic treatment of one year, however, there is considerable evidence to suggest that in practice patients receive biologic treatment for a longer period of time. There is, however, no clinical data support the long-term effectiveness of biologic therapies assumes that patients transition using the same transition probabilities as were used in the maintenance period. This is likely to overestimate the effectiveness of biologic therapy as it is common for patients to lose response to therapy over time, for example due to the development anti-bodies that prevent the drugs from working properly.	5.2.7, 5.2.8
Concerns relating to HRQoL	
The utility values for four health states were estimated by mapping from a disease specific measure of HRQoL or SF36 to EQ-5D. However is unclear why the company did not make use of the utilities used in TA352 which were based on EQ-5D data from GEMINI studies.	
Concerns relating to resource and costs	
In CS base-case, it is assumed that patients receiving biologic treatment receive 50% of the dose of convention care therapies concomitantly. This value is largely arbitrary and is not justified given the limited information on concomitant therapies presented in the CSR of the UNITI trials.	5.2.10

The ERG is unclear why the company did not use the updated IBD audit and why they did not update the costs using the latest costs from the BNF rather than applying an inflation rate.	5.2.10
The costs used do not actually reflect what was received by patients in the conventional care arm of the UNITI trials and there is therefore a mismatch between effectiveness data and cost data used.	
Magnitude of health states costs: The health state costs used are very high and significantly greater than the health state costs used in TA352. Furthermore, the ERG note that they are substantially higher than estimated in number of recent costing studies.	5.2.10
Differential costs for biologic patients: The ERG has concerns regarding the justification for the use of differential costs for biologic patients. Differential costs were not used in the previous technology appraisals of biologic therapies for CD. Furthermore, advice from the clinical advisor to the ERG suggests that there was no clear reason to expect costs for patients receiving biologic therapy to be significantly different to those for patients receiving conventional care.	5.2.10
Additional surgical costs are included in health state costs such that patients in all health states may undergo surgery independent of the separate surgery health state. The ERG expressed concern at the inclusion of these costs at the clarification stage due the potential for double counting of surgery costs given the separate surgery health state. In an acknowledgement of the ERG's concerns the company also included a scenario analysis in their clarification response which excludes these additional surgery costs.	5.2.10
The base-case health state costs used in CS are likely to overestimate the management and monitoring costs associated with Crohn's disease. The ERG therefore has a preference for the values used in the in TA352 base-case as these health state costs are more in-line with evidence from published UK costing studies	5.2.10
Adverse event costs: The value used for injection site reactions. The value used in the CS is far in excess of the £1,363 value used in TA352 and it is likely to overestimate the costs associate with treating infection site reactions.	5.2.10

The ERG consider that the economic analysis presented by the company was inadequate to fully address the decision problem specified in NICE's scope and that the presented base-case is very likely to significantly overestimate the benefits of ustekinumab relative to conventional care. It is not possible to ascertain the benefits of ustekinumab over currently used biologic therapies due to a lack of appropriate effectiveness data.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analysis presented in Section 5. Section 6.2 details the impact of a number of minor corrections to company model identified in ERG's validation of the electronic model; Section 6.3 details a series of exploratory analyses carried out the ERG based on concerns raised in Section 5. Section 6.4 presents the ERG base-case that the ERG consider to be at least as plausible as the base-case presented by the company. In this section the ERG also presents additional exploratory analysis to assess impact of alternative treatment duration on the ERG's preferred base-case. Section 6.5 presents a brief conclusion summarising the ERG's additional analyses.

As discussed previously, the benefit is difficult to interpret due to relatively small QALY gains between the treatments, therefore the results are expressed in both incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) using a willingness to pay (WTP) threshold of £30,000 (NMB > £0 indicates cost-effectiveness at the specified threshold).

6.2 ERG corrections and adjustments to the company's base case model

The CS original economic model was corrected by company and also by ERG during the clarification process. The ERG made further correction after clarification process. Details of the all errors are presented in section 5.2.12. The results of ERG's corrections to the company's base-case model are presented in Table 85 and Table 86 for conventional care failure and TNF failure population, respectively. The results show very small differences in total QALYs (not shown in Table) after the correction and a small increase in total costs for all treatments, resulting in small increase in ICERs and decrease in NMB estimates for all active treatments relative to conventional in both population. Ustekinumab remains dominant in both conventional care failure and TNF failure populations.

Table 85 Results of ERG's corrections to the company's base-case model- Conventional care failure population

	CS base-case					CS base-case with ERG's corrections				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,053	13.08	Dominant		£27,499	£263,292	13.08	Dominant	-	£27,152
Conventional care	£278,542	12.68	-	Dominated	-	£278,542	12.68	-	Dominated	-
Infliximab - Inflectra	£278,693	12.85	£883	Dominated	£4,971	£278,730	12.85	£1,105	Dominated	£4,929
Infliximab - Remsima	£278,693	12.85	£883	Dominated	£4,971	£278,730	12.85	£1,105	Dominated	£4,929
Infliximab - Remicade	£279,698	12.85	£6,772	Dominated	£3,965	£279,739	12.85	£7,017	Dominated	£3,921
Adalimumab	£283,762	12.94	£19,999	Dominated	£2,610	£283,714	12.94	£19,787	Dominated	£2,670
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

Table 86 Results of ERG's corrections to the company's base-case model - TNF failure population

	CS base-case					CS base-case with ERG's corrections				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£288,088	12.98	Dominant		£13,234	£287,780	12.99	Dominant	-	£13,643
Conventional care	£294,600	12.76	-	Dominated	-	£294,600	12.76	-	Dominated	-
Vedolizumab	£302,820	12.85	£91,779	Dominated	-£5,533	£302,258	12.85	£83,169	Dominated	-£4,896
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

6.3 Additional ERG Scenario analyses

This Section presented additional scenario and analysis carried out by the ERG. These exploratory analyses focus on the following issues:

- Inclusion of CERTIFI trial to estimate treatment efficacy during induction phase for the anti-TNF failure population (section 4.4.);
- Inclusion of alternative utility values from the GEMINI studies (section 5.2.9);
- Inclusion of alternative costs for injection site reactions (section 5.2.10);
- Inclusion of alternative starting values in the valuation of the transition probabilities used during the maintenance phase (section 5.2.7);

- Alternative assumption regarding the time horizon of the model (section 5.2.5);
- Additional scenario analysis exploring alternative assumption regarding the maximum duration of biologic treatment (section 5.2.8).

6.3.1 Inclusion of CERTIFI trial to estimate efficacy during induction phase for anti-TNF failure population

In the CS base-case analysis, the CERTIFI study was not included to estimate efficacy during the induction phase for the anti-TNF failure population. As discussed in section 4.4, the ERG is not satisfied with the explanation provided in the CS for the exclusion of this evidence from the induction phase NMA. The ERG, therefore, conducted the induction phase NMA including the CERTIFI trial. Table 87 presents the results of the economic model including the results of this NMA. The results show a decrease in total QALYs and in increase in total costs for all treatments. Ustekinumab remains dominant. However, the ICER for vedolizumab verses conventional care increases significantly.

Table 87 Results including CERTIFI trial to estimate efficacy during induction phase for TNF failure population

	CS base-case (corrected)					ERG's scenario: Inclusion of CERTIFI				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	£292,754	12.90	Dominant	-	£12,897
Conventional care	£294,600	12.76	-	Dominated	-	£299,062	12.68	-	Dominated	-
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	£307,102	12.77	£92,782	Dominated	-£5,441
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

6.3.2 Alternative utility values

As noted in section 5.2.9, the ERG identified an alternative source of utility values form previous Technology appraisal TA352 which use data from GEMINI studies. ERG believes that these estimated values are superior to the values estimated from the mapping algorithm. The ERG conducted analysis using alternative assumption of utility values of 0.82, 0.73, 0.57 and 0.57 for remission, mild, moderate to severe and surgery health states, respectively.

The results of alternative utility assumption are presented in Table 88 and Table 89 for conventional care failure and TNF failure population, respectively. The results show an increase in total QALYs (cost remain unchanged). The impact of this change is a small decrease in NMBs for all biologic

therapies. Ustekinumab remains dominant in both conventional care failure and TNF failure populations.

Table 88 Results of alternative utility assumption - conventional care failure population

	CS base-case (corrected)					ERG's scenario: Alternative utility values				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	£263,292	13.54	Dominant	-	£27,108
Conventional care	£278,542	12.68	-	Dominated	-	£278,542	13.14	-	Dominated	-
Infliximab - Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	£278,730	13.31	£1,111	Dominated	£4,902
Infliximab - Remsima	£278,730	12.85	£1,105	Dominated	£4,929	£278,730	13.31	£1,111	Dominated	£4,902
Infliximab - Remicade	£279,739	12.85	£7,017	Dominated	£3,921	£279,739	13.31	£7,054	Dominated	£3,894
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	£283,714	13.40	£19,899	Dominated	£2,625
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

Table 89 Results of alternative utility assumption - TNF failure population

	CS base-case (corrected)					ERG's scenario: Alternative utility values				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	£287,780	13.44	Dominant	-	£13,670
Conventional care	£294,600	12.76	-	Dominated	-	£294,600	13.21	-	Dominated	-
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	£302,258	13.30	£82,952	Dominated	-£4,889
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

6.3.3 Impact of alternative costs used for injection site reactions

As noted in section 5.2.10, the ERG has concerns about the value used for injection site reactions while estimating adverse events costs. The value used is the CS is far in excess of that used in the TA 352 of £1,363 and is likely to overestimate the costs associate with treating infection site reactions. As discussed, this is unlikely to have a significant impact on the total costs associated with delivering ustekinumab, though may have greater impact on comparator costs particularly adalimumab for which skin reaction are more common. Therefore, the ERG used a more appropriate value based on a weighted average of the costs of treating skin disorders with and without interventions (Sourced: NHS

Reference Costs 2014/15, HRGs JD07A-K[80]). This gives an alternative cost of treating for injection site reactions of £1621.

The results using this alternative value are presented in Table 90 and Table 91 for the conventional care failure and TNF failure population, respectively. The results show a significant decrease in total costs for all treatments in both populations. As expected, the result for adalimumab has changed significantly and is now dominant against conventional care. Net monetary benefit also increases significantly from £2,670 to £9,727.

Table 90 Results of alternative assumption of cost used for injection site reactions – conventional care failure population

	CS base-case (corrected)					ERG's scenario: Alternative reaction cost					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Ustekinumab	£233,895	13.08	Dominant	-	£26,540
Conventional care	£278,542	12.68	-	Dominated	-	Adalimumab	£246,647	12.94	Dominant	Dominated	£9,727
Infliximab - Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Conventional care	£248,532	12.68	-	Dominated	£0
Infliximab - Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Inflectra	£249,165	12.85	£3,708	Dominated	£4,485
Infliximab - Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab - Remsima	£249,165	12.85	£3,708	Dominated	£4,485
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Infliximab - Remicade	£250,173	12.85	£9,619	Dominated	£3,477
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 91 Results of alternative assumption of cost used for injection site reactions - TNF failure population

	CS base-case (corrected)					ERG's scenario: Alternative reaction cost					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Ustekinumab	£257,666	12.99	Dominant	-	£13,137
Conventional care	£294,600	12.76	-	Dominated	-	Conventional care	£263,979	12.76	-	Dominated	£0
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£272,125	12.85	£88,460	Dominated	-£5,383
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

6.3.4 Exploration of impact of alternative starting matrices to estimate transition probabilities during maintenance phase

As discussed in section 5.2.7.1**Error! Reference source not found.**, the ERG has significant oncerns regarding the methods used to generate transition probabilities and the potential influence arbitrary staring values have on the transition probabilities generated. To illustrate the influence of alternative staring values the ERG used the ERG generated two sets of transition probabilities based on the staring values presented in Table 92. The two sets of transition probabilities are presented in Appendix 10.2.

Table 92 ERG's alternative solver solution starting matrices

	Staring matrices A		***Staring matrices B***	
From/to	**Remission**	**Mild**	**Remission**	**Mild**
Remission	0.100	0.100	0.900	0.100
Mild	0.100	0.100	0.900	0.100
Moderate-severe	0.100	0.100	0.897	0.100

The results using alternative *starting matrices A* are presented in Table 93 and Table 94 for conventional care failure and TNF failure population, respectively. The results show that choosing an alternative set of starting matrices to estimate transition probabilities during maintenance phase has a significant impact on the ICERs. There results show a significant increase in total costs and significant decrease in total QALYs for all biologic treatments in both conventional care failure and TNF failure populations. Ustekinumab is no longer dominant but remains cost-effective for both populations. However, no other biologics is cost-effective at a willingness to pay thresholds of £30,000/QALY.

Table 93 Results of alternative *starting matrices A* to estimate transition probabilities during maintenance phase – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: *Starting matrices A*					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£323,015	11.93	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£323,420	12.06	£3,084	£3,084	£3,536
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Inflectra	£328,072	12.02	£57,380	Dominated	-£2,413
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Remsima	£328,072	12.02	£57,381	Dominated	-£2,413
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab - Remicade	£329,080	12.02	£68,822	Dominated	-£3,421
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Adalimumab	£336,652	12.04	£115,580	Dominated	-£10,098
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 94 Results of alternative *starting matrices A* to estimate transition probabilities during maintenance phase – TNF failure population

	CS base-case (corrected)					ERG's scenario: *Starting matrices A*					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£337,298	12.03	-		
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£338,103	12.13	£8,201	£8,201	£2,141
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£348,156	12.07	£288,639	Dominated	-£9,729
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 95 and Table 96 present the results using alternative *starting matrices B* to estimate transition probabilities during maintenance phase for conventional care failure population and TNF failure population, respectively. The results show similar pattern as alternative *starting matrices A,* however, there is a moderate decrease in the ICER for ustekinumab verses conventional care (comparing *starting matrices A* vs. *starting matrices B)*.

Table 95 Results of alternative *starting matrices B* to estimate transition probabilities during maintenance phase – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: *Starting matrices B*					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£322,881	11.93	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£322,932	12.07	£365	£365	£4,075
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Inflectra	£327,952	12.02	£57,691	Dominated	-£2,434
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Remsima	£327,952	12.02	£57,691	Dominated	-£2,434
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab - Remicade	£328,960	12.02	£69,163	Dominated	-£3,442
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Adalimumab	£336,488	12.05	£114,802	Dominated	-£10,051
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 96 Results of alternative *starting matrices B* to estimate transition probabilities during maintenance phase – TNF failure population

	CS base-case (corrected)					ERG's scenario: S*tarting matrices B*					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£342,260	11.95	-	-	-
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£342,790	12.05	£5,146	£5,146	£2,559
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£353,270	11.99	£314,337	Dominated	-£9,959
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

6.3.5 Exploration of alternative assumption of time horizon

As discussed in section 5.2.5, there is considerable uncertainty over the long-term benefits and costs of ustekinumab given the short duration of the clinical effectiveness data available (maximum 52 weeks) and the failure of the model structure to incorporate retreatment. Given this uncertainty, the ERG, considers it worth considering the impact of a shorter time horizon, which effectively imposes the assumption that costs and benefits are the same for the treatment and comparator arms after the time horizon. The ERG therefore presents scenario analysis considering the alternative time horizons of 5-year and 10-year.

The results assuming 5-year time horizon are presented in Table 97 and Table 98 for the conventional care failure and TNF failure population, respectively. The results show that assuming a shorter time horizon has significant impact on ICERs and NMBs. Ustekinumab remains dominant in both populations. For conventional care failure population, infliximab – Inflectra and infliximab – Remsima become cost-effective at awillingness to pay thresholds of £30,000/QALY, and ICERs for infliximab – Remicade is just over the £30,000 thresholds.

Table 97 Results assuming 5-year of time horizon – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: Time horizon 5-year				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	£57,315	3.08	Dominant	-	£16,385
Conventional care	£278,542	12.68	-	Dominated	-	£65,420	2.80	-	Dominated	-
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	£68,264	2.93	£22,617	Dominated	£928
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	£68,264	2.93	£22,617	Dominated	£928
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	£69,273	2.93	£30,638	Dominated	-£80
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	£74,802	2.99	£49,312	Dominated	-£3,674
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

Table 98 Results assuming 5-year of time horizon – TNF failure population

	CS base-case (corrected)					ERG's scenario: Time horizon 5-year				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	£68,263	2.87	Dominant	-	£6,312
Conventional care	£294,600	12.76	-	Dominated	-	£70,220	2.72	-	Dominated	-
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	£79,863	2.78	£164,785	Dominated	-£7,887
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

The results assuming a 10-year time horizon are presented in Table 99 and Table 100 for the conventional care failure and TNF failure population, respectively. The results show ustekinumab remains dominant in both populations. However, all biologics are cost-effective at a willingness to pay thresholds of £30,000/QALY, except vedolizumab in the TNF failure population.

Table 99 Results assuming 10-year of time horizon – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: Time horizon 10-year				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	£101,282	5.53	Dominant	-	£24,084
Conventional care	£278,542	12.68	-	Dominated	-	£114,496	5.17	-	Dominated	-
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	£115,441	5.32	£5,990	Dominated	£3,789
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	£115,441	5.32	£5,990	Dominated	£3,789
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	£116,449	5.32	£12,380	Dominated	£2,781
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	£120,867	5.41	£26,426	Dominated	£862
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

Table 100 Results assuming 10-year of time horizon – TNF failure population

	CS base-case (corrected)					ERG's scenario: Time horizon 10-year				
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	£116,863	5.25	Dominant	-	£11,093
Conventional care	£294,600	12.76	-	Dominated	-	£121,992	5.05	-	Dominated	-
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	£130,341	5.13	£103,823	Dominated	-£5,936
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years										

6.3.6 Exploration of alternative maximum durations of treatment

As discussed in section 5.2.8, a large proportion of people continue with biologics treatment beyond one year in current practice. In acknowledgment of this issue the CS conducted scenario analyses considering 2 years and 3 years of treatment duration. However, the evidence is limited to define the most plausible duration of treatment that reflect the current UK practice and it therefore worth considering a wide range of maximum treatment duration periods. The ERG therefore conducted additional exploratory analysis to assess the alternative assumption of 5 years, 10 years and lifelong maximum treatment durations for biologic therapy.

The results of 5 years treatment duration are presented in Table 101 and Table 102 for the conventional care failure and TNF failure population, respectively. Total costs are increased for all

biologic treatments in both the conventional care failure and TNF populations. Total, QALYs for ustekinumab increases and total QALYs for other biologics decrease, resulting significant different ICERs and NMBs than CS base-case. The decrease in the total QALYs of other biologics results from the issues raised in Section 5.2.7 that the maintenance phase transition probabilities for adalimumab are predicted to result in worse outcomes for patients receiving adalimumab compared with those receiving conventional care. Ustekinumab is no longer dominant but remains cost-effective for the conventional care failure population. However, none of the biologics are cost-effective for the TNF failure population.

Table 101 Results of alternation assumption of 5 years treatment duration – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: 5 years treatment					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£278,542	12.68	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£289,392	13.14	£23,320	£23,320	£3,108
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Inflectra	£318,575	12.70	£1,592,240	Dominated	-£39,279
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Remsima	£318,575	12.70	£1,592,244	Dominated	-£39,279
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab - Remicade	£322,842	12.70	£1,761,960	Dominated	-£43,546
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Adalimumab	£357,500	12.74	£1,258,380	Dominated	-£77,076
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 102 Results of alternation assumption of 5 years treatment duration – TNF failure population

	CS base-case (corrected)					ERG's scenario: 5 years treatment					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£294,600	12.76	-	-	-
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£308,961	12.96	£70,728	£70,728	-£8,270
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£323,423	12.84	£355,422	Dominated	-£26,391
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

The results of alternative assumption of 10 years treatment duration are presented in Table 103 and Table 104 for conventional care failure and TNF failure population, respectively. Total costs for all active treatments increase significantly in the conventional care failure population. Comparing 5 years treatment and 10 years treatment duration assumptions, total QALYs for ustekinumab increases further and total QALYs for other biologics decrease further, resulting in significant different ICERs None of the biologics are cost-effective for either the conventional care failure or the TNF failure population.

Table 103 Results of alternation assumption of 10 years treatment duration – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: 10 years treatment					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£278,542	12.68	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£312,533	13.20	£65,208	£65,208	-£18,353
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Inflectra	£343,697	12.65	Dominated	Dominated	-£66,048
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Remsima	£343,697	12.65	Dominated	Dominated	-£66,048
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab - Remicade	£350,275	12.65	Dominated	Dominated	-£72,626
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Adalimumab	£403,470	12.67	Dominated	Dominated	-£125,363
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 104 Results of alternation assumption of 10 years treatment duration – TNF failure population

	CS base-case (corrected)					ERG's scenario: 10 years treatment					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£294,600	12.76	-	-	-
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£324,333	12.95	£158,631	£158,631	-£24,110
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£336,472	12.83	£563,104	Dominated	-£39,641
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

The results of alternative assumption of lifelong treatment duration are presented in Table 105 and Table 106 for conventional care failure and TNF failure population, respectively. The results show none of the biologics are cost-effective either for the conventional care failure or TNF failure population.

Table 105 Results of alternation assumption of lifelong treatment duration – Conventional care failure population

	CS base-case (corrected)					ERG's scenario: Lifelong treatment					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£278,542	12.68	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£345,065	13.28	£111,037	£111,037	-£48,550
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Inflectra	£359,561	12.63	Dominated	Dominated	-£82,649
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab - Remsima	£359,561	12.63	Dominated	Dominated	-£82,649
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab - Remicade	£367,670	12.63	Dominated	Dominated	-£90,758
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Adalimumab	£433,453	12.63	Dominated	Dominated	-£156,417
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 106 Results of alternation assumption of lifelong treatment duration – TNF failure population

	CS base-case (corrected)					ERG's scenario: Lifelong treatment					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£294,600	12.76	-	-	-
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£338,068	12.93	£249,766	£249,766	-£38,247
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£347,406	12.83	£767,844	Dominated	-£50,743
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

6.4 ERG's preferred base-case

Table 107 (for conventional care failure) and Table 108 (for TNF failure population) present the ERG's preferred base-case which combines a number of the changes to the company base-case

explored in Section 6.3 and a number of CS scenario analyses. Specifically, the ERG base-case makes the following amendments to the CS's base-case:

- Inclusion of CERTIFI trial to estimate efficacy during induction phase for TNF failure population;
- Inclusion of alternative utility values from the GEMINI studies;
- Inclusion of alternative cost value of £1621 applied for injection site reactions adverse events costs;
- Inclusion of IM-UNITI data to estimate maintenance phase efficacy;
- Health state costs are based on the health state costs used in theTA352 original submission.

Further to the above, all analyses are present using the CDAI-100 and CDAI-70 response definition as the ERG considers these to equally plausible criteria to define response (see discussion in section 5.2.1)

The ERG considers this alternative base-case to be at least as plausible as the company's base-case. Combining these modifications to the company model leads to a substantial decrease in total cost and small increase in total QALYs. The resulting ICERs are increased substantially and none of the biologics is cost-effective compared to conventional care.

Table 107 Results deterministic analysis of ERG's preferred base-case – conventional care failure

	CS base-case (corrected)					ERG's preferred base-case (CDAI-100)					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£107,150	13.11	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£114,670	13.18	£109,279	£109,279	-£5,456
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab – Inflectra	£116,756	13.17	£172,467	Dominated	-£7,936
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab – Remsima	£116,756	13.17	£172,467	Dominated	-£7,936
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab – Remicade	£117,767	13.17	£190,612	Dominated	-£8,946
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Adalimumab	£119,479	13.19	£170,228	£1,331,179	-£10,156
	CS base-case (corrected)					**ERG's preferred base-case (CDAI-70)**					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£263,292	13.08	Dominant	-	£27,152	Conventional care	£107,097	13.12	-	-	-
Conventional care	£278,542	12.68	-	Dominated	-	Ustekinumab	£114,782	13.18	£111,878	£111,878	-£5,624
Infliximab – Inflectra	£278,730	12.85	£1,105	Dominated	£4,929	Adalimumab	£120,188	13.19	£171,435	£705,040	-£10,800
Infliximab – Remsima	£278,730	12.85	£1,105	Dominated	£4,929	Infliximab – Inflectra	£120,838	13.22	£130,488	£22,466	-£10,582
Infliximab – Remicade	£279,739	12.85	£7,017	Dominated	£3,921	Infliximab – Remsima	£120,838	13.22	£130,488	Dominated	-£10,582
Adalimumab	£283,714	12.94	£19,787	Dominated	£2,670	Infliximab – Remicade	£122,331	13.22	£144,669	Dominated	-£12,075

ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years

Table 108 Results deterministic analysis of ERG's preferred base-case – TNF failure population

	CS base-case (corrected)					ERG's preferred base-case (CDAI-100)					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£123,303	12.46	-	-	-
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£129,531	12.52	£110,967	£110,967	-£4,544
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£136,581	12.49	£408,844	Dominated	-£12,303
	CS base-case (corrected)					**ERG's preferred base-case (CDAI-70)**					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Ustekinumab	£287,780	12.99	Dominant	-	£13,643	Conventional care	£123,259	12.46	-	-	-
Conventional care	£294,600	12.76	-	Dominated	-	Ustekinumab	£129,792	12.52	£110,507	£110,507	-£4,760
Vedolizumab	£302,258	12.85	£83,169	Dominated	-£4,896	Vedolizumab	£137,322	12.50	£368,806	Dominated	-£12,920
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Results of probabilistic sensitivity analysis of ERG's preferred base-case:

The results of probabilistic sensitivity analysis are presented in Table 109 and Table 110 for conventional care failure and TNF failure population, respectively. The results show an increase in total QALYs and decrease in total costs (compare deterministic analysis and probabilistic analysis results). The impact is minimum on ICERs and NMBs.

Table 109 Results probabilistic sensitivity analysis of ERG's preferred base-case – conventional care failure

	ERG's preferred base-case (CDAI-100)					ERG's preferred base-case (CDAI-70)					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Conventional care	£103,778	15.39	-	-	-	Conventional care	£103,414	15.35	-	-	-
Ustekinumab	£111,304	15.45	£110,371	£110,371	-£5,480	Ustekinumab	£111,095	15.41	£112,111	£112,111	-£5,625
Infliximab - Remicade	£114,825	15.44	£200,273	Dominated	-£9,392	Adalimumab	£116,475	15.42	£171,298	£695,455	-£10,773
Adalimumab	£116,072	15.46	£168,231	£974,791	-£10,101	Infliximab - Remicade	£119,091	15.45	£153,379	Dominant	-£12,610
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Table 110 Results probabilistic sensitivity analysis of ERG's preferred base-case – TNF failure population

	ERG's preferred base-case (CDAI-100)					ERG's preferred base-case (CDAI-70)					
Technologies	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**	**Technologies**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**ICER**	**NMB vs. conventional care**
Conventional care	£133,696	13.97	-		-	Conventional care	£134,063	14.01	-	-	-
Ustekinumab	£140,081	14.01	£139,037	£139,037	-£5,007	Ustekinumab	£140,755	14.06	£137,643	£137,643	-£5,234
Vedolizumab	£147,094	13.99	£516,521	Dominated	-£12,620	Vedolizumab	£148,241	14.04	£462,511	Dominated	-£13,258
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years											

Further exploratory analysis assuming alternative maximum durations of 2, 3, 5, 10 and life longer treatment:

The ERG preferred base-case assume a maximum treatment duration of 1 year for biologic therapy. This parameter is however subject to considerable uncertainty. The ERG presents additional scenario using the ERG base-case to explore the impact of alterative assumptions about the maximum duration of biologic treatment. These analyses consider the alternative maximum durations of 2, 3, 5, 10 and life longer treatment with biologic therapy.

A summary results of the exploratory analyses are presented in Table 3 and Table 4 for the conventional care failure and TNF failure population. The results show that the assumptions of alternative treatment duration have a huge impact on the ICERs and NMBs.

Table 111 Summary results of ERG's preferred base-case (CDAI-100/CDAI-70) with alternative assumptions of treatment duration – Conventional care failure population

	Ustekinumab				Infliximab-Remicade $				Adalimumab				Conventional care	
scenario	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. conventional care**	**Total costs**	**Total QALYs**
CS base-case (corrected)	*£263,292*	*13.08*	*Dominant*	*£27,152*	*£279,739*	*12.85*	*£7,017*	*£3,921*	*£283,714*	*12.94*	*£19,787*	*£2,670*	*£278,542*	*12.68*
ERG's analysis including CDAI-100														
ERG base-case (CDAI-100)	£114,670	13.18	£109,279	-£5,456	£117,767	13.17	£190,612	-£8,946	£119,479	13.19	£170,228	-£10,156	£107,150	13.11
2 years treatment	£122,848	13.23	£131,811	-£12,125	£127,615	13.20	£224,802	-£17,735	£131,049	13.23	£204,447	-£20,393	£107,150	13.11
3 years treatment	£129,529	13.28	£132,910	-£17,328	£136,142	13.24	£235,817	-£25,304	£142,763	13.27	£226,897	-£30,905	£107,150	13.11
5 years treatment	£143,111	13.36	£143,101	-£28,422	£153,547	13.29	£257,770	-£40,997	£164,487	13.34	£250,727	-£50,477	£107,150	13.11
10 years treatment	£168,889	13.51	£154,201	-£49,728	£187,582	13.40	£279,627	-£71,803	£206,277	13.48	£272,181	-£88,201	£107,150	13.11
Lifelong treatment	£208,149	13.74	£160,165	-£82,081	£247,714	13.59	£293,572	-£126,200	£281,612	13.72	£287,939	-£156,286	£107,150	13.11
ERG's analysis including CDAI-70														
ERG base-case (CDAI-70)	£114,782	13.18	£111,878	-£5,624	£122,331	13.22	£144,669	-£12,075	£120,188	13.19	£171,435	-£10,800	£107,097	13.12
2 years treatment	£123,334	13.24	£134,400	-£12,612	£139,308	13.28	£193,652	-£27,220	£132,808	13.24	£206,256	-£21,971	£107,097	13.12
3 years treatment	£130,260	13.29	£134,765	-£18,007	£154,010	13.34	£211,904	-£40,271	£145,567	13.28	£228,687	-£33,423	£107,097	13.12
5 years treatment	£144,339	13.37	£144,448	-£29,507	£184,024	13.44	£240,556	-£67,333	£169,214	13.36	£252,241	-£54,729	£107,097	13.12
10 years treatment	£171,062	13.53	£155,115	-£51,594	£242,721	13.62	£268,329	-£120,461	£214,690	13.51	£273,274	-£95,781	£107,097	13.12
Lifelong treatment	£211,760	13.77	£160,769	-£85,132	£346,426	13.95	£286,578	-£214,275	£296,671	13.77	£288,657	-£169,871	£107,097	13.12

$ Results of other infliximab biosimilar are presented in Appendix 10.4; ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years

Table 112 Summary results of ERG's preferred base-case (CDAI-100/CDAI-70) with alternative assumptions of treatment duration – TNF failure population

	Ustekinumab				Vedolizumab				Conventional care	
scenario	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. Conventional care**	**Total costs**	**Total QALYs**	**ICER vs. Conventional care**	**NMB vs. Conventional care**	**Total costs**	**Total QALYs**
CS base-case (corrected)	*£287,780*	*12.99*	*Dominant*	*£13,643*	*£302,258*	*12.85*	*£83,169*	*-£4,896*	*£294,600*	*12.76*
ERG's analysis including CDAI-100										
ERG base-case (CDAI-100)	£129,531	12.52	£110,967	-£4,544	£136,581	12.49	£408,844	-£12,303	£123,303	12.46
2 years treatment	£135,126	12.57	£111,122	-£8,631	£143,036	12.52	£324,022	-£17,906	£123,303	12.46
3 years treatment	£139,616	12.61	£107,907	-£11,777	£149,081	12.55	£305,823	-£23,249	£123,303	12.46
5 years treatment	£148,542	12.69	£110,477	-£18,385	£158,972	12.58	£297,430	-£32,071	£123,303	12.46
10 years treatment	£165,013	12.83	£114,282	-£30,760	£173,212	12.63	£296,691	-£44,862	£123,303	12.46
Lifelong treatment	£188,386	13.02	£116,268	-£48,289	£182,801	12.66	£297,416	-£53,496	£123,303	12.46
ERG's analysis including CDAI-70										
ERG base-case (CDAI-70)	£129,792	12.52	£110,507	-£4,760	£137,322	12.50	£368,806	-£12,920	£123,259	12.46
2 years treatment	£135,919	12.58	£111,359	-£9,250	£144,983	12.54	£301,774	-£19,565	£123,259	12.46
3 years treatment	£140,792	12.63	£108,035	-£12,665	£152,196	12.56	£289,887	-£25,942	£123,259	12.46
5 years treatment	£150,479	12.71	£110,577	-£19,835	£163,961	12.61	£286,213	-£36,436	£123,259	12.46
10 years treatment	£168,356	12.86	£114,361	-£33,267	£180,903	12.66	£288,698	-£51,654	£123,259	12.46
Lifelong treatment	£192,310	12.70	£290,700	-£61,926	£193,725	13.07	£116,326	-£52,293	£123,259	12.46

ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life year

6.5 Conclusions from ERG analyses

In this section the ERG has presented a number of additional analyses. These analyses were carried in a number of stages. The first stage address minor errors in the electronic model submitted by the company. The impact of these errors was very small and did not impact on the results of the model in a decisive way. Using the corrected model the ERG then presented a number of sensitivity analyses to explore a number of issues raised in Section 5. These scenario analyses addressed the following issues:

- Inclusion of CERTIFI trial to estimate treatment efficacy during the induction phase for the anti-TNF failure population;
- Inclusion of alternative utility values from the GEMINI trial;
- Inclusion of alternative costs for injection site reactions;
- Inclusion of alternative starting values in the calculation of the transition probabilities used during the maintenance phase;
- Alternative assumption regarding the time horizon used in the model;
- Additional scenario analysis exploring alternative assumption regarding the maximum duration of biologic treatment.

The results of this analysis show that both alternative time-horizons and alternative assumption regarding the maximum duration of biologic treatment have a significant impact on the estimated cost-effectiveness of ustekinumab.

The ERG then present an alternative base-case which combined a number scenarios carried out by the ERG and a number of scenarios presented by the company. The ERG's base-case analysis suggests that the ICER for ustekinumab compared with conventional care is £109,279 per QALY in the conventional care failure subpopulation (assuming CDIA 100 response criteria). In the anti-TNF subpopulation the estimated ICER in the ERG base case is £111,878 per QALY (assuming CDIA 100 response criteria).

The final part of this section carried out a further series of exploratory analyses that explored the impact of alternative assumption regarding the maximum duration of biologic treatment using the ERG's base-case. These analyses explore maximum treatment durations of of 2, 3, 5, 10 and life-long. The respective estimate ICERS for ustekinumab in the conventional care failure subpopulation are £131,811, £132,910, £143,101, £154,201, £160,165 per QALY. In the anti-TNF failure

subpopulation the respective ICERS are £111,122, £107,907, £110,477, £110,477, £114,282 and £116,268 per QALY.

Based on the ERG's base case analysis ustekinumab is unlikely to represent good value to the NHS considering typical WTP thresholds.

7 End of life

The end of life criteria published by NICE. It is recognised that this will be decided by the relevant NICE appraisal committee and this section may have no bearing upon their decision.

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;

There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

These criteria are not relevant to this appraisal.

8 Overall conclusions

There is no reliable estimate of the one year effectiveness of ustekinumab relative to conventional care (placebo), nor relative the comparator biologics.

The company's economic model estimates that for the conventional care failure subgroup, ustekinumab is dominant (lower costs greater effectiveness) compared with adalimumab and conventional care. In the scenario analysis including infliximab, the biosimilar Inflectra is the most cost-effective therapy with an ICER of £504 per QALY compared with ustekinumab and dominating all other therapies. Within the anti-TNF failure subgroup, the company's model estimates ustekinumab to be dominant compared to vedolizumab and conventional care.

The ERG considers the economic analysis presented by the company was inadequate to fully address the decision problem specified in NICE's scope as it contains serious problems relating to the structure of the model and the way in which clinical data has been incorporated into the model. The ERG was unable to fully rectify all the identified issues with the company's model, but was able to carry out a number of analyses using assumptions and data inputs it believes are more plausible than those used in the company's base-case analysis. The ERG's base-case analysis using the alternative

input values estimate the ICER for ustekinumab compared with conventional care to be £109,279 per QALY in the conventional care failure subpopulation and £111,878 per QALY in the anti –TNF failure subpopulation. Based on the ERG's base case analysis ustekinumab is unlikely to represent good value to the NHS considering typical WTP thresholds.

8.1 Implications for research

The failure of the existing cost-effectiveness models of CD to appropriately represent the chronic, life-long nature of the disease and the need for continuous treatment or retreatment over time and the impact of surgery needs to be addressed. A new, fully researched, appropriately structured and populated, decision-analytic model of CD is required.

There is a complete lack of real long term (longer than 92 weeks) data for ustekinumab in CD. As Crohn's disease is a chronic condition further research is required to establish the benefit or other wise of continuing treatment (continuously or intermittently as patients' disease relapses and remits) indefinitely.

9 REFERENCES

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;**380**:1590-605. http://dx.doi.org/10.1016/S0140-6736(12)60026-9

2. Kalla R, Ventham NT, Satsangi J, Arnott ID. Crohn's disease. *BMJ* 2014;**349**:g6670. http://dx.doi.org/10.1136/bmj.g6670

3. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, *et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46-54. http://dx.doi.org/10.1053/j.gastro.2011.10.001

4. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol* 2015;**12**:205-17. http://dx.doi.org/10.1038/nrgastro.2015.34

5. Gower-Rousseau C, Vasseur F, Fumery M, Savoye G, Salleron J, Dauchet L, *et al.* Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry (EPIMAD). *Dig Liver Dis* 2013;**45**:89-94. http://dx.doi.org/10.1016/j.dld.2012.09.005

6. Henriksen M, Jahnsen J, Lygren I, Aadland E, Schulz T, Vatn MH, *et al.* Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). *Scand J Gastroenterol* 2007;**42**:602-10. http://dx.doi.org/10.1080/00365520601076124

7. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995;**30**:699-706.

8. Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J, *et al.* Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol* 2007;**5**:1430-8. http://dx.doi.org/10.1016/j.cgh.2007.09.002

9. National Institute for Health and Care Excellence (NICE). *NICE Pathways: Crohn's disease overview*. NICE; 2016. URL: http://pathways.nice.org.uk/pathways/crohns-disease (accessed 10 October 2016).

10. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, *et al.* Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**:711-21.

11. National Institute for Health and Care Excellence (NICE). *TA352. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Costing report.* NICE; 2015. URL: https://www.nice.org.uk/guidance/ta352/costing (accessed 15 October 2016).

12. National Institute for Health and Care Excellence (NICE). *TA187: Infliximab (review) and adalimumab for the treatment of Crohn's disease*. NICE; 2010. URL: https://www.nice.org.uk/guidance/ta187 (accessed 16 April 2015).

13. Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, *et al.* A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008;**135**:1130-41. http://dx.doi.org/10.1053/j.gastro.2008.07.014

14. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;**337**:1029-35. http://dx.doi.org/10.1056/NEJM199710093371502

15. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**:323-33. http://dx.doi.org/10.1053/j.gastro.2005.11.030

16. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, *et al.* Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. *J Crohns Colitis* 2012;**6**:160-73. http://dx.doi.org/10.1016/j.crohns.2011.07.013

17. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**:829-38.

18. Sands BE, Feagan BG, Rutgeerts P, Colombel J, Sandborn WJ, Sy R, *et al.* Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;**147**:618-27.

19. Sandborn W, Gasink C, Blank M, Lang Y, Johanns J, Gao LL, *et al.* O-001 A multicenter, double-blind, placebo-controlled phase 3 study of ustekinumab, a human IL-12/23P40 mAB, in moderate-servere Crohn's disease refractory to anti-TFNalpha: UNITI-1. *Inflamm Bowel Dis* 2016;**22 Suppl 1**:S1. http://dx.doi.org/10.1097/MIB.0000000000000720

20. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, *et al.* Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;**375**:1946-60. http://dx.doi.org/10.1056/NEJMoa1602773

21. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, *et al.* Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;**367**:1519-28. http://dx.doi.org/10.1056/NEJMoa1203572

22. Janssen Research and Development. *A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease (UNITI 2)*; 2015.

23. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52-65. http://dx.doi.org/10.1053/j.gastro.2006.11.041

24. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541-9. http://dx.doi.org/10.1016/S0140-6736(02)08512-4

25. Janssen Research and Development. *A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab maintenance therapy in subjects with moderately to severely active Crohn's disease (44-week Clinical Study Report). (EDMS-ERI-97847519, 1.0)* Janssen Research and Development; 2015.

26. National Institute for Health and Care Excellence (NICE). *CG152: Crohn's disease: management*. NICE; 2016. URL: https://www.nice.org.uk/guidance/cg152 (accessed 2016).

27. Lindsay J, Punekar YS, Morris J, Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease - modelling outcomes in active luminal and fistulizing disease in adults. *Aliment Pharmacol Ther* 2008;**28**:76-87. http://dx.doi.org/10.1111/j.1365-2036.2008.03709.x

28. Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Aliment Pharmacol Ther* 2009;**30**:265-74. http://dx.doi.org/10.1111/j.1365-2036.2009.04033.x

29. Saito S, Shimizu U, Zhang N, Yokoyama J, Watanabe M, Terajima K, *et al.* A health economic analysis of combination therapy with infliximab plus elemental diet for moderately to severely active Crohn's disease (Provisional abstract), In Health, pp 107-114. 2014.

30. Loftus EV, Jr., Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther* 2002;**16**:51-60.

31. Scottish Medicines Consortium. vedolizumab (Entyvio), In Advice, NHS Scotland Scotland 2015.

32. Buxton MJ, Lacey LA, Feagan BG, Niecko T, Miller DW, Townsend RJ. Mapping from disease-specific measures to utility: an analysis of the relationships between the Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's disease and measures of utility. *Value Health* 2007;**10**:214-20. http://dx.doi.org/10.1111/j.1524-4733.2007.00171.x

33. Royal College of Physicians. *National clinical audit of biological therapies: UK inflammatory bowel disease (IBD) audit*. 2013. URL: http://www.rcplondon.ac.uk/sites/default/files/national_clinical_audit_report_of_biological_therapies_-_adult_report._29_august_2013.pdf (accessed 8 May 2015).

34. Janssen Research and Development. *A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapy (UNITI 1)*: Janssen Research and Development; 2015.

35. Sandborn W, Feagan B, Reinisch W, Smyth M, Parikh A, Fox I. P497 Efficacy of continued vedolizumab therapy in patients with Crohn's disease who did not respond to vedolizumab induction therapy at week 6. Paper presented at: European Crohn's and Colitis Organisation; Copenhagen, 20-22 February 2014.

36. European Medicines Agency (EMA). *Adalimumab summary of product characteristics*. 2016. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf (accessed 10 October 2016).

37. Panaccione R, Sandborn W, Colombel J, Pollack P, Chen N, Chao J*, et al.* Impact of adalimumab therapy after 12 Weeks in patients with Crohn's disease who were non responders at week 4: P-0059. *Inflamm Bowel Dis* 2008;**14**:S28.

38. National Institute for Health and Care Excellence (NICE). *TA352: Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy*. NICE; 2015. URL: https://www.nice.org.uk/guidance/ta352 (accessed 12 December 2015).

39. Rafia R, Scope A, Harman S, Stevens JW, Stevenson M, Sutton A*, et al. Vedolizumab for the treatment of adults with moderately to severely active Crohn's disease: A Single Technology Appraisal*. School of Health and Related Research (ScHARR); 2014. URL: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/133650/ERGReport-13-128-01.pdf (accessed 11 October 2016).

40. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE*, et al.* Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**:711-21. http://dx.doi.org/10.1056/NEJMoa1215739

41. Janssen Research and Development. *A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab maintenance therapy in subjects with moderately to severely active Crohn's disease (44-week Clinical Study Report)*: Janssen Research and Development; 2015.

42. Sands B, Gasink C, Jacobstein D, Gao LL, Johanns J, Szapary P*, et al.* Efficacy and safety of dose adjustment and delayed response to ustekinumab in moderate–severe Crohn's disease patients: results from the IM-UNITI maintenance study. Paper presented at: United European Gastronenterology (UEG) Week 2016; Vienna, 15-19 October.

43. Gisbert JP, Marin AC, Chaparro M. The Risk of Relapse after Anti-TNF Discontinuation in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2016;**111**:632-47. 10.1038/ajg.2016.54

44. Spoor W. *Hospital Episode Statistics (HES) admitted patient care data set 2011-2014*. 2015. URL: http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22Hospital+Episode+Statistics%2C+Admitted+patient+care+-+England%22&area=&size=10&sort=Relevance (accessed 16 October 2016).

45. Takeda Pharmaceuticals. *Vedolizumab for the for the treatment of adult patients with moderately to severely active Crohn's disease. Manufacturer's submission to the National Institute for Health and Care Excellence*. 2014. URL: https://www.nice.org.uk/guidance/indevelopment/gid-tag461 (accessed 16 April 2015).

46. Ramadas A, Gunesh S, Thomas GAO, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986e2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010;**59**:1200e6.

47. Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF*, et al.* Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;**142**:1102-11. http://dx.doi.org/10.1053/j.gastro.2012.01.035

48. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG*, et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;**56**:1232-9. http://dx.doi.org/10.1136/gut.2006.106781

49. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D*, et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383-95. http://dx.doi.org/10.1056/NEJMoa0904492

50. McLeod RS, Wolff BG, Ross S, Parkes R, McKenzie M, Investigators of the CT. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. *Dis Colon Rectum* 2009;**52**:919-27. http://dx.doi.org/10.1007/DCR.0b013e3181a4fa58

51. Milsom JW, Hammerhofer KA, Bohm B, Marcello P, Elson P, Fazio VW. Prospective, randomized trial comparing laparoscopic vs. conventional surgery for refractory ileocolic Crohn's disease. *Dis Colon Rectum* 2001;**44**:1-8.

52. Zurbuchen U, Kroesen AJ, Knebel P, Betzler MH, Becker H, Bruch HP*, et al.* Complications after end-to-end vs. side-to-side anastomosis in ileocecal Crohn's disease - early postoperative results from a randomized controlled multi-center trial (ISRCTN-45665492). *Langenbecks Arch Surg* 2013;**398**:467-74. http://dx.doi.org/10.1007/s00423-012-0904-1

53. Kusunoki M, Ikeuchi H, Yanagi H, Shoji Y, Yamamura T. A comparison of stapled and hand-sewn anastomoses in Crohn's disease. *Dig Surg* 1998;**15**:679-82.

54. Fazio VW, Marchetti F, Church M, Goldblum JR, Lavery C, Hull TL*, et al.* Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. *Ann Surg* 1996;**224**:563-71.

55. Irvin TT, Goligher JC, Johnston D. A randomized prospective clinical trial of single-layer and two-layer inverting intestinal anastomoses. *Br J Surg* 1973;**60**:457-60.

56. Eshuis EJ, Slors JF, Stokkers PC, Sprangers MA, Ubbink DT, Cuesta MA*, et al.* Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. *Br J Surg* 2010;**97**:563-8. http://dx.doi.org/10.1002/bjs.6918

57. Maartense S, Dunker MS, Slors JF, Cuesta MA, Pierik EG, Gouma DJ, *et al.* Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. *Ann Surg* 2006;**243**:143-9. http://dx.doi.org/10.1097/01.sla.0000197318.37459.ec

58. Ikeuchi H, Kusunoki M, Yamamura T. Long-term results of stapled and hand-sewn anastomoses in patients with Crohn's disease. *Dig Surg* 2000;**17**:493-6.

59. Cameron JL, Hamilton SR, Coleman J, Sitzmann JV, Bayless TM. Patterns of ileal recurrence in Crohn's disease. A prospective randomized study. *Ann Surg* 1992;**215**:546-51.

60. Stocchi L, Milsom JW, Fazio VW. Long-term outcomes of laparoscopic versus open ileocolic resection for Crohn's disease: follow-up of a prospective randomized trial. *Surgery* 2008;**144**:622-7. http://dx.doi.org/10.1016/j.surg.2008.06.016

61. Funayama Y, Fukushima K, Shibata C, Takahashi K-I, Ogawa H, Haneda S, *et al.* Early postoperative results of novel procedure of side-to-side isoperistaltic ileocolonic anastomosis for Crohn's disease - randomized controlled trial. Paper presented at: 47th Annual Meeting of the Society for Surgery of the Alimentary Tract (SSAT); LA, California, 20-24 May 2006.

62. Office for National Statistics. *Life Tables for England and Wales, 2011 to 2013*. 2014. URL: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-365199 (accessed 04 March 2016).

63. Royal College of Physicians. *National clinical audit of biological therapies: UK inflammatory bowel disease (IBD) audit*. 2015. URL: https://www.rcplondon.ac.uk/projects/outputs/national-clinical-audit-report-biological-therapies-adult-report-2015 (accessed 21 November 2016).

64. Billiet T, Cleynen I, Ballet V, Ferrante M, Van Assche G, Gils A, *et al.* Prognostic factors for long-term infliximab treatment in Crohn's disease patients: a 20-year single centre experience. *Aliment Pharmacol Ther* 2016;**44**:673-83. 10.1111/apt.13754

65. Peyrin-Biroulet L, Salleron J, Filippi J, Reenaers C, Antunes O, Filipe V, *et al.* Anti-TNF Monotherapy for Crohn's Disease: a 13-year Multicentre Experience. *Journal of Crohn's and Colitis* 2016;**10**:516-24. 10.1093/ecco-jcc/jjw008

66. Cosnes J, Sokol H, Bourrier A, Nion-Larmurier I, Wisniewski A, Landman C, *et al.* Adalimumab or infliximab as monotherapy, or in combination with an immunomodulator, in the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2016;**44**:1102-13. 10.1111/apt.13808

67. De Bie CI, Hummel TZ, Kindermann A, Kokke FTM, Damen GM, Kneepkens CMF, *et al.* The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited. *Aliment Pharmacol Ther* 2011;**33**:243-50. 10.1111/j.1365-2036.2010.04507.x

68. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Value Health* 2007.

69. Janssen Research and Development. *Utility mapping and analysis for ustekinumab in Crohn's disease: report*: Janssen Research and Development; 2016.

70. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. *Pharmacoeconomics* 2001;**19**:1091-102.

71. Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. *BMC Public Health* 2006;**6**:157. http://dx.doi.org/10.1186/1471-2458-6-157

72. Hornberger J, Reyes C, Lubeck D, Valente N. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. *Leuk Lymphoma* 2008;**49**:227-36. http://dx.doi.org/10.1080/10428190701769665

73. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, *et al.* Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes* 2010;**8**:50. http://dx.doi.org/10.1186/1477-7525-8-50

74. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, *et al.* Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *Br J Cancer* 2009;**101**:387-9. http://dx.doi.org/10.1038/sj.bjc.6605187

75. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509-18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

76. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, *et al.* Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;**147**:618-27 e3. http://dx.doi.org/10.1053/j.gastro.2014.05.008

77. Rafia R, Scope A, Harman S, Stevens JW, Stevenson M, Sutton A, *et al. Vedolizumab for the treatment of adults with moderately to severely active Crohn's disease: A Single Technology Appraisal*. 2014. URL: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0018/133650/ERGReport-13-128-01.pdf (accessed 11 October 2016.

78. Monthly Index of Medical Specialities (MIMS). 2015. URL: http://www.mims.co.uk/ (accessed 16 April 2015).

79. Sandborn W, Gasink C, Blank M, Lang Y, Johanns J, Gao LL, *et al.* O-001 A Multicenter, Double-Blind, Placebo-Controlled Phase3 Study of Ustekinumab, a Human IL-12/23P40 mAB, in Moderate-Service Crohn's Disease Refractory to Anti-TFNalpha: UNITI-1. *Inflamm Bowel Dis* 2016;**22 Suppl 1**:S1. 10.1097/MIB.0000000000000720

80. National Health Service. *Department of Health Reference Costs 2014-15*. 2015. URL: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 (accessed 27 March 2016).

81. National Institute for Health and Care Excellence (NICE). *TA65: Rituximab for aggressive non-Hodgkin's lymphoma*. NICE; 2003. URL: https://www.nice.org.uk/guidance/ta65 (accessed 16 April 2015).

82. National Institute for Health and Care Excellence (NICE). *TA243: Rituximab for the first-line treatment of stage III-IV follicular lymphoma: (review of NICE technology appraisal guidance 110)*. NICE; 2012. URL: https://www.nice.org.uk/guidance/ta243 (accessed 16 April 2015).

83. National Institute for Health and Care Excellence (NICE). *TA226: Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma*. NICE; 2011. URL: https://www.nice.org.uk/guidance/ta226 (accessed 8 May 2015).

84. Curtis L. *Unit Costs of Health and Social Care 2015*. Personal Social Services Research Unit; 2015. URL: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php (accessed 16 April 2016).

85. Sprakes MB, Ford AC, Suares NC, Warren L, Greer D, Donnellan CF, et al. Costs of care for Crohn's disease following the introduction of infliximab: a single-centre UK experience. Aliment Pharm Ther 2010;32:1357-63. Available from: <Go to ISI>://WOS:000283948000008

86. Choi GKH, Collins SDE, Greer DP, Warren L, Dawson G, Clark T, et al. Costs of adalimumab versus infliximab as first-line biological therapy for luminal Crohn's disease. J Crohns Colitis 2014;8:375-83. Available from: <Go to ISI>://WOS:000335280700006

10 Appendices

10.1 ERG risk of bias assessment for the trials included in induction and maintenance phases using Cochrane risk of bias tool

Induction phase [a]							
		Targan 1997	**CLASSIC I**	**Watanabe 2012**	**GAIN**	**GEMINI II**	**GEMINI III**
Sequence generation	Risk of bias judgement	Unclear	Low	Unclear	Low	low	Low
	Support for judgement	No information provided	Patients were assigned using an interactive voice response system	No information provided	Participants were assigned through a central computer-generated scheme	Participants were assigned through a central computer-generated scheme	Patients were assigned using an interactive voice response system
Allocation concealment	Risk of bias judgement	Unclear	Low	Unclear	Low	Unclear	Low
	Support for judgement	No information provided	Patients were assigned using an interactive voice response system	No information provided	Patient numbers were centrally assigned by an interactive voice-response system.	No information provided	An interactive voice response system was used during patients assignment
Baseline comparability	Risk of bias judgement	Low	Low	Low	Low	Low	Low
	Support for judgement	No major difference in baseline characteristics between placebo and intervention groups.	Participants had similar baseline characteristics	Participants had similar baseline characteristics	Baseline characteristics were similar among the placebo and intervention groups	Baseline characteristics were similar among the placebo and intervention groups	Baseline characteristics were similar among the placebo and intervention groups
Blinding of participants and personnel	Risk of bias judgement	Low	Low	Low	Low	Low	Low
	Support for judgement	Patients and study personnel were blinded to assignments	The patients and study coordinators were blinded to assignment	It was a double-blind, placebo-controlled trial	Patients and study site personnel, and Abbott Laboratories were blinded.	It was a double-blind trial	It was a double-blind placebo controlled trial
Blinding of outcome assessment	Risk of bias judgement	Low	Low	Unclear	Low	Unclear	Low

	Support for judgement	Investigators were blinded to the treatment assignments	Study investigators were all blinded to treatment assignment	No information provided	Investigators were blinded	No information provided	Investigators were blinded during assignment
Incomplete outcome data	Risk of bias judgement	Unclear	Low	Low	high	Unclear	Unclear
	Support for judgement	No information provided	last observation carried forward (LOCF) was used for missing data	Missing data were imputed using last observation carried forward (LOCF) method	Participants with missing data were assumed to be non-responders and for all continuous variables, only complete cases analyses were carried out.	No information provided.	No sufficient information provided
Selective reporting	Risk of bias judgement	Low	Low	Low	Unclear	Low	Low
	Support for judgement	Reported outcomes matched the protocol	CDAI-70, CDAI-100 and CDAI-150 were all reported	CDAI-70, CDAI-100 and CDAI-150 were all reported	Only remission outcomes were reported	CDAI-100 and CDAI-150 were reported	Clinical response and remission outcomes were reported.

Maintenance phase [b]

		ACCENT I	**CHARM**	**GEMINI II**
Sequence generation	Risk of bias judgement	Low	Low	Low
	Support for judgement	Patients were assigned using an interactive voice response system	Patients were assigned using an interactive voice response system	Participants were assigned using a computer-generated centrally located system.
Allocation concealment	Risk of bias judgement	Low	Low	Low
	Support for judgement	Patients were assigned using an interactive voice response system	Patients were assigned using an interactive voice response system	Participants were assigned using a computer-generated centrally located system.
Baseline comparability	Risk of bias judgement	Low	Low	Low
	Support for judgement	No major imbalance of baseline characteristics of participants	No major imbalance of baseline characteristics of participants	Baseline characteristics of the placebo and intervention groups appeared to be similar..

Blinding of participants and personnel	Risk of bias judgement	High	High	Low
	Support for judgement	At week 14 or later, patients who initially responded but then worsened were eligible to cross over to active episodic retreatment	Patients experiencing a disease flare or sustained nonresponse at or after week 12 were switched to open-label treatment with 40 mg adalimumab every other week	Randomization was computer-generated and was performed at a central location
Blinding of outcome assessment	Risk of bias judgement	High	High	Unclear
	Support for judgement	It is highly likely that investigators/assessors knew the disease status of those who switched-over	It is highly likely that investigators/assessors knew the disease status of those who switched-over	Report mentioned that randomization was computer-generated and was performed at a central location but it is unclear if assessors were blinded.
Incomplete outcome data	Risk of bias judgement	Unclear	High	Unclear
	Support for judgement	No sufficient information provided	Patients without CDAI assessments at weeks 26 or 56 were classified as remission failures	No information provided
Selective reporting	Risk of bias judgement	Low	Low	Low
	Support for judgement	Both clinical response and clinical remission outcomes were reported.	Clinical response and clinical remission outcomes were reported	Clinical response and clinical remission outcomes were reported

Key: [a], see risk of bias assessment for UNITI 1, UNITI 2 and CERTIFI in [ ] respectively; [b], see risk of bias assessment for IM-UNITI trial

10.2 Details of differences between the ERG and company inputs for treatment sequence analysis for TNF failure population

Table 113 Details of differences between the ERG and CS inputs for treatment sequence analysis for TNF failure population

Induction phase data source	Maintenance phase data source	Treatment	CS estimates provided during clarification process (CS response to clarificatrion table 3, pg. 15)			ERG's estimates		
			N	CDAI-100 (n)	CDAI<150 (n)	N	CDAI-100 (n)	CDAI<150 (n)
GEMINI II and GEMINI III pooled data	GEMINI II	Placebo-placebo	227	28	23	227	*29*	*26*
GEMINI II and GEMINI III pooled data	GEMINI II	Vedolizumab 300 - vedolizumab 300 q8w	263	35	32	263	*34*	32
GEMINI II and GEMINI III pooled data	GEMINI II	Vedolizumab 300 - vedolizumab 300 q4w	263	45	32	263	44	31
UNITI I and CERTITI pooled data	IM-UNITI	Placebo-placebo	379	46	42	379	*46*	41
UNITI I and CERTITI pooled data	IM-UNITI	Ustekinumab 6 - ustekinumab 90 q12w	380	80	65	380	80	*67*
UNITI I and CERTITI pooled data	IM-UNITI	Ustekinumab 6 - ustekinumab 90 q8w	380	84	68	380	*82*	*70*
GAIN and Watanabe pooled data	CHARM	Placebo-placebo	179	22	20	179	*23*	20
GAIN and Watanabe pooled data	CHARM	Adalimumab 160 80 - adalimumab 40 eow	178	34	28	178	33	28
GAIN and Watanabe pooled data	CHARM	Adalimumab 160 80 - adalimumab 40 weekly	178	36	32	178	35	31
In italics: significant differences compared with CS estimates								

10.3 Maintenance NMA transition matrices

Results from executable model using the CS starting values are presented in Table 114:

Table 114 NMA transition matrices (CS estimates, Executable model)

Failed conventional

Ust 6mg/kg Ust q12w

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Failed TNF

From \To	Rem	Mild	Mod-sev	Surgery
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ust 6mg/kg [redacted]

From \To	Rem	Mild	Mod-sev	Surgery
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

From \To	Rem	Mild	Mod-sev	Surgery
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 Vedo q8w

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]

Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 Vedo q4w

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 Ada eow

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 Ada weekly

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 80/40 Ada eow

From \To	Rem	Mild	Mod-sev	Surgery
Rem				
Mild				
Mod-sev				
Surgery				

From \To	Rem	Mild	Mod-sev	Surgery
Rem				
Mild				
Mod-sev				
Surgery				

Ada 80/40 Ada weekly

From \To	Rem	Mild	Mod-sev	Surgery
Rem				
Mild				
Mod-sev				
Surgery				

From \To	Rem	Mild	Mod-sev	Surgery
Rem				
Mild				
Mod-sev				
Surgery				

Placebo Placebo-placebo

From \To	Rem	Mild	Mod-sev	Surgery
Rem				
Mild				
Mod-sev				
Surgery				

From \To	Rem	Mild	Mod-sev	Surgery
Rem				
Mild				
Mod-sev				
Surgery				

Results from executable model including CERTIFI trial using the CS starting values are presented in Table 115.

Table 115 NMA transition matrices including CERTIFI trial (ERG estimates, Executable model)

Failed conventional

Ust 6mg/kg

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild		[redacted]	[redacted]	[redacted]	OK
Mod-sev			[redacted]	[redacted]	OK
Surgery					

Ust q12w

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild		[redacted]	[redacted]	[redacted]	OK
Mod-sev			[redacted]	[redacted]	OK
Surgery					

Failed TNF (including CERTIFI)

Ust 6mg/kg

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild		[redacted]	[redacted]	[redacted]	OK
Mod-sev			[redacted]	[redacted]	OK
Surgery					

Ust q8w

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild		[redacted]	[redacted]	[redacted]	OK
Mod-sev			[redacted]	[redacted]	OK
Surgery					

Vedo 300

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK

Vedo q8w

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]

Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 Vedo q4w

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 Ada eow

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 Ada weekly

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 80/40 **Ada eow**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 80/40 **Ada weekly**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

******* ******* ******* *******

Placebo **Placebo-placebo**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	*******	*******	*******	*******
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Results from executable model using the ERG's alternative starting values are presented in Table 116 and Table 117:

Table 116 NMA transition matrices using alternative *starting matrices A* (ERG estimates, Executable model)

Failed conventional

Ust 6mg/kg **Ust q12w**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

Failed TNF

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ust 6mg/kg **Ust q8w**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 Vedo q8w

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 Vedo q4w

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 Ada eow

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 **Ada weekly**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 80/40 **Ada eow**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Table 117 NMA transition matrices using alternative *starting matrices B* (ERG estimates, Executable model)

Failed conventional

Ust 6mg/kg **Ust q12w**

From \To	Rem	Mild	Mod-sev	Surgery	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK

Failed TNF

From \To	Rem	Mild	Mod-sev	Surgery
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]

Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ust 6mg/kg **Ust q8w**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 **Vedo q8w**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Vedo 300 **Vedo q4w**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]

Surgery	[redacted]	[redacted]	[redacted]	[redacted]		**Surgery**	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 **Ada eow**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**		**From \To**	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Rem**	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Mild**	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Mod-sev**	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]		**Surgery**	[redacted]	[redacted]	[redacted]	[redacted]

Ada 160/80 **Ada weekly**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**		**From \To**	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Rem**	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Mild**	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Mod-sev**	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]		**Surgery**	[redacted]	[redacted]	[redacted]	[redacted]

Ada 80/40 **Ada eow**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**		**From \To**	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Rem**	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK	**Mild**	[redacted]	[redacted]	[redacted]	[redacted]

Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Ada 80/40 **Ada weekly**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Placebo **Placebo-placebo**

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**	
Rem	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mild	[redacted]	[redacted]	[redacted]	[redacted]	OK
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]	OK
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	

From \To	**Rem**	**Mild**	**Mod-sev**	**Surgery**
Rem	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Mod-sev	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]

10.4 Description and comments on searches for measurement and valuation of health effects

The manufacturer provided the methods and search strategies used to identify studies reporting HRQoL in patients with CD in Appendix 8.

The searches were carried out on 21st July 2015 and were updated on 12th October 2016. The following electronic databases were searched: MEDLINE, MEDLINE In Process and EMBASE. To supplement the electronic database searches, the manufacturer hand searched the proceedings of five conferences: European Crohn's and Colitis Organisation, American College of Gastroenterology, United European Gastroenterology Week, Digestive Disease Week and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Ongoing trials were sought from ClinicalTrials.gov, EU Clinical Trials Register and the WHO International Clinical Trials Registry Platform Search Portal. In addition, several UK, European and International HTA agency websites were searched.

The methods used to identify HRQoL studies were appropriate, with some minor issues noted. The reporting of the database searches was clear with sufficient detail to allow the searches to be reproduced. The databases searched, the service providers used, the date of the searches and complete strategies were all clearly reported.

The search strategies for MEDLINE and EMBASE contained a search line to remove clinical trials from the search results. This seems an unnecessary restriction and may have caused relevant trials containing details on HRQoL to be missed.

10.5 Detailed results of ERG's further exploratory analysis (deterministic results)

10.5.1 ERG's preferred base-case (CDAI-100)

Results of ERG's preferred base-case (CDAI-100) with alternative assumptions of treatment duration are presented in Table 118 to Table 129.

Table 118 Results of ERG's preferred base-case (CDAI-100) - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,150	13.11	-	-	-
Ustekinumab	£114,670	13.18	£109,279	£109,279	-£5,456
Infliximab - Inflectra	£116,756	13.17	£172,467	Dominated	-£7,936
Infliximab - Remsima	£116,756	13.17	£172,467	Dominated	-£7,936
Infliximab - Remicade	£117,767	13.17	£190,612	Dominated	-£8,946
Adalimumab	£119,479	13.19	£170,228	£1,331,179	-£10,156
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 119 Results of ERG's preferred base-case (CDAI-100) - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,303	12.46	-		
Ustekinumab	£129,531	12.52	£110,967	£110,967	-£4,544
Vedolizumab	£136,581	12.49	£408,844	Dominated	-£12,303
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 2 years

Table 120 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 2 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,150	13.11	-	-	-
Ustekinumab	£122,848	13.23	£131,811	£131,811	-£12,125
Infliximab - Inflectra	£125,650	13.20	£203,212	Dominated	-£15,769
Infliximab - Remsima	£125,650	13.20	£203,212	Dominated	-£15,769

Infliximab - Remicade	£127,615	13.20	£224,802	Dominated	-£17,735
Adalimumab	£131,049	13.23	£204,447	Dominated	-£20,393
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 121 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 2 years treatment duration - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,303	12.46	-	-	-
Ustekinumab	£135,126	12.57	£111,122	£111,122	-£8,631
Vedolizumab	£143,036	12.52	£324,022	Dominated	-£17,906
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 3 years

Table 122 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 3 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,150	13.11	-	-	-
Ustekinumab	£129,529	13.28	£132,910	£132,910	-£17,328
Infliximab - Inflectra	£133,336	13.24	£212,992	Dominated	-£22,498
Infliximab - Remsima	£133,336	13.24	£212,993	Dominated	-£22,498
Infliximab - Remicade	£136,142	13.24	£235,817	Dominated	-£25,304
Adalimumab	£142,763	13.27	£226,897	Dominated	-£30,905
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 123 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 3 years treatment duration - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,303	12.46	-	-	-
Ustekinumab	£139,616	12.61	£107,907	£107,907	-£11,777
Vedolizumab	£149,081	12.55	£305,823	Dominated	-£23,249
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 5 years

Table 124 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 5 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,150	13.11	-	-	-
Ustekinumab	£143,111	13.36	£143,101	£143,101	-£28,422
Infliximab - Inflectra	£149,036	13.29	£232,709	Dominated	-£36,486
Infliximab - Remsima	£149,036	13.29	£232,709	Dominated	-£36,487
Infliximab - Remicade	£153,547	13.29	£257,770	Dominated	-£40,997
Adalimumab	£164,487	13.34	£250,727	Dominated	-£50,477
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 125 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 5 years treatment duration - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,303	12.46	-	-	-
Ustekinumab	£148,542	12.69	£110,477	£110,477	-£18,385
Vedolizumab	£158,972	12.58	£297,430	Dominated	-£32,071
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 10 years

Table 126 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 10 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,150	13.11	-	-	-
Ustekinumab	£168,889	13.51	£154,201	£154,201	-£49,728
Infliximab - Inflectra	£179,739	13.40	£252,362	Dominated	-£63,960
Infliximab - Remsima	£179,739	13.40	£252,362	Dominated	-£63,960
Infliximab - Remicade	£187,582	13.40	£279,627	Dominated	-£71,803
Adalimumab	£206,277	13.48	£272,181	Dominated	-£88,201
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 127 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of 10 years treatment duration - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,303	12.46	-	-	-
Ustekinumab	£165,013	12.83	£114,282	£114,282	-£30,760
Vedolizumab	£173,212	12.63	£296,691	Dominated	-£44,862
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: lifelong

Table 128 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of lifelong treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,150	13.11	-	-	-
Ustekinumab	£208,149	13.74	£160,165	£160,165	-£82,081
Infliximab - Inflectra	£233,978	13.59	£264,884	Dominated	-£112,464
Infliximab - Remsima	£233,978	13.59	£264,885	Dominated	-£112,465
Infliximab - Remicade	£247,714	13.59	£293,572	Dominated	-£126,200
Adalimumab	£281,612	13.72	£287,939	Dominated	-£156,286
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 129 Results of ERG's preferred base-case (CDAI-100) with alternative assumption of lifelong treatment duration - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,303	12.46	-	-	-
Vedolizumab	£182,801	12.66	£297,416	£297,416	-£53,496
Ustekinumab	£188,386	13.02	£116,268	£15,525	-£48,289
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

10.5.2 ERG's base-case (CDAI-70)

Results of ERG's base-case (CDAI-100) with alternative assumptions of treatment duration are presented in Table 130 to Table 141.

Table 130 Results of ERG's preferred base-case (CDAI-70) - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,097	13.12	-	-	-
Ustekinumab	£114,782	13.18	£111,878	£111,878	-£5,624
Adalimumab	£120,188	13.19	£171,435	£705,040	-£10,800
Infliximab - Inflectra	£120,838	13.22	£130,488	£22,466	-£10,582
Infliximab - Remsima	£120,838	13.22	£130,488	Dominated	-£10,582
Infliximab - Remicade	£122,331	13.22	£144,669	Dominated	-£12,075
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 131 Results of ERG's preferred base-case (CDAI-70) - TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,259	12.46	-	-	-
Ustekinumab	£129,792	12.52	£110,507	£110,507	-£4,760
Vedolizumab	£137,322	12.50	£368,806	Dominated	-£12,920
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 2 years

Table 132 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 2 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,097	13.12	-	-	-
Ustekinumab	£123,334	13.24	£134,400	£134,400	-£12,612
Adalimumab	£132,808	13.24	£206,256	£2,459,938	-£21,971
Infliximab - Inflectra	£136,168	13.28	£174,777	£80,620	-£24,081
Infliximab - Remsima	£136,168	13.28	£174,778	Dominated	-£24,081
Infliximab - Remicade	£139,308	13.28	£193,652	Dominated	-£27,220
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 133 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 2 years treatment duration -TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,259	12.46	-	-	-
Ustekinumab	£135,919	12.58	£111,359	£111,359	-£9,250
Vedolizumab	£144,983	12.54	£301,774	Dominated	-£19,565
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 3 years

Table 134 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 3 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,097	13.12	-	-	-
Ustekinumab	£130,260	13.29	£134,765	£134,765	-£18,007
Adalimumab	£145,567	13.28	£228,687	Dominated	-£33,423
Infliximab - Inflectra	£149,421	13.34	£191,176	£387,006	-£35,682
Infliximab - Remsima	£149,421	13.34	£191,176	Dominated	-£35,682
Infliximab - Remicade	£154,010	13.34	£211,904	Dominated	-£40,271
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 135 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 3 years treatment duration -TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,259	12.46	-	-	-
Ustekinumab	£140,792	12.63	£108,035	£108,035	-£12,665
Vedolizumab	£152,196	12.56	£289,887	Dominated	-£25,942
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 5 years

Table 136 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 5 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,097	13.12	-	-	-
Ustekinumab	£144,339	13.37	£144,448	£144,448	-£29,507
Adalimumab	£169,214	13.36	£252,241	Dominated	-£54,729
Infliximab - Inflectra	£176,496	13.44	£217,013	£518,932	-£59,805
Infliximab - Remsima	£176,496	13.44	£217,014	Dominated	-£59,805
Infliximab - Remicade	£184,024	13.44	£240,556	Dominated	-£67,333
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 137 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 5 years treatment duration -TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,259	12.46	-	-	-
Ustekinumab	£150,479	12.71	£110,577	£110,577	-£19,835
Vedolizumab	£163,961	12.61	£286,213	Dominated	-£36,436
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: 10 years

Table 138 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 10 years treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,097	13.12	-	-	-
Ustekinumab	£171,062	13.53	£155,115	£155,115	-£51,594
Adalimumab	£214,690	13.51	£273,274	Dominated	-£95,781
Infliximab - Inflectra	£229,447	13.62	£242,065	£627,334	-£107,186
Infliximab - Remsima	£229,447	13.62	£242,066	Dominated	-£107,186
Infliximab - Remicade	£242,721	13.62	£268,329	Dominated	-£120,461
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Table 139 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of 10 years treatment duration -TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,259	12.46	-	-	-
Ustekinumab	£168,356	12.86	£114,361	£114,361	-£33,267
Vedolizumab	£180,903	12.66	£288,698	Dominated	-£51,654
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

Treatment duration: lifelong

Table 140 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of lifelong treatment duration - Conventional care failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£107,097	13.12	-	-	-
Ustekinumab	£211,760	13.77	£160,769	£160,769	-£85,132
Adalimumab	£296,671	13.77	£288,657	£14,826,419	-£169,871
Infliximab - Inflectra	£322,988	13.95	£258,512	£147,531	-£190,836
Infliximab - Remsima	£322,988	13.95	£258,513	Dominated	-£190,837
Infliximab - Remicade	£346,426	13.95	£286,578	Dominated	-£214,275

ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years	

Table 141 Results of ERG's preferred base-case (CDAI-70) with alternative assumption of lifelong treatment duration -TNF failure population

Technologies	Total costs	Total QALYs	ICER vs. Conventional care	ICER	NMB vs. conventional care
Conventional care	£123,259	12.46	-	-	-
Vedolizumab	£192,310	12.70	£290,700	£290,700	-£61,926
Ustekinumab	£193,725	13.07	£116,326	3841.0128	-£52,293
ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit at willingness to pay = £30,000/QALY; QALYs, quality-adjusted life years					

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ustekinumab for previously treated moderate to severe active Crohn's disease [ID843]

You are asked to check the ERG report from the Centre for Reviews and Dissemination and Centre for Health Economics – York, to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 21 February 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Systematic literature review methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 18: *"The CS described a systematic review which was conducted to identify all studies containing clinical data on patients with moderately to severely active CD treated with biologics. Although the reporting of the review process lacked detail in the submissions, and results were largely omitted from the submission, the review as originally conducted was likely to have found all relevant literature. Study selection criteria were not made obvious in placesit was also not clear why studies identified in the updated searches were excluded from the NMA. Methodology, where reported, was generally appropriate."*	*"The CS described a systematic review which was conducted to identify all studies containing clinical data on patients with moderately to severely active CD treated with biologics. Details on the methodology used for the review process are reported in section 4.1 of the company submission and the Appendix 2 of the CS reports further details on the methods used to conduct both the original and updated SLR. Although the ERG considers that more details of the review process and the results could have been provided, the review as originally conducted was likely to have found all relevant literature. Study selection criteria are reported in section 4.1.2 of the company submission however, in places that followed the methodology of the original searches. Methodology, where reported, was generally appropriate."*	The same methodology was used for both the original and updated SLR. Details are presented in section 4.1 and in Appendix 2 of the CS. Janssen could have presented additional details about the methodology if they would have been requested in the clarification questions. To address additional questions about the methodology, the full SLR report will be attached together with this pro-forma.	Amendment made. Study selection criteria were indeed presented, application of criteria still lacked clarity. *'Application of selection criteria lacked clarity in places, it was also not clear why studies identified in the updated searches were excluded from the NMA'*
The ERG states on page 33: *"…no single coherent methodology was provided for the review of clinical effectiveness data. As such, the presentation of review methodology and results in the CS is fragmented, inconsistent, irrelevant or outdated in places, and generally lacking in*	Janssen suggests the following amendment: *Appendix 2 of the company submission reports the methods used to conduct both the original and updated SLR*	Details on the search strategies for both the original and updated SLRs are reported in Appendix 2.	No amendment made – the ERG acknowledges the detail of search strategies provided but the original statement applied to the SLR process as a whole. This includes the original and updated SLR through to the NMA.

detail and transparency."			
The ERG states on page 33-34: *"Due to the lack of information provided regarding the methodology of the original SLR…"*	Janssen suggests the amendment as details were provided on the appendices.	The methodology of the original SLR is presented in Section 4.1 of the submission and Appendix 2.1.	No amendment made – as above.
The ERG states on page 36-37: *"The CS presented the number of studies identified as eligible for inclusion in the systematic review but details of data extraction methods, or a data extraction plan, were not provided; the CS states only that data was extracted and verified against the source by a second reviewer. While the ERG believes that reporting of data extraction procedures was not adequate, the data reported in the clinical effectiveness section of the CS matches the scope and was without significant obvious errors."*	Janssen suggests the following wording: *The CS presented the number of studies identified as eligible for inclusion in the systematic review but a data extraction plan was not provided; the CS states only that data was extracted and verified against the source by a second reviewer. While the ERG believes that reporting of data extraction procedures was not adequate, the data reported in the clinical effectiveness section of the CS matches the scope and was without significant obvious errors."*	As stated on page 57 of Janssen submission, data were extracted from the included full text article by one reviewer, and all extracted data verified against the original source paper by a second reviewer. Any query raised during the quality check was resolved through discussion and/or involvement of a third reviewer.	Amendment made.
The ERG states on page 38 (Section 4.1.5 – Evidence Synthesis) *'' The CS states that a narrative synthesis of the 41 publications identified in the original searches was performed; however, evidence of this, or any*	Janssen suggests removing or amending.	Data on evidence synthesis where reported in appendix 5 and section 4.10 of the Janssen submission. For the SLR, Amaris conducted a quality assessment at the study level in line with the NICE STA template and in the guidance by the Centre for Reviews and	No amendment made - comment refers to the absence of evidence of the original narrative review as mentioned in 4.1.3 and 4.10.2 of the original submission, rather than the more recent NMA.

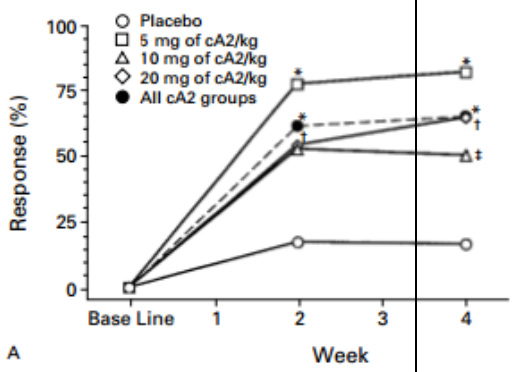
information on the methodological approach was not presented in the submission documents, nor was there any mention of the studies identified in the review update. As such, there is a hypothetical risk that bias could have been introduced into the analyses at this stage due to a lack of transparency in this process. ‘’		Dissemination at the University of York for the NICE submission. To address further questions on the methodology, the full Amaris NMA report is attached.	Quality assessment was only provided for 30 trials. The CS states that 34 trials were selected for inclusion (31 in original SLR + 3 in search update)

Issue 2 Network meta-analysis/treatment sequence analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 75 the ERG states: *“In the CS the Targan 1997 trial of infliximab is particularly criticised for this issue (as well as it being a ‘small and relatively old phase II study’(CS page 121). However, it is not clear from the publication that missing data were classed as non-response; the publication states only that, “When we assessed the response or remission rates in all evaluation periods after the initial blinded infusion, patients who received an open-label infusion or those with a*	Janssen suggests the following statement. *“In the CS the Targan 1997 trial of infliximab is particularly criticised for this issue of the effect of missing data. This is based on the FDA memorandum. As a result of this, the NMA results compared to infliximab in patients who failed conventional treatment should be interpreted with caution.”*	The correct reference for the missing data is and FDA document provided in the link below (Page14 and 15). This documents present the high proportion of missing data in the placebo arm of the Targan study. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107710.pdf	Amendment made

change in concomitantly administered medications were considered to have had no response."		Adalimumab GAIN trial presents a different the selection criteria of inclusion for patients. While in ustekinumab UNITI 1 trial at least 50% of the patients have failed at least 2 TNF (primary or secondary failure), GAIN trial includes only patients with secondary failure to infliximab. This means that GAIN includes only 1 TNF failure and only includes patients that have shown a response to a previous TNF. This fact was acknowledged by ScHARR ERG report in TA352 "*As noted in the CS, Sandborn et al., 2007 (GAIN) included those who were intolerant or lost response (secondary non-responders), whilst GEMINI II and GEMINI III included primary non-responders as well as secondary non-responders and those who were intolerant. As such, the populations in the GEMINI trials are potentially likely to be less responsive to treatment, and in comparison to Sandborn et al.,52 may produce underestimates of efficacy. This should be borne in mind when interpreting the results of this network."* Janssen agree with the ERG's comment about the issues identified with the inclusion criteria of the anti-TNFα failure population	
On page 79 the ERG states: *"With respect to the anti-TNFα failure population there are also differences in the treatment history of the patients recruited. In the GAIN trial only secondary anti-TNFα failure patients were recruited i.e. patients who had failed anti-TNFα following initial response."*	Janssen suggests the following statement. *"With respect to the anti-TNFα failure population there are also differences in the treatment history of the patients recruited. In the GAIN trial only secondary anti-TNFα failure patients were recruited i.e. patients who had failed anti-TNFα following initial response. As a result, the NMA results in compared to adalimumab in the anti-TNFα failure population may be overestimated and need to be interpreted with caution"*		Not a factual inaccuracy

		included in the adalimumab studies (GAIN, Watanabe, CHARM). As pointed out in the CS, two comparisons in the NMA are less robust: • With infliximab in the TNF-refractory population • With adalimumab in the anti-TNFα failure population.	
On page 75: *"The CS also states that the induction results reported in Targan 1997 were not corroborated by the induction phase of ACCENT-1. The ERG found from the published papers the CDAI-70 response rates in the two studies to be 61% and 58%, i.e. statistically similar."*	*"The CS also states that the induction results reported in Targan 1997 were not corroborated by the induction phase of ACCENT-1. The ERG found from the published papers the CDAI-70 response rates in the two studies to be ~80% and 58%, which in fact were substantially different."*	The CDAI-70 response of the 5mg arm, with is the recommended dose of infliximab show response on week 2 of ~80% and of 81% and week 4. In ACCENT-1, the observed CDAI response of the same 5mg arm is 58% as stated by the ERG. When we state that the results from Targan 1997 were not corroborated by the induction phase of ACCENT-1, we are referring to the difference between ~80% to 58%.	Amendment made

			
On page 79, the ERG report states that anti-TNF failure patients from the Watanabe trial included in the anti-TNF failure indirect comparison were anti-TNF experienced patients who have not necessarily failed an anti-TNF. *"The anti-TNFα failure population from the adalimumab Watanabe trial(1) comprised anti-TNFα experienced patients but who had not necessarily failed an anti-TNFα"*	Janssen agree with this statement and acknowledges that the publication of the Watanabe trial does not explicitly state that anti-TNF experienced patients must have failed the anti-TNF they were previously exposed to. However, Janssen would like to request that the ERG amends the quoted statement to the following: *'The anti-TNFα failure population from the adalimumab Watanabe trial(1) comprised anti-TNFα experienced patients but who had not necessarily failed an anti-TNFα. As a result of this, the response and remission rates displayed by the anti-TNFα experienced patients in the Watanabe trial may be an overestimation of adalimumab's ability to induce response or remission in patients who have experienced treatment failure with a previous anti-TNFα agent. Therefore, by*	Previous failure of an anti-TNFα agent is known to be a treatment effect modifier for achieving and maintaining response and remission in Crohn's disease. This was pointed out in the original ERG report for TA352 (Rafia et al, 2014) pointed out that anti-TNF naive and anti-TNF refractory patients should be treated as a separate population when the Takeda submission in TA352 presented a mixed population analysis for their NMA. In the UNITI trial program and GEMINI trial program (Sands et al, 2017), refractory patients to anti-TNFs displayed lower levels of response and remission. This was also observed to some extent in Watanabe's study where it is noted that patients without prior anti-TNF	Not a factual inaccuracy

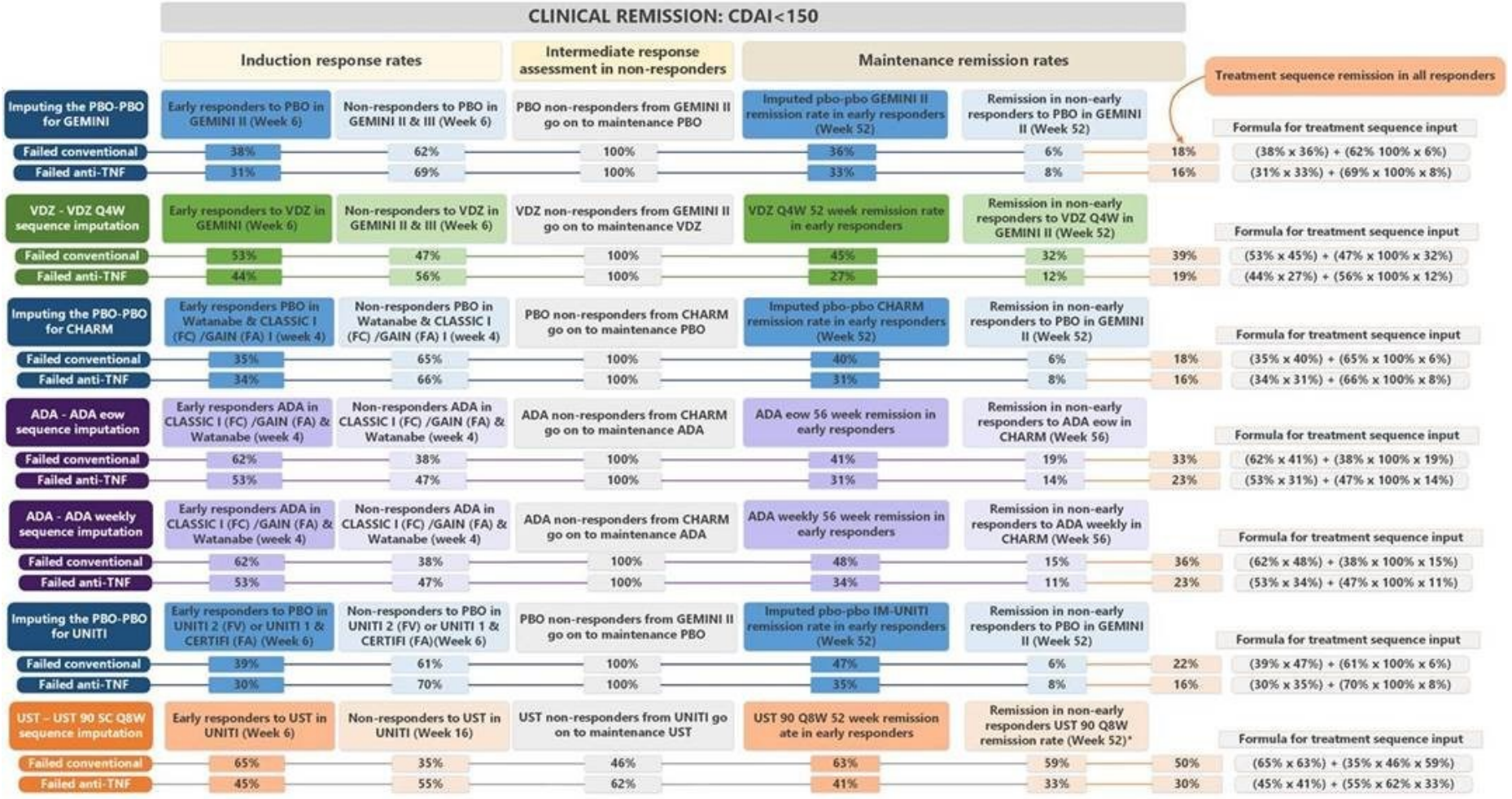
	including the induction response and remission data in anti-TNFα experienced patients from Watanabe in the indirect treatment comparisons for the anti-TNFα failure population, there is a chance that the company is over-estimating the efficacy of adalimumab in inducing response and remission in anti-TNFα failure patients and the indirect comparison for this population may be biased in adalimumab's favour.'	exposure had higher rates of response and remission at week 4 relative to patients with prior anti-TNF exposure (but not necessarily prior failure). Therefore, by assuming that the response and remission rates observed Watanabe anti-TNF exposed patients are also applicable to anti-TNF refractory patients, Janssen NMA runs the risk of overestimating adalimumab's efficacy in inducing remission and/or response in this population.	
The ERG states on page 81: *"There are however, two important points to note. Firstly, the placebo maintenance data for all biologic therapies used to perform the adjustment (A and C in the formula below) is sourced from the non-randomised placebo patients from IM-UNITI, i.e. the patients who were randomised to placebo in UNITI-1 or -2 trials and had responded to placebo, and therefore remained on placebo throughout follow-up. They are* ***not*** *the placebo patients in the randomised comparison with ustekinumab."*	Janssen suggests the following changes: *"There is however, an important point to note. The placebo maintenance data for all biologic therapies used to perform the adjustment (A and C in the formula below) is sourced from the placebo patients from IM-UNITI, i.e. the patients who were randomised to placebo in UNITI-1 or -2 trials and had responded to placebo, and therefore remained on placebo throughout follow-up in the open label arm."*	The 'true' placebo patients from the UNITI studies were randomised at the time of induction. While it is correct that these patients were not re-randomised at the beginning of maintenance, they continued blinded and were initially randomised. These patients are the patients initially randomised to placebo. They are not the patients initially randomised to ustekinumab and then re-randomised to placebo. Since the ERG acknowledges in other parts of the document that these latter patients are not true placebo patients, the sentence is removed to avoid confusion between 'true' and 're-randomised'	Not a factual inaccuracy

		placebo patients.	
The ERG states on page 86: *"In summary, due to the reasons that have been highlighted above, the ERG considers that the results based on the treatment sequence analysis to be potentially unreliable and the ERG have significant concerns about how they have been interpreted particularly with respect to the economic model (see section 5.2.6 for further discussion)."*	Janssen suggests the following changes: *"In summary, while there are limitations to the treatment sequence analysis, a number of steps in treatment sequence NMA erring on biasing against ustekinumab have been taken. While these steps do not necessarily resolve the uncertainty with the NMA per se, this conservative approach reduces the risk of decision making within this specific context of evaluating ustekinumab in Crohn's disease.* *However, it is correct that the data for ustekinumab in the treatment sequence NMA are the only data in which the same patients provided induction and maintenance data for the whole treatment sequence. Data for other biologics, and thus used in the prior assessments by NICE, rely on data generated for induction and maintenance in similar but not identical patients. Given the potential overestimation of the maintenance effect after open-label induction for these comparators, the uncertainty is situated more likely on the overestimation of the maintenance effect of the comparators, whereas the data for ustekinumab provide the most robust estimates performed in one single experiment."*	Consecutive conservative steps have been taken in the treatment sequence NMA that are described throughout this response document: • Non-inclusion of delayed responders, which inclusion would have increased the efficacy of ustekinumab compared to the other biologic treatments and placebo. See Figure 1. • The inclusion of maintenance trials for the comparators that used open label induction. While this approach does not maintain the randomisation after induction, results of the GEMINI II study suggests that results obtained with open label induction (cohort II) were better than with randomised induction (cohort I), thus potentially biasing against ustekinumab. • Inclusion & exclusion criteria of the different trials with biologics are similar, as well as placebo induction response rates, indicating similar populations have been studied in these trials. Nevertheless, the placebo-to-placebo rates were	Not a factual inaccuracy

		adjusted for the proportion of induction responders versus induction remitters at the end of induction, reducing the treatment-sequence placebo rates obtained for comparators. • A sensitivity analysis was conducted to assess the effect of prediction uncertainty for the placebo-to-placebo rates, with very little effect on the obtained results.	
The ERG states on page 90: *"The CS presented treatment sequence NMA results (Figure 36-39, pages 139-142 of the CS). The results found that ustekinumab was comparable in terms of clinical response and remission with the other biologics for both populations. However, the analysis is complex and based on the concerns expressed above about the process of data analysis (see section 4.4), the ERG believess that the results are highly unreliable and not a realistic evaluation of the relative treatment effectiveness over the first year of treatment, and so are not presented here."*	Janssen suggests the following changes: *"While there are limitations to the treatment sequence analysis, a number of steps in treatment sequence NMA erring on biasing against ustekinumab have been taken. While these steps do not necessarily resolve the uncertainty with the NMA per se, this conservative approach reduces the risk of decision making within this specific context of evaluating ustekinumab in Crohn's disease."*	This section should be revised in line with previous comments. The treatment sequence analysis approach for this submission was develop in collaboration with professor Keith Abrams, from Leicester University. Previous approaches, such and a meta-regression and a MAIC, were attempted but were considered unfeasible. In this situation the treatment sequence approach was considered the best method to deal with the limitations. (Pacou et al. 2016) Janssen hopes to have clarified the methodology of the NMA sufficiently to remove references to its 'complexity'. As mentioned above, a number of	Not a factual inaccuracy

		conservative steps were taken in the approach to the treatment sequence analysis, thereby reducing the risk associated with decision making on the basis of the NMA.	

Figure 1: Treatment sequence clinical remission CDAI<150 results with delayed responders



FA: Failed anti-TNF population, FC: Failed conventional therapy population
* Delayed remitters among CDAI-70 non-responders at week 6

Issue 3 Response definition selection for induction inputs in the treatment sequence analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 81: *"It should be noted that the induction response rate used in this calculation was defined with respect to a 70 points drop rather than a 100 point drop, as CDAI-100 was not reported for infliximab."*	Janssen suggests the following changes: *"It should be noted that the induction response rates used in the calculation was defined with respect to a 70 point drop for infliximab rather than a 100 point drop, based on the re-randomisation criteria of ACCENT1 and not lack of data."*	This rationale behind response definition selection was adopted to optimise comparability of infliximab and ustekinumab data across the entire treatment sequence. Time points were also selected accordingly based on this same randomisation criterion rationale (week 4 for infliximab versus week 6 for ustekinumab). CDAI-70 rates at week 6 (for ustekinumab and vedolizumab) or week 4 (for adalimumab and infliximab). CDAI-70 was selected for all trials. The rationale for selecting this definition of clinical response for ustekinumab when it was not its re-randomization criterion for entry into maintenance was to optimize the comparability of ustekinumab to other biologics. Based on ustekinumab data, CDAI-70 at week 6 and CDAI-100 at week 8 (the original re-randomisation criterion) were comparable endpoints at the end of induction and resulted in very similar maintenance response rates (Naessens, J., Gasink. Different	Not a factual inaccuracy
The ERG states on page 85: *"In addition, when the maintenance placebo response rates for each of the trials were imputed, the induction CDAI scores used were not consistent across the trials (e.g. CDAI-70 for infliximab and CDAI-100 for ustekinumab)"*	Janssen suggests the following changes: *"In addition, when the maintenance placebo response rates for each of the trials were imputed, the induction CDAI scores used were based on the re-randomisation criterion used for entry into maintenance."*		Not a factual inaccuracy

		induction response criteria do not influence 1-year response and remission rates of ustekinumab 90 mg q8w in phase III program. United European Gastroenterology Week October 15-19, 2016, Vienna, Austria (April 29 2016).	

Issue 4 Placebo treatment inputs, use of historical controls, and adjustments for confounding factors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 81: *"Secondly, this data is adjusted for the proportion of responders who achieve remission based on the response and remission rates in the relevant induction trials."*	Janssen suggests the following changes: *"Secondly, this data is adjusted for the proportion of responders who achieve remission based on the response and remission rates in the relevant induction trials. This adjustment was made to account for differences in baseline characteristics at the start of maintenance trials."*	The proportion of responders who achieve remission based on the response and remission rates in induction is used as an adjustment in order to reduce the uncertainty around confounding factors. Placebo patients from the UNITI program are not historical control. They are part of the randomised trial. Patients were initially randomised to receive placebo. It is true that they were not re-randomised at the beginning of maintenance, but they remained blinded in the trial after the initial randomisation at the beginning of the induction trial. At the beginning of induction, trials have comparable entry criteria, key baseline characteristics are comparable across trials, and	Not a factual inaccuracy
The ERG states on page 84: *"The use of the UNITI trials' data in this way has substantial implications. Primarily, it removes the randomised placebo from the maintenance trials of ustekinumab, infliximab, adalimumab and vedolizumab and replaces them with an historical control."*	Janssen suggests the following changes: *"The use of the UNITI trials' data in this way has substantial implications. Primarily, it removes the randomised placebo from the maintenance trials of ustekinumab, infliximab, adalimumab and vedolizumab. The patients used in the analysis are not historical controls but randomised placebo patients."*		The suggest change is misleading as a historical control was used for infliximab, adalimumab and vedolizumab. We have, however, amended the text as a historical control was not used in the comparison of ustekinumab with placebo. Note historical control is considered a generic term for a non-randomised comparison and does not refer to the age of the comparator

		induction placebo response rates are similar. This points to the fact that patient populations were similar at the outset of the study. This reduces the probability of prognostic factors to affect the estimation of placebo-placebo. Moreover, small differences and the risk for confounding factors on long-term placebo rates are accounted for by including responders and responder non-remitters at the end of induction in the calculations.	data.
The ERG page 84: *"Therefore, the analysis is not based on randomised comparisons and there is a risk of confounding due to differences in setting, treatments received and severity of disease. The extent that these differences are prognostic will influence the corresponding performance of the placebo arm and undermine the reliability of the presented treatment sequence analysis. It is very difficult to quantify these differences, but no attempt was made to adjust for them."*	Janssen suggests the following changes: *"While re-randomisation is lost, the initial randomisation from the beginning of the induction trial is conserved (induction trials have comparable entry criteria). Small differences in confounding factors and their impact on long-term placebo rates were accounted for by including responders and responder non-remitters at the end of induction in the calculations."*		Not a factual inaccuracy
The ERG states on page 84: *"The ERG considers that caution should be taken in interpreting the present analyses due to the potential for unobserved confounding."*	Janssen suggests the following changes: *"While there are limitations to the treatment sequence analysis, a number of steps in treatment sequence NMA erring on biasing against ustekinumab have been taken. While these steps do not necessarily resolve the uncertainty with the NMA per se, this conservative approach reduces the risk of decision making within this specific context of evaluating ustekinumab in Crohn's disease."*		Not a factual inaccuracy

Issue 5 On the overestimation of placebo rates for other biologics

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 84: *"In addition, the ERG notes that the placebo response rate was higher in ustekinumab trials than in the trials of anti-TNFαs, particularly infliximab and adalimumab (see Figure 18 page 58, appendices of the CS). Therefore, after adjustment, the placebo rates of the other biologics will be higher than the ustekinumab trials' comparators. This means that in the treatment sequence analysis the effectiveness of the other biologics relative to placebo will be diminished and the relative effectiveness of ustekinumab will be increased."*	Janssen suggests the following changes: *"By accounting for induction response rates, a conservative approach was taken to estimate ustekinumab trial placebo rates at the end of the treatment sequence."*	Placebo rates at the end of maintenance are highest in ustekinumab trials. At the end of the treatment sequence, the number of events (r) in the placebo arm is lower in comparator trials compared to the ustekinumab trial. Figure 18 refers to induction rates, and not maintenance rates. As it was stated before, the inclusion of maintenance trials for the comparators that used open label induction. While this approach does not maintain the randomisation after induction, results of the GEMINI II study suggests that results obtained with open label induction (cohort II) were better than with randomised induction (cohort I), thus potentially biasing against ustekinumab.	Not a factual inaccuracy. The point the ERG made is about adjusting for placebo rates. As placebo response rate from the ustekinumab trials were high, using these rates to adjust the comparator placebo rates could diminish the relative effectiveness of the comparators.

Issue 6 ITT vs. complete case

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 85: *"The ERG noted that in the*	Janssen suggests the following changes: *"The ERG noted that in the treatment*	The numbers reported in table 16 are all results from the ITT population. Moreover, numbers	Amendment made

treatment sequence analysis, the type of active treatment response rates utilised in the model were not consistent across the trials (see figure 30 page 131 of the CS). For the adalimumab, infliximab and vedolizumab trials, the ITT response rates were used, whilst for ustekinumab trial the complete case response rates were used; complete cases response rates are generally higher than ITT. For example, based on the IM-UNITI trial results (see table 16 page 91 of the CS), the ITT clinical remission rates at week 44 for the 90mg q8w and 90mg q12w dosage groups were 53.1% (68/128) and 48.8% (63/129) respectively compared to rates for complete cases of 66.7% (52/78) and 56.4% (44/78). This means that the active treatment maintenance phase and the overall active treatment response rates (induction + maintenance) for ustekinumab will be inflated, whilst the rates for the other biologics remain the same."	*sequence analysis, the type of active treatment response rates utilised in the model were consistent across the trials (see figure 30 page 131 of the CS). ITT response rates were used for all trials, including ustekinumab trials."*	cited by the ERG on page 85 were not used in the treatment sequence analysis as they correspond to results obtained in the general population (no subgroup data). Numbers used in the treatment sequence analysis are indeed those from the ITT population and can be found in attachment TEFCRES13B of the IM-UNITI CSR, reporting results from the IM-UNITI trial by sub-group (failed conventional care vs. failed anti-TNF therapy patients). Finally, the ERG is using numbers from patients in clinical remission at week 44 among those who were in clinical remission at baseline 66.7% (52/78) and 56.4% (44/78) to cite results from a complete cases analysis. The figures cited are in fact for the ITT subgroup population and not actually from a complete cases analysis.	

Issue 7 Quality assurance and validity issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 85: *"The ERG found quite significant differences in the rates of response and remission for vedolizumab, ustekinumab and placebo-placebo. Details of all differences between the ERG and company inputs are provided in appendix 10.2."*	Janssen suggests the removal of the sentence	Inputs provided during the clarification process (reported in table 3 pg. 15) were cross-checked with those actually used in the statistical analyses. There were typos in the CDAI-100 inputs reported: the wrongly reported inputs were not used in the statistical analyses and do not impact the results of the statistical analyses. Inputs used in the statistical analyses are much closer to those re-estimated by the ERG and match the % response rates reported in figure 31 of the CS. See table 1 of this proforma response document for said inputs.	While not a factual inaccuracy, we have soften the wording used to reflect the fact that the inputs used in the statistical analyses are much closer to those re-estimated by the ERG

Table 1: Inputs used in Janssen statistical analysis

Induction phase data source	Maintenance phase data source	Treatment	CS estimates provided during clarification process (CS response to clarificatrion table 3, pg. 15)			ERG's estimates		
			N	CDAI-100 (n)	CDAI<150 (n)	N	CDAI-100 (n)	CDAI<150 (n)
GEMINI II and GEMINI III pooled data	GEMINI II	Placebo-placebo	227	28	23	227	*29*	*26*

GEMINI II and GEMINI III pooled data	GEMINI II	Vedolizumab 300 - vedolizumab 300 q8w	263	35	32	263	*34*	32
GEMINI II and GEMINI III pooled data	GEMINI II	Vedolizumab 300 - vedolizumab 300 q4w	263	45	32	263	44	31
UNITI I and CERTITI pooled data	IM-UNITI	Placebo-placebo	379	46	42	379	*46*	41
UNITI I and CERTITI pooled data	IM-UNITI	Ustekinumab 6 - ustekinumab 90 q12w	380	80	65	380	80	*67*
UNITI I and CERTITI pooled data	IM-UNITI	Ustekinumab 6 - ustekinumab 90 q8w	380	84	68	380	*82*	*70*
GAIN and Watanabe pooled data	CHARM	Placebo-placebo	179	22	20	179	*23*	20
GAIN and Watanabe pooled data	CHARM	Adalimumab 160 80 - adalimumab 40 eow	178	34	28	178	33	28
GAIN and Watanabe pooled data	CHARM	Adalimumab 160 80 - adalimumab 40 weekly	178	36	32	178	35	31
In italics: significant differences compared with CS estimates								

Issue 8 Conventional care failure population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 15: *"For conventional care failures the company submission presents*	Janssen suggests that the reconsideration of the strength and the balance of argument in all discussions of the generalisability of the	In clinical practice, there may be patients who have received and were tolerant of TNFα inhibitor	Not a factual inaccuracy

evidence mainly for conventional care failures who are not necessarily anti-TNF naïve; it is unclear how well this will reflect the NHS population."	conventional care failure population to scope and clinical practice.	therapy, but who are not considered to have responded inadequately or stopped responding to the treatment (for instance a patient with high levels of inflammation at diagnosis may receive a dose of infliximab to reduce the inflammation before starting treatment on conventional therapy, i.e. it was discontinued for a reason other than lack or loss of efficacy or intolerance). These patients cannot be considered part of the TNF failure population and would likely be considered eligible for further TNFα inhibitor therapy; and, therefore, should be considered as part of the conventional care failure population. The UNITI-2 trial population includes both patients who are "truly naïve" (~70%) and patients who have been exposed to treatment with TNFα inhibitor therapy but are not considered part of the TNF failure population (~30%). We consider that the full UNITI-2 trial population represents the conventional care failure population and that considering the "truly naïve" population to be representative of the conventional care failure population may lead to the exclusion of patients who are eligible for ustekinumab treatment	
The ERG states on page 18: *"Regarding the conventional failure trial, the population was a mixture of anti-TNF naïve and experienced patients (though none were anti-TNF failures). It is unclear whether this reflects the NHS population eligible for ustekinumab or whether or not it implies that the results from the trial may overestimate the benefit likely to be achieved in practice."*			Not a factual inaccuracy
The ERG states on page 31: *"There is an issue for consideration about whether or not a population of patients who has responded inadequately to, or is no longer responding to conventional therapy includes only patients who have never taken an anti-TNFα (anti-TNFα naïve), or includes patients who have previously taken an anti-TNFα but not 'failed'. This issue arises in trials of CD because biologic therapy is recommended only for a period of one year, with treatment*			Not a factual inaccuracy

being stopped if patients are in remission. It is likely that a group patients who have previously responded but not failed' are more likely to respond than a group of patients who have not been tested. This is discussed further in Section 4.2."		under its licensed indication from the decision problem. Furthermore, the UNITI-2 population is randomised, whereas considering the "truly naïve" subgroup of patients breaks randomisation and results in a smaller sample size which increases uncertainty.	
The ERG states on page 51: *"There is an issue for consideration about whether the trial population truly reflects the 'conventional care failure' population to be treated in NHS practice. It can be argued reasonably that patients who have previously responded to but not 'failed' an anti-TNFα are more likely to respond to ustekinumab than a group of patients who have not been exposed. The proportion of anti-TNFα exposed patients in UNITI-2 is 42% and therefore the response rates in this trial may overestimate that to be expected in NHS clinical practice."*		Data were presented for the truly naïve population from UNITI-2 at week 6 of induction and week 44 of maintenance in response to ERG clarification question A8 and were consistently similar to the overall population.	Not a factual inaccuracy
The ERG states on page 22: *"The effectiveness of ustekinumab in a truly anti-TNF naïve population is uncertain."*	Janssen suggests the removal of these statement.	The scope of the submission is for people with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-	Amendment made

		α inhibitor, or who are intolerant to either of them. Subgroup analysis is suggested for people who have not previously received a tumour necrosis factor-α inhibitor, if data allows; but this is not specified as a main population of interest. This statement puts too much emphasis on this population of patients. In Section 4.8 it states: *"in subgroup analysis of UNITI-2, patients who had not previously received a TNFα inhibitor demonstrated similar efficacy (clinical response and clinical remission rates at Week 6) to those patients who had previously been exposed to a TNFα inhibitor (but who did not meet the failure criteria specified for UNITI-1)."* Results for this subgroup are presented in Appendix 4.4 and the response to ERG clarification question A8, which also presents a full discussion around the TNF-naïve population.	
The ERG states on page 33: *"The CS covers conventional care failure (people who have not previously received a tumour necrosis factor-alpha inhibitor) and anti-TNFα failure (people for whom at least 1 tumour necrosis*	Janssen suggests the removal of these statement.	UNITI-1 included patients who had failed, or who were intolerant to anti-TNFα in line with the indication for ustekinumab and the scope of the submission.	Amendment made

factor-alpha inhibitor has failed) population subgroups. However, people for whom tumour necrosis factor-alpha inhibitors are not suitable because of intolerance or contraindication are not covered in the CS evidence."			
On page 55-56 the ERG does not state that the subgroup analyses of UNITI-2 demonstrated similar efficacy of ustekinumab for patients who had not previously received a TNFα inhibitor (TNF-naïve) compared to those who had previously been exposed to a TNFα inhibitor (but who did not meet the failure criteria specified for UNITI-1).	Janssen suggests adding the following sentence: In subgroup analysis of UNITI-2, patients who had not previously received a TNFα inhibitor (TNF-naïve) demonstrated similar efficacy (clinical response and clinical remission rates at Week 6) to those patients who had previously been exposed to a TNFα inhibitor (but who did not meet the failure criteria specified for UNITI-1).	The point about TNF-naïve patients within UNITI-2 is raised throughout the submission, so this is an important point to make in order to address these concerns.	Amendment made

Issue 9 Spontaneous improvement of patients on conventional care

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 21: *"The use of the treatment sequence analysis to populate the transitions in this phase of the model makes the implicit assumption that non-responders to induction therapy remain in the moderate to severe health state for the entire maintenance period. The ERG considers this*	Janssen suggests the following amendment: *"The use of the treatment sequence analysis to populate the transitions in this phase of the model makes the implicit assumption that non-responders to induction therapy remain in the moderate to severe health state for the entire maintenance period. ~~The ERG considers this assumption to be unreasonable and that is likely to overestimate the cost-effectiveness of ustekinumab relative to conventional care.~~"*	The ERG based these statements under the assumption that induction non-responders to conventional care may spontaneously improve while only receiving conventional care. However, this is not observed in the clinical evidence available. The results from the GEMINI-II study, in which there is a group of conventional care non-responders	Not a factual inaccuracy, this is the opinion of the ERG.

assumption to be unreasonable and that is likely to overestimate the cost-effectiveness of ustekinumab relative to conventional care."		that continued with the same treatment, clearly demonstrate that very few patients achieved remission or response at week 52, only both 7.2% of placebo non responder patients at week 6. (Sandorn poster 2014) (Journal of Crohn's and Colitis 8.Supplement 1 (2014): S274-S275) & G-BA, Dossier zur Nutzenbewertung gemäß § 35a SGB V, Vedolizumab (Entyvio®), Module 4B, Morbus Crohn's, tables 4-27 and 4-36) In light of this the assumption of the ERG, placebo non responder with spontaneous improvement, may not be not maintained.	
The ERG states on pages 114-115. *"This misinterpretation has important consequences for the calculated transition probabilities as by interpreting the treatment sequence analysis in this way it makes the implicit assumption that non-responders to treatment remain in the moderate to severe health state for the entire maintenance period. There is, however, no reason to believes that this is the case as patients will often spontaneously improve even while only receiving conventional care as observed in the placebo arms of the induction trials. The impact of this implicit assumption is that it underestimates the likelihood that patients who are in the moderate to severe health state at the end of induction will move either to mild or remission health states during the course of the maintenance phase*"	Janssen suggests the removal of this paragraph.		Not a factual inaccuracy, there is no way to know how well these patients would do and even a small number of non-responders moving to remission could have a sizable impact on model estimates.

Issue 10 Longer-term data availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 16: *"One trial (IM_UNITI) was of maintenance therapy treatment (up to ~one year)…"*	Janssen suggests the following amendment: *One trial (IM-UNITI) was of maintenance therapy treatment (up to two years)…*	Two-year efficacy data for the IM-UNITI trial are presented in Section 4.7.9.	Amendment made
The ERG states on page 16: *"Based on the short term clinical effectiveness results, ustekinumab appears to be more effective than placebo in terms of both clinical response and remission in both the conventional care failure and anti-TNF failure populations."*	Janssen suggests the following amendment: *"Based on the clinical effectiveness results, ustekinumab appears to be more effective than placebo in terms of both clinical response and remission in both the conventional care failure and anti-TNF failure populations."*	Efficacy data for ustekinumab is presented for up to 2-years.	Not a factual inaccuracy
The ERG states on page 17: *"The trials provide no evidence on the effect of ustekinumab in Crohn's disease in the long term, i.e. beyond one year."*	Janssen suggests to remove or revise statement to reflect data available beyond one year.	Efficacy data for IM-UNITI is presented for up to 2-years in Section 4.7.9.	Amendment made
The ERG states on pages 17, 74 and 91: *"Data on adverse effects in long term are lacking."*	Janssen suggests the following amendment: *"Data on adverse events for ustekinumab in Crohn's disease is limited to one-year, however safety data across other indications are available for up to five-years."*	Safety data for ustekinumab in Crohn's disease are available for up to one-year from the IM-UNITI trial. The pooled safety analysis for ustekinumab across indications (presented in Section 4.12.3 and Appendix 6) presents additional safety data for ustekinumab in PsA (1-year) and psoriasis (5-years) and	Not a factual inaccuracy

		a pooled analysis of ustekinumab across indications.	
The ERG states on page 90: *"One trial was of maintenance therapy treatment (up to one year)"*	Janssen suggests the following amendment: *"One trial was of maintenance therapy treatment (up to two years)"*	This statement is factually incorrect. Efficacy data for the IM-UNITI trial are presented for up to 2 years.	Amendment made

Issue 11 CERTIFI trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG state on page 16, page 73 and page 90: *"Four well conducted placebo-controlled, double-blind RCTs provided data on the licensed dose of ustekinumab in Crohn's disease."*	Janssen suggests the following amendment: *"Three well conducted placebo-controlled, double-blind RCTs provided data on the licensed dose of ustekinumab in Crohn's disease and one additional placebo-controlled, double-blind RCT included one arm on which patients were treated with a dose that was similar to the licensed dose."*	The CERTIFI trial did not strictly use the licensed dose for ustekinumab. Janssen agrees with the ERG decision to incorporate CERTIFI in the analysis, however the statement discussed it factually incorrect.	Amendment made
The ERG states on page 37-38: *"The company presented a review of three pivotal Phase III randomised controlled trials (RCTs) that provided data for 8-week induction period (UNITI-1 and UNITI-2 trials) and 44-week maintenance period (IM-UNITI trial). The ERG has also identified a fourth trial which is relevant to the submission."*	Janssen suggests the following amendment: *"The company presented a review of three pivotal Phase III randomised controlled trials (RCTs) that provided data for 8-week induction period (UNITI-1 and UNITI-2 trials) and 44-week maintenance period (IM-UNITI trial). They also presented evidence for a Phase II RCT (CERTIFI), however this was not considered relevant as it does not provide comparable evidence to these data in the respect that patients received a 1, 3 or 6 mg/kg induction dose, rather than the vial-based dose*	The statement is misleading and technically incorrect. The CERTIFI trial is discussed in Section 4.2 and presented in Appendix 3 of the submission. The focus of the submission is on the Phase III UNITI data, on which marketing authorisation was granted and on which the cost-effectiveness modelling has been based. The CERTIFI study does not provide comparable evidence to these data in the respect that patients received	CERTIFI was in the CS - No amendment necessary

	approximating to 6mg/kg as per licence terms. The focus was on the Phase III UNITI data, on which marketing authorisation was granted and on which the cost-effectiveness modelling has been based."	a 1, 3 or 6 mg/kg induction dose, rather than the vial-based dose approximating to 6mg/kg as per licence terms.	
Page 65, discussion of the CERTIFI trial.		Worth bearing in mind that although limited data are presented for the CERTIFI trial, it is discussed in Section 4.2 and outcomes are presented in Appendix 3 of the submission.	No amendment necessary
Page 69-70: the write-up of the CERTIFI trial does not mention mean CDAI score or CRP score.	Janssen suggests the following addition: *"Among patients with an induction response, reductions in mean CDAI scores and CRP levels were sustained in those who continued to receive ustekinumab maintenance therapy but were not sustained in those receiving placebo."*	This is an important point that was made on the IM-UNITI trial data and would provide consistency if added here.	Amendment made
The ERG states on page 73 and page 90: *"Three trials were of induction therapy (single dose of ~6mg/kg followed for 8 weeks)"*	Janssen suggests the following amendment: Three trials were of induction therapy (two using the single licensed dose of ~6mg/kg and one using 6mg/mg, followed for 8 weeks)	It is an important distinction that the CERTIFI trial did not use the licensed dose for ustekinumab.	No amendment necessary

Issue 12 Use of IM-INITI transition probabilities versus NMA transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG state on page 180, the preferred ERG base case:	Janssen suggests the inclusion of some of the considerations	Janssen believes that the IM-UNITI transition probabilities does not represent a plausible	This not a factual inaccuracy and the ERG do note that the IM-UNITI

• *Inclusion of alternative starting values in the calculation of the transition probabilities used during the maintenance phase*	explained in the justification for amendment.	clinical scenario because of the following reasons: - Under this scenario, all biologics are assumed to have the same efficacy in the maintenance than ustekinumab. Clinical evidence on anti TNF suggests otherwise as explained in section 5.3.3 of the CS; TNF trials seems to loose efficacy over time and this effect is not observed in ustekinumab trial. - Conventional care is represented by patients that were treated and responded to ustekinumab IV and are randomised to placebo in maintenance. This will likely inflate the results of conventional care and may explain why in the preferred ERG base-case no biological therapy is found cost-effective, where in previous TA187 and TA352 were found cost-effective. - When looking at how patients transition in the model, with IM-UNITI transition probabilities 75% of the patients reach a response in maintenance in conventional care, 50% of patients in the TNF failure population. With NMA transition probabilities 30% of the patients on conventional care reached response in conventional care failure population and approximately 20% of patients in TNF failure population. NMA	data is subject to significant limitations including the issues cited by the company. Furthermore, it is not clear that these predictions are clinically implausible just that they differ significantly from the NMA transition probabilities which suffer from very serious limitations.

		transition probabilities provide estimates that are more similar to response rates observed in clinical studies, unlike IM-UNITI transitions that do not seem clinically plausible. See Figure 2 and Figure 3	

Figure 2: Comparison of IMUNITI and NMA transition probabilities in conventional care failure population

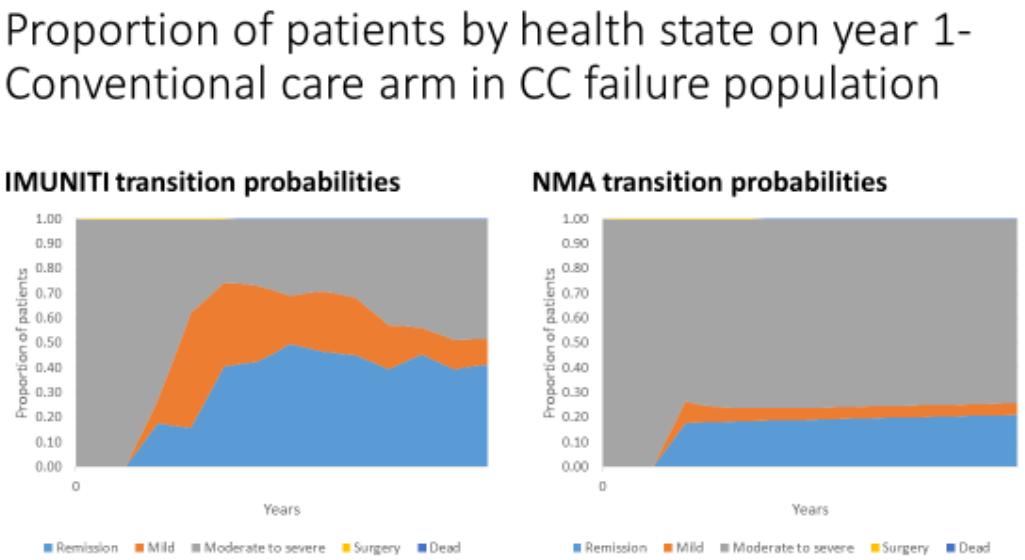
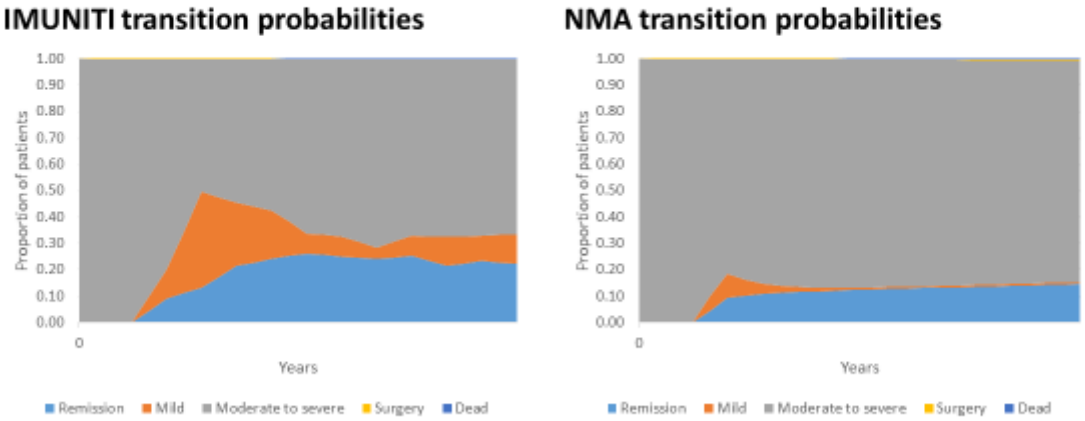


Figure 3. Comparison of IMUNITI and NMA transition probabilities in TNF failure population

Proportion of patients by health state on year 1- Conventional care arm in TNF failure population



Issue 13 Misrepresentations of data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states on page 16: *"Differences in inflammatory*	Janssen suggests the following amendment: *"Ustekinumab was efficacious in reducing both*	The statement is factually incorrect.	Amendments made.

biomarker levels between the treatment arms were generally non-significant, though patients randomised to ~6mg/kg ustekinumab in the UNITI-1 and UNITI-2 trials had a greater reduction of CRP levels at 8 weeks (UNITI-1: PLA +3.30 vs UST -5.55; UNITI-2: PLA -0.14 vs UST -8.56).”	*serum- (CRP) and faecal (calprotectin and lactoferrin) based biomarkers of inflammation. Patients randomised to ~6mg/kg ustekinumab had significantly greater median reductions from baseline in CRP at week 8 (UNITI-1: PLA +3.30 vs UST -5.55; UNITI-2: PLA -0.14 vs UST -8.56), faecal calprotectin at week 6 (UNITI-1: PLA 0.00 vs UST -41.25; UNITI-2: PLA 0.00 vs UST -106.32) and faecal lactoferrin at week 6 (UNITI-1: PLA 0.00 vs UST -6.43; in UNITI-2: PLA 0.00 vs UST -25.93). A significantly greater proportion of patients treated with ustekinumab achieved normalised inflammatory biomarkers.”*		
The ERG states on page 17: *“The results of the follow-up of placebo responders from UNITI-1 and -2 also indicate that placebo response in Crohn’s disease is common and can be sustained. Of the placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% achieved clinical response (CDAI-100) and 48% achieved clinical remission at one year.”*	Jansen suggests removing the introductory sentence to paragraph.	Janssen believes this statement may be misleading. Placebo response is shown not to be common and is not maintained long-term n the clinical evidence: 21.5% of placebo patients achieved CDAI-100 response at week 6 in UNITI-1 and 28.7% in UNITI-2 (20.2% and 32.1%, respectively at week 8). Of these patients, 120 placebo induction responders entered IM-UNITI and continued to receive placebo. At week 8, 74.2% had maintained this response (53.3% were in remission) and at week 44, 55.9% had maintained this response (47.5% were in remission).	Not a factual inaccuracy

On page 17 the ERG states: *"Since there were no head-to-head comparative trials available to allow direct comparisons of ustekinumab with its comparators in CD…"*	Janssen suggests the following amendment: *"Since there were no head-to-head comparative trials available to allow direct comparisons of ustekinumab with alternative biologics in CD…"*	The UNITI trial does provide direct comparisons of ustekinumab with placebo that acts as a proxy for conventional care.	Minor point – sense is clear – no amendment necessary
The ERG states on page 33: *"Location of CD was also included as a subgroup to be considered in the NICE scope. CD can be in the ileum, colon or perianal area. This was not addressed in the company submission. The analysis of included ustekinumab trials were not stratified on site of CD."*	Janssen suggests the following amendment: *"Location of CD was also included as a subgroup to be considered in the NICE scope. In subgroup analysis across the UNITI trial programme, ustekinumab was shown to be effective irrespective of location of CD."*	Janssen believes the statement does not represent the data that were provided in the submission. Subgroup analyses are presented in Section 4.8 of the submission with forest plots presented in Appendix 4.3 through 4.5.	Amendment made. Text amended to, "*Location of CD was also included as a subgroup to be considered in the NICE scope. CD can be in the ileum, colon or perianal area. This was addressed very briefly in the CS, with a statement that in subgroup analysis across the UNITI trial programme, ustekinumab was shown to be effective irrespective of location of CD."*
The ERG states on page 43: *"With regard to UNITI-1 and -2, the largest difference between the trials was for the proportion of patients with both ileum and colon disease – less than 20% compared with around 60%."* *"The trials included a mixture of GI area involved (ileum only, colon only, ileum and colon, proximal GI tract and perianal GI*	Janssen suggests the removal of the statements	These statement are factually incorrect. In UNITI-1 there were 68.7% and 67.5% with ileum and colon involvement, and 56.0% and 61.4% in UNITI-2, receiving ustekinumab ~6mg/kg and placebo, respectively.	Amendments made.

tract) but the actual percentages varied across the trials. With regard to UNITI-1 and -2, the largest difference between the trials was for the proportion of patients with both ileum and colon disease – less than 20% compared with around 60%. The trial analysis was not stratified by site of CD. It is unclear to the ERG if this affects the generalisability or comparability of the trials' results."			
The ERG states on page 43: *"Biologics for CD are given against a background of conventional care, i.e. almost all patients in clinical practice will be receiving some form of conventional therapy as well as the biologic. In the ustekinumab trials (Table 7) only 70 to 80% of patients were taking any medication for CD at baseline. As a population they may therefore not be as optimally treated with conventional care as the clinical practice patients should be; the benefits of ustekinumab seen in the trials may be greater than those achieved in practice."*	Janssen suggests the following modification: *"Biologics for CD are given against a background of conventional care, i.e. almost all patients in clinical practice will be receiving some form of conventional therapy as well as the biologic. In the ustekinumab trials (Table 7) only 70 to 80% of patients were taking any medication for CD at baseline. ~~As a population they may therefore not be as optimally treated with conventional care as the clinical practice patients should be; the benefits of ustekinumab seen in the trials may be greater than those achieved in practice.~~"*	It is important to remember that all patients included in UNITI 2 trials will have failed conventional care. There may be different clinical reasons why the patients discontinue the conventional medication, e.g. medication side effects. While it is important to notice the fact that some patients have discontinue medication the insinuation that this may be biasing the efficacy in favour of ustekinumab is misleading.	Not a factual inaccuracy
The ERG states on page 44:	Janssen suggests the removal of the	Ustekinumab is administered in induction via IV with an average	Not a factual inaccuracy

"The ERG has the following comments about the UNITI-1 trial. First, the follow-up period for the primary (6 weeks) and secondary (8 weeks) outcomes were very short. In fact, patients had received only one IV dose of active treatment or placebo. The committee of human medicinal products (CHMP) guidance recommends that primary outcome (endpoint) should be considered after at least 2 cycles of therapy. Therefore, the ERG believess that the follow-up period was not sufficient."	statement	dose of 360mg which is indeed 4 times higher than the 90mg subcutaneous maintenance dose. This dose was selected in the phase 3 based on CERTIFI study were 6mg/kg arm show sufficient effect to induce response. The ERG refers to the CHMP guidance to make the statement that the follow up is not sufficient. However, CHMP did recommended ustekinumab for human used based on ustekinumab trial design. Janssen believes this statement is therefore misleading and should be removed.	
On page 45, the ERG (in discussing the study methods for CDAI) states: *"Based on this statement, the ERG identifies the following issues. First, it is not clear why "4" was used a cut-off value for the number of available (complete) components. It is not clear as to why imputing missing data was only applicable to those who had at least 4 components available. In fact, this method would unfairly exclude participants with 3 available components. Therefore,*	Janssen suggests to state that that the approach taken was conservative.	It is worth to mention that this is a conservation approach. And the ERG does acknowledge: *"The ERG notes that sensitivity analyses (page 67 of the CSR) using complete cases, multiple imputation and worst cases were carried out for the primary outcome data (i.e. clinical response outcome at week 6) and all the methods appear to have reached at the same conclusion."*	Not a factual inaccuracy

the ERG considers the approach to be inconsistent. *Second, although participants may have had 3 components available, they were assumed to be non-responders. In fact, based on the number of components available, there were 2 types of non-responders (i.e. those with <4 components available and those who had <100 CDAI score change). This introduces additional uncertainty to the results of the trial."*			
The ERG states on page 47: *"…participants who were randomised to ~6mg/kg ustekinumab showed a significantly higher reduction of CRP during the 8-week follow-up period than those who were randomised to placebo (Table 10). However, there were no significant difference in the mean changes of faecal lactoferrin and faecal calprotectin between the two ustekinumab dosages and placebo group (Table 10)."*	Janssen suggests the following amendment: …participants who were randomised to ~6mg/kg ustekinumab showed a significantly higher reduction of CRP during the 8-week follow-up period and significantly higher reductions in faecal lactoferrin and faecal calprotectin at week 6 than those who were randomised to placebo.	The statement from the ERG is factually incorrect.	Amendment made.
The ERG states in page 48: *"Based on these SF-36 results, the ERG considers that on average, there appears to be little*	Janssen suggests the following amendment: *"Based on these SF-36 results of the physical component, the ERG considers that on average, there appears to be little*	As it is reflected in Table 11 of the ERG report the statement of the ERG regarding SF-36 is only accurate for the physical	Amendment made

improvement in health related quality of life over the placebo group during the 8-week follow-up period."	*improvement in health related quality of life over the placebo group during the 8-week follow-up period. However, there was an improvement in the SF-36 mental component compared to placebo at week 8."*	component but not for the mental component where there is improvement compared to placebo.	
The ERG states on page 50: *"The UNITI-2 trial compared the clinical effectiveness of ustekinumab and placebo in 628 adult patients…"*	Janssen suggests the following amendment: *"The UNITI-2 trial compared the clinical effectiveness of ustekinumab and placebo in 627 adult patients…"*	209 patients were included in each arm for the efficacy analyses.	Amendment made
The ERG states on page 55: *"The results indicated that participants who were in the ustekinumab dosages and placebo appear to have identical endoscopic response outcomes, see Table 17 below."*	Janssen suggests the following amendment: *"The results showed improvements for ustekinumab compared to placebo for all endoscopic outcomes, although the differences between the study groups were relatively small."*	This statement is not factually correct and the use of "identical" may be misleading. Although the results are similar they are still numerically superior in favour of ustekinumab across all endoscopic outcomes. Furthermore, in UNITI-2, patients on ustekinumab 6mg/kg were shown to have a statistically significant improvement in faecal calprotectin and faecal lactoferrin levels at week 6 relative to patients in the placebo arm (refer to page 98 and 99 of Janssen submission). Improvement in faecal calprotectin and faecal lactoferrin levels have been shown to be highly correlated with endoscopic improvement (Sipponen et. al., 2009; D'Haens et al, 2012).	Amendment made: "identical" changed to "similar"

The ERG states on page 56: *"The ERG considers that whilst the IM-UNITI randomised trial provides vital information about long-term loss of response and safety of ustekinumab it must be noted that participants of the trial were only those who were randomised to ustekinumab and had achieved clinical response at week 8 of the UNITI-1 and UNITI-2 trials. Those who were randomised to placebo during the induction period (irrespective of the clinical response), and those non-responders who were randomised to the ustekinumab dosages, were not included in the trial. This means that results from the IM-UNITI randomised trial are not applicable to the wider CD patient population or that the trial lacks external validity."*	Janssen suggests the following amendment: *"The ERG considers that whilst the IM-UNITI randomised trial provides vital information about long-term loss of response and safety of ustekinumab it must be noted that participants of the trial were only those who were randomised to ustekinumab and had achieved clinical response at week 8 of the UNITI-1 and UNITI-2 trials. Those who were randomised to placebo during the induction period (irrespective of the clinical response), and those non-responders who were randomised to the ustekinumab dosages, were followed as part of the open label arm of IM-UNITI. The design of IM-UNITI randomised trial is representative of the UK clinical practice where biologic treatment therapy is only continued in case that the patients responds to the treatment."*	The statement of the ERG is factually incorrect. All patients randomised in the induction trials are followed in the maintenance phase; the responders of ustekinumab as part of the re-randomised population and the non-responders to ustekinumab and placebo patients as part of the open label arms of IMUNITI. Moreover, the design of clinical trials in Crohn's dose reflect the standard clinical practice where the biologic therapies induced and if response is observed patients continue on treatment, otherwise biologic treatments is discontinued. It is also important to state here that it would be unethical to keep patients on placebo when if they have not shown response to placebo. For this reason, in IM-UNITI trial patients that do not respond to placebo in the induction are induced with ustekinumab in the maintenance phase.	Amendment made
The ERG states on page 58: *"Baseline data of the IM-UNITI trial are presented in Table 13 of*	Janssen suggests that this paragraph is amended in line with the information provided on page 82, Section 4.5.2 of the submission.	As stated on page 82, Section 4.5.2 of the submission, the baseline characteristics presented	This text has been amended

the CS and also in Table 8 page 23 of the CS appendices document for CDAI mean scores, CRP mean values, proportion of participants with faecal calprotectin >250mg/kg and faecal lactoferrin 7.24µg/g. However, the information presented in these two parts of the submission are not consistent. The ERG have been unable to confirm to their satisfaction that these baseline characteristics do indeed relate to the start of the maintenance trial rather than the start of the induction trials as there is insufficient information in the CSR provided to the ERG, and what there (page 60-62 of the CSR) would suggests that these presented 'baseline data' are from the week 0 of the induction studies (UNITI-1 or UNITI-2). *In summary the baseline characteristics at the start of the maintenance study as presented in the CS are uncertain and do not allow any differences between the ustekinumab responders and the true baseline populations to be determined."*		in Table 13 are for randomised patients in the IM-UNITI trial at the start of induction therapy. The baseline characteristics presented in Table 8, page 23, Appendix 4.2 are for patients at the start of maintenance therapy.	
The ERG states on page 59: *"The IM-UNITI trial results are not*	Janssen suggests the removal: "*or anti-TNFα failure patients"*	Clinical remission at week 44 is presented for patients who were refractory or intolerant to TNFα	Amendment made

presented separately for the two induction dose groups (fixed 130 mg or the licensed ~6mg/kg dose) nor for previously conventional care failure or anti-TNFα failure patients."		inhibitor therapy in Table 16 (page 91) of the submission. This has not been presented in the ERG report, but has been suggested below.	
Table 20, page 60, does not report clinical remission at week 44 in patients who were refractory or intolerant to TNFα inhibitor therapy.	Janssen suggests the addition of: *clinical remission at week 44 in patients who were refractory or intolerant to TNFα inhibitor therapy:* *Placebo: 16/61 (26.2)* *Ustekinumab q8w: 23/56 (41.1)* *Ustekinumab q12w: 22/57 (38.6)*	The ERG has commented that evidence from IM-UNITI is not presented for patients who are refractory or intolerant to TNFα inhibitor therapy; so these results are important to consider.	Amendment made
The ERG states on page 61: *"The data on long-term response for up to 92 weeks were provided in the CS and the clarification response (Table 21). The numbers are quite difficult to interpret but indicate that of the 264 ustekinumab responders, 120 (45%) were in clinical remission on ustekinumab q8w or q12w at week 92. Of those 133 ustekinumab responders randomised to placebo 22 (16.5%) were in remission at week 92, demonstrating the need for retreatment in most patients."*	Janssen suggests the following amendment: *283 randomised patients who were in clinical response at week 44 continued into the study extension (227 on ustekinumab and 56 on placebo). At week 92, 156 patients (68.7%) on ustekinumab q8w or q12w were in clinical remission compared to 22 (39.3%) of patients receiving placebo.*	The current interpretation of the data is not factually correct.	Amendment made

In “Inflammatory Biomarkers” on page 62 faecal calprotectin and faecal lactoferrin are not mentioned.	Janssen suggests the addition: *Results for faecal calprotectin and faecal lactoferrin are also consistent with these findings, with increases over time for placebo patients and stabilised results for patients treated with ustekinumab.*	Currently two of the three inflammatory biomarkers are overlooked and these add support to the long-term use of ustekinumab.	Amendment made
The ERG states on page 73 and page 91: *“Differences in inflammatory biomarker levels between the treatment arms were generally non-significant…”*	Janssen suggests the following amendment: *“Ustekinumab was efficacious in reducing both serum- (CRP) and faecal (calprotectin and lactoferrin) based biomarkers of inflammation, with statistically significant improvements in favour of ustekinumab. A significantly greater proportion of patients treated with ustekinumab achieved normalised inflammatory biomarkers.”*	The current statement is factually incorrect.	Amendment made.
The ERG states on page 74 and 91: *“In comparison only 16.5% of those ustekinumab responders withdrawn from treatment were in remission at week 92, demonstrating the need for retreatment in most patients.”*	Janssen suggests the following amendment: *“In comparison, only 16.5% of those ustekinumab responders withdrawn from treatment were in remission at week 92, demonstrating the need for continuous treatment in most patients”.*	Re-treatment implies that patients stopped treatment and then received treatment again. Whereas the evidence is presented for patients that continued to receive treatment.	Not a factual inaccuracy
The ERG states on page 74 and 91: *“The data indicate that the placebo response in CD is substantial. The proportion of placebo responders to induction was high (22% in anti-TNFα*	Please consider adding the point here that most “placebo” patients would also have been receiving conventional therapy (as would be the case in UK clinical practice), so this could help to explain the level of response in the placebo group.	It is important to note here that most of those patients receiving placebo would also have been receiving conventional therapy, which likely accounts for their level of response; some patients do have a good response to	No a factual inaccuracy

failure patients and 29% conventional care failure patients). The results of the follow-up of placebo responders from UNITI-1 and -2 also indicate that placebo response can be sustained. Of the placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% achieved clinical response (CDAI-100) and 48% achieved clinical remission at one year. At 44 weeks 12% of all those randomised to placebo were in remission."		conventional therapy in clinical practice. As noted on page 96 of the submission; although this patient group represents a pure placebo group, it positively selects patients who respond well to conventional therapy, as reflected in the high levels of clinical response and clinical remission observed. We would not expect similarly high levels to be observed in a true placebo group. Please also consider the interpretation of a 20-30% induction response rate to conventional therapy as 'high'.	
The ERG states on page 74 and 91: *"Of the placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% achieved clinical response (CDAI-100) and 48% achieved clinical remission at one year."*	Janssen suggests the following amendment: *"Of those placebo responders who continued to receive placebo after the Week 8 assessment in IM-UNITI (16 weeks post treatment initiation), 56% maintained their clinical response (CDAI-100) and 48% were in clinical remission at one year."*	Currently it may be misinterpreted as 56% of placebo patients reach clinical response. It is more accurate to state that of those 22% or 29% of placebo patients who achieved response in UNITI-1 and UNITI-2, respectively, 56% maintained this response at one year.	Not a factual inaccuracy
On page 75, the ERG report states that dose adjustment for IM-UNITI patients who met the loss of response criteria resulted in unblinding of patients,	Janssen suggests to change the statement to: *"Firstly, in the ACCENT (infliximab), CHARM (adalimumab) studies, blinding of patients, personnel, and assessors was broken as the*	According to the IMUNITI protocol (page 547 of linked PDF document), under Section 6 Dosage and Administration, it is stated that *'All subjects in the*	Amendment made

personnel and assesors. *"Firstly, in the ACCENT (infliximab), CHARM (adalimumab) and IM-UNITI (ustekinumab) studies, blinding of patients, personnel, and assessors was broken as the trials allowed for some participants to be switched over to alternative treatment if they lost response during the follow-up period."*	*trials allowed for some participants to be switched over to alternative treatment if they lost response during the follow-up period. However, in the IM-UNITI (ustekinumab) study, blinding was preserved in the event of dose adjustment from week 8 to week 32 of IMUNITI for patients who met the loss of response criteria."*	*primary population will receive a SC administration of study agent (either placebo or ustekinumab) every 4 weeks from Week 0 to Week 40 with the exception of Week 4. Placebo administrations are given at dosing visits in which an active administration is not planned in order to maintain the blind with respect to SC regimen dosing interval (eg, a subject in the 90 mg ustekinumab q12w treatment group will receive SC placebo at visits occurring 4 weeks and 8 weeks after receiving 90 mg ustekinumab).'* . Therefore, as subjects are already receiving a placebo dose when they are not receiving active treatment, it was possible to preserve blinding of patients, personnel and assessors in the event of dose adjustment for a patient who met the loss of response criteria as this patient would instead receive an active drug dose where they were receiving a placebo dose previously. This means that the observed regain in response and/or remission achieved using dose adjustment is not likely to be the result of the patient or assessor knowing that the patient has received the active drug and thus,	

		influencing the observed response and remission rates in dose adjusted patients.	
On page 107: *"While the dosing regimens used by the company are reflective of the respective marketing authorisation, the ERG notes that there are significant difference in when response is assessed for infliximab patients (2 weeks) and other biologic therapies."*	Janssen suggests the removal of the sentence or the correction of week 4, instead of week 2.	The economic model uses the results of week 4 of infliximab as discussed in the NMA section, not the week 2. The ERG agreed that considering the data available this was the most appropriate approach as it was the most comparable time point between trials (week 4 for infliximab and adalimumab and week 6 for ustekinumab and vedolizumab)	Amendment made (corrected to 4 weeks)

Issue 14 Minor clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG
On page 15 the ERG states that the marketing authorisation for ustekinumab is for the treatment of moderate to severe CD.	The marketing authorisation for ustekinumab is: *"for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies".*	Janssen believes the full marketing authorisation should be detailed or it should be made clear that is a summary of the marketing authorisation.	Not a factual inaccuracy
In Table 6 on page 38 the stratification factors for the randomisation of UNITI-1 and	Janssen suggests the following amendment: *"Randomisation was stratified by study region, CDAI score (and initial response to anti-TNFα in*	Clarification that the stratification by initial response to anti-TNFα only applies to UNITI-1 and avoids any	Sense clear – amendment not necessary

UNITI-2 are listed as: *"Randomisation was stratified by study region, CDAI score (and initial response to anti-TNFα)"*	*UNITI-1)"*	potential confusion.	
The ERG states on page 43: *"The trial consisted three arms, that is, two arms of intervention treatment (Ustekinumab 130mg IV and Ustekinumab 6mg/kg IV) and one arm of a comparator (placebo)."*	Janssen suggests the following amendment: *"The trial consisted three arms, that is, two arms of intervention treatment (Ustekinumab 130mg IV and Ustekinumab ~6mg/kg IV) and one arm of a comparator (placebo)."*	It is important to emphasise that the ustekinumab dose is a tiered, weight-based dose that approximates 6mg/kg, as this is the licensed dose and differs from 6mg/kg (as used in the CERTIFI trial).	Amendment made
The ERG states on page 50: *"The trial consisted three arms, that is, two arms of intervention treatment (Ustekinumab 130mg IV and Ustekinumab 6mg/kg IV) and one arm of a comparator (placebo)."*	Janssen suggests the following amendment: *"The trial consisted three arms, that is, two arms of intervention treatment (Ustekinumab 130mg IV and Ustekinumab ~6mg/kg IV) and one arm of a comparator (placebo)."*	It is important to emphasise that the ustekinumab dose is a tiered, weight-based dose that approximates 6mg/kg, as this is the licensed dose and differs from 6mg/kg.	Amendment made
The ERG states on page 54: *"…the mean IBDQ score changes and SDs from baseline for the three arms were…"*	Janssen suggests the following amendment: *"…the mean IBDQ score changes and SDs from baseline for the two arms were…"*	Only the placebo and ~6mg/kg groups are presented in the ERG report.	Amendment not necessary
In Table 20, page 60 the following outcome is reported: Clinical remission at week 0 (induction period) and week 44	Janssen suggests the following amendment: *"Clinical remission at week 0 (of maintenance study) and week 44"*	Currently this suggests that there were patients in remission at week 0 of the induction study, which is factually incorrect.	Amendment made
The ERG states twice on page 71	Janssen suggests the following amendment:	The use of identical may be misleading and lead people to	Amendment made

(for UNITI-1 and UNITI-2): *"…the proportions of subjects who had at least 1 adverse event were identical across the treatment groups…"*		assume that the results are exactly the same.	
The ERG state on page 91: *"The results of IM-UNITI indicate that around half of patients who respond to ustekinumab are in clinical remission at week 44."*	Janssen suggests the following amendment: *"The results of IM-UNITI indicate that around half of patients who respond to ustekinumab and continue to receive ustekinumab maintenance therapy are in clinical remission at week 44."*	Current statement may be unclear.	Not factual inaccuracy
The ERG state on page 117: *The ERG did request that the company provide IM-UNITI IPD data for patients randomised to placebo at induction, but this was not provided by the company in its response as it was unavailable.*	Janssen suggests the removal of the statement.	This statement is factually incorrect. In clarification question the ERG requested A.2: "*Please provide the placebo-placebo imputed data for the responder's non-remitters and responders in the maintenance phase (figures 28 & 29) that were used in the treatment sequence analysis."* These data were provided by Janssen in Table 1. IM-UNITI IPD were not actually requested in the ERG clarification questions, therefore Janssen suggests the removal of the statement as it is factually incorrect.	The ERG did request the data during clarification process *"B3 priority question: Please provide a modified version of the IM-UNITI maintenance transitions scenario in which the transitions for the placebo arm are generated from the patients randomised to placebo at the induction phase (this should ideally include both placebo responders and non-responders).* *We have modified the text to indicate that we request a scenario analysis rather than* IPD.

Issue 15 Utility estimates in base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (Table 41, page 97; Table 42, page 103): *"Utilities were generated using a published mapping tool to map CDAI to EQ5D."* *"HRQoL data was sourced by mapping CDAI score on to EQ-5D using a published algorithm presented in Buxton et al.[32] No directly reported HRQoL were collected as part of the UNITI clinical trials."*	Janssen suggests the amendment of these sections to state that IBDQ, not CDAI, was mapped to EQ-5D in the base case.	A number of measures were mapped to EQ-5D; however, IBDQ was selected as the base case. This statement could cause confusion as the EQ5D utility values mapped from CDAI and IDBQ are different.	We thank the company for correcting these errors. Table 41, page 97 and Table 42, page 103 have been amended reflecting the correction.

Issue 16 Description of second induction for biologic treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 101): *"Patients who fail to respond in the induction period are assumed to move directly to conventional care after the induction phase."*	Janssen suggests to include a reference the second induction which is available for patients on treatment with ustekinumab, vedolizumab and adalimumab.	This statement may cause confusion on the structure of the induction phase.	We have amended to make it clear patients only move to conventional care to after second induction where allowed.

Issue 17 Representation of model structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 100): *"Specifically, the model does not account for the fact that CD is a relapsing condition."*	Janssen recommends to amend this section to reflect that the model structure does allow for patients relapsing and remitting as part of the maintenance transition probabilities; for instance, patients in remission may deteriorate and patients in moderate to severe may improve.	The wording used implies it is not possible for patients to worsen once having remitted. This is a misrepresentation of the possible transitions in the model.	This is not a factual inaccuracy the model does fully capture the relapsing nature of CD as it does allow for secondary treatment with biologics.

Issue 18 Moderate to severe responders

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 110): *"The ERG accepts the need to make some assumptions, but highlights that data for vedolizumab were available from the TA352 submission and demonstrate quiet different rates of moderate to severe responders (see Table 48). The potential influence of this assumption may be quite significant as fewer QALYs and greater costs are associated with the moderate to severe health state. It is, however, uncertain whether the figures used represent an overestimation of the proportion of moderate to*	Janssen suggests the following amendment: *"The ERG accepts the need to make some assumptions and highlights that data for vedolizumab were available from the TA352 submission and demonstrate quiet different rates of moderate to severe responders (see Table 48); The potential influence of this assumption may be quite significant as fewer QALYs and greater costs are associated with the moderate to severe health state. It is, however, uncertain whether the figures used represent an overestimation of the proportion of moderate to severe responders for the comparator therapies. However, this was a conservative approach favouring comparators therapies over ustekinumab"*	The proportion of moderate to severe responders were obtained from ustekinumab IM-UNITI trial data. The proportion of ustekinumab are lower than those of vedolizumab used in TA352. This difference means that in the ustekinumab trial more patients reach the remission and the mild health states compared to the vedolizumab trial; this seems to be aligned with the numerically better response and remission rates of ustekinumab and vedolizumab trials. The proportion of moderate to severe responders was not available for anti TNF therapies. In	We amended partially incorporating the company's suggested revision. It is, however, unclear whether this a conservative approach or not as we have no data for other biologics.

severe responders for the comparator therapies."		a conservative approach, Janssen assumed that all comparators have the same proportion of moderate to severe responders for all comparator, including vedolizumab. This probably has inflated the efficacy results of vedolizumab.	

Issue 19 Representation of inputs used for the calibration method

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 101; page 116): *"The constraints implied in this process are however, only partially justified and the starting values are entirely arbitrary."* *"the estimated transition probabilities are highly dependent on the constraints imposed and starting values used, both of which are not well justified by the company."*	Janssen recommends the amendment of these sections to reflect that the constraints and starting matrix values were taken from TA352, and that work was conducted to improve on these based on the ERG's critique of the manufacturer's submission in TA352.	Starting values and constraints were not arbitrary, but were based on values used in TA352, thus achieving consistency across HTA submissions. Further, the submission aims to improve on TA352 by using the same starting matrix for both conventional care and biologics. TA352 used a different starting matrix for the two treatment types, which was criticised by the ERG (TA352 ERG report page 159). Use of the same starting matrix assumes that the same patient receiving either treatment type has an equal probability of improving or deteriorating at baseline. This is a more conservative assumption than used in TA352 and Janssen	This is not a factual in accuracy, but we have amended the text for clarity.

		believes is the correct starting point.	

Issue 20 Inclusion of adalimumab in the TNF failure population

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 105): *"It is unclear why the company did not opt to include the results of this analysis in the economic model, as this would have been relevant given current practice in the UK."*	Janssen propose the following amendment: *"Adalimumab was the second TNFα antagonist approved and was used in one trial in patients with secondary failure to infliximab.[152] This trial excludes patients with primary failure to infliximab (i.e. patients that initially did not respond; see Section 5.2.1), including only secondary non-responders to infliximab (i.e. patients who initially responded but subsequently lost response; see Section 5.2.1) and may therefore reflect a population of patients who are likely to respond to adalimumab, as both treatments have the same mode of action. Therefore, anti-TNFs are only considered as comparators in conventional care failure population"*	This statement does not acknowledge the reasons given in the manufacturer's submission as to why this decision was reached. Additionally, a similar approach was taken in TA352 and was accepted by the NICE Committee.	Amendment made

Issue 21 Usage of conventional care for biologic patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (page 134):	Janssen recommends the amendment of this section to reflect that the figure of 50% is taken	Rather than being arbitrary, this value was taken from TA352, thereby keeping consistency	This is not a factual inaccuracy, but we have amended for clarity.

"AS stated above it is assumed that patients receiving biologic treatment receive 50% of the dose of convention care therapies concomitantly. This value is largely arbitrary "	from TA352. *"AS stated above it is assumed that patients receiving biologic treatment receive 50% of the dose of convention care therapies concomitantly. This value is taken from TA352"*	across appraisals.	

Issue 22 Resource use costing studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
On page 136 of the ERG report, the ERG reference two recent costing studies however provide no reference for this. Further, it is not clear if costs related to surgery are included in these cost estimates, while they are included in the cost of monitoring within the model, likely increasing the cost.	Janssen recommends the amendment of this section to include the references to these studies, as these are currently not included in the ERG report. Please also provide description of which costs were looked at specifically.	Currently there is no reference included for either study, nor do the ERG go into detail on which costs are considered within these studies. Therefore, currently Janssen is unable to identify whether the comparison with either study is justifiable or relevant. Janssen would like to reiterate that the methods in the submitted base case ICER aimed to improve on the methods used in the ACD responses for TA352 which were accepted by the committee. The resource use estimates were sourced as part of a modified Delphi panel including 11 gastroenterology consultants and nurses from a geographic spread	The references are now added on page 136. 1. Choi GKH, Collins SDE, Greer DP, Warren L, Dawson G, Clark T, et al. Costs of adalimumab versus infliximab as first-line biological therapy for luminal Crohn's disease. J Crohns Colitis 2014;8:375-83. Available from: <Go to ISI>://WOS:000335280700006 2. Sprakes MB, Ford AC, Suares NC, Warren L, Greer D, Donnellan CF, et al. Costs of care for Crohn's disease following the introduction of infliximab: a single-centre UK experience. Aliment Pharm Ther 2010;32:1357-63. Available from: <Go to

		of hospitals across the UK. The need to update the Bodger costs was noted in TA352 as the health state costs came from a cohort study conducted in 2000/01, meaning values are potentially 16 years old and are therefore unlikely to reflect current practice in the UK.	ISI>://WOS:000283948000008

Issue 23 Differential resource use costs for biologic patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (p. 136): *"The ERG has some concerns regarding the justification for the use of differential costs for biologic patients. Differential costs were not used in the previous technology appraisals of biologic therapies for CD. Furthermore, advice from the clinical advisor to the ERG suggests that there was no clear reason to expect costs for patients receiving biologic therapy to be significantly different to those for patients receiving conventional care."*	Janssen recommends the amendment of this section to note that the differential resource use costs between biologic and non-biologic patients was suggested by the 11 clinicians and nurses involved in the modified Delphi panel. *"Differential costs for biologic patients compared to the costs for conventional care were used in the CS following the recommendation of the Delphi panel conform by 11 healthcare professional. The reason that monitoring costs would be different, for instance biologic patients would require more frequent tests blood tests. However differential costs were not used in the previous technology appraisals of biologic therapies for CD and advice from the clinical advisor to the ERG suggests that there was no clear reason to expect costs for patients receiving biologic therapy to be significantly*	This amendment was agreed by all participants of the modified Delphi panel for the reason that monitoring costs would be different, for instance biologic patients would require more frequent tests blood tests. Consequently, these are captured within the health state costs in the submission base case.	Not a factual inaccuracy.

	different to those for patients receiving conventional care."		

Issue 24 Description of model health states

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (Table 41, page 97): "The mode had 5 health states, Remission, responder, moderate to server, surgery and death."	Janssen suggests the following amendment: "The model has 5 health states, Remission, mild, moderate to severe, surgery and death."	No impact	We thank the company for correcting this error. Table 41, page 97 has been amended reflecting the correction.

Description of comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The ERG report states (Table 41, page 97): Ustekinumab was compared with adalimumab and conventional care in the anti-TNF naive population. A scenario analysis was also presented comparing ustekinumab with infliximab. Ustekinumab was compared with vedolizumab and convention care in the anti-TNF experience population.	Janssen suggests the following amendment: "Ustekinumab was compared with adalimumab and conventional care in the conventional care failure population.. A scenario analysis was also presented comparing ustekinumab with infliximab. Ustekinumab was compared with vedolizumab and convention care in the anti-TNF failure population."	The text has implications for how the populations are considered – as opposed to 'TNF naïve', the conventional care failure population may have had prior exposure to anti-TNFs, as long as they had not failed treatment. Similarly, the anti-TNF failure population differs from an anti-TNF experienced population, as patients must have failed treatment with an anti-TNF to be within this population. This reflects the trial regimens for UNITI-	We thank the company for correcting this error. Table 41, page 97 has been amended reflecting the correction.

		1 UNITI-2 and IM-UNITI.	

Issue 25 Use of updated surgery costs following ERG request for clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 68, page 138; Table 69, page 139: *These tables reflect the tables in the submission, but before they were corrected in the company response to clarification letter*	Janssen recommends the amendment of these tables to use or acknowledge the updated tables in the report from the clarification questions	Presentation of the original values, as opposed to the corrected values may cause confusion.	We have amended the table as requested.

1. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohns Colitis. 2012 Mar;6(2):160-73. PubMed PMID: 22325170.