Lead team presentation
Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy– STA

1st Appraisal Committee meeting, 9th March 2017

Committee A

Background and Clinical Effectiveness

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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?

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

Clinical management of Crohn's Disease

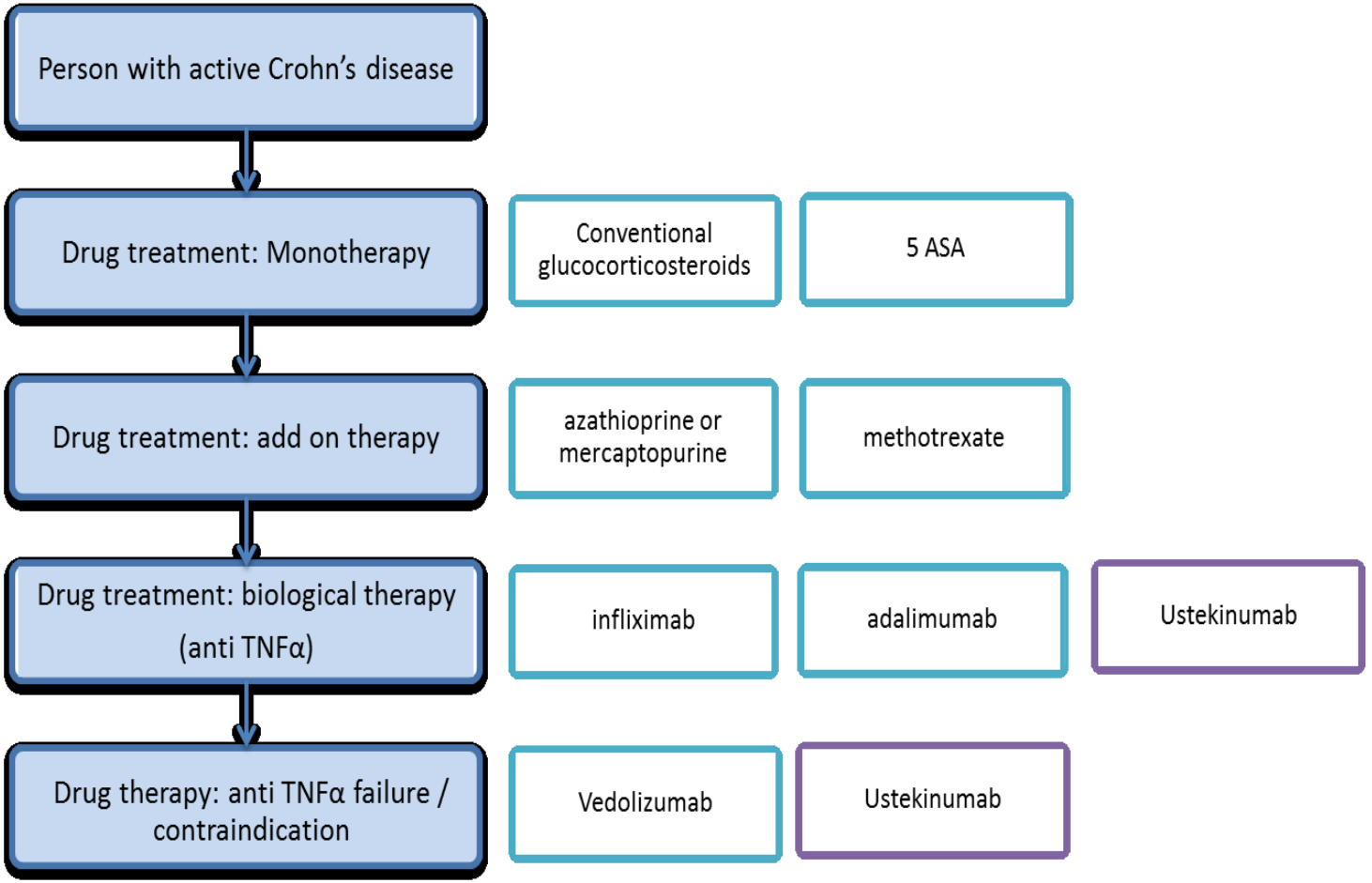

Figure 4, Company submission

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

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 (recommended in NICE Technology appraisal [TA] 180 when criteria are met)
  - adult patients with active psoriatic arthritis (recommended in TA 340 when criteria are met)

Ustekinumab (2)

Mode of administration	• Administered as intravenous infusion at induction and as subcutaneous injection at maintenance.
Dosage	• 1 intravenous induction treatment (dose depends 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 • XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

The Patient's Perspective 1 (Crohn's and Colitis UK)

- The condition follows an unpredictable, relapsing & remitting course
- Common symptoms include: abdominal pain, diarrhoea, weight loss and profound fatigue. Anaemia is a common complication. Increased risk of developing bowel cancer
- At least 50% of people with Crohn's Disease may require surgery within 10 years of diagnosis and 70-80% during their lifetime. "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?"
- Active Crohn's Disease can present a major barrier to people's ability to participate in daily life
- "…It's not just me it affects, It's everyone, my wife, work and family"

The Patient's Perspective 2

- Current treatments are suboptimal. There is a pressing need for additional treatment options which offer a different mode of action and potential for people with Crohn's disease to resume their lives and restore quality of life
- While the initial dose of ustekinumab is given intravenously, further doses are subcutaneous. Patients favour less time spent at hospital and reduced travel costs
- *"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"*
- *"Up until 4 years ago, I'd known nothing other than being unwell for as long as I can remember. To have had the opportunity to have ustekinumab has been nothing less than life-changing"*
- *"It sounds like a cliché, but this really was a turning point in my life. … (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"*

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

Outcome measures in the trials – the Crohn's disease activity Index (CDAI)

- Measurement of clinical, biochemical and physical parameters of disease activity, 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 score of less than 150 is considered to be remission
- A score greater than 220 defines moderate to severe disease
- A score greater than 300 defines severe disease
- CDAI-100 is defined as a reduction from baseline in CDAI score of 100 points or more; CDAI-70 as a reduction of 70 points or more
- The company reports that the CDAI is a widely accepted and validated method for assessing disease activity

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

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

Adverse event data from UNITI trial programme

- Ustekinumab was generally well tolerated. The proportions of patients with adverse events (AEs) and serious adverse events (SAEs) were comparable across treatment groups
- Common AEs (≥5% of patients) included arthralgia, headache, nausea, pyrexia, nasopharyngitis, abdominal pain, upper respiratory tract infection, diarrhoea and fatigue
- Low incidence of SAEs (7.2% and 2.9% in UNITI-1 and UNITI-2 respectively in the ~6mg/kg groups, and 11% in IM-UNITI)
- Low rates of treatment discontinuation due to AEs (2.8% and 0.5% in the ~6mg/kg group of UNITI-1 and UNITI-2 and 5.3% in IM-UNITI)
- Safety profile reported to be in line with that observed for other indications (psoriasis and psoriatic arthritis)

Network meta-analysis (NMA)

- NMA approach adopted by the company to provide comparative efficacy estimates for ustekinumab versus alternative biologics
- Analyses were performed separately for induction trials and maintenance trials and for patients who had failed conventional therapy and patients who had failed, or were contraindicated to TNF-alpha inhibitors
- Induction phase trials were considered similar enough in terms of study design and patient characteristics for the results to be pooled
- Maintenance phase trials were not deemed similar enough for the results to be pooled in a conventional NMA. A treatment sequence analysis, combining data from induction and maintenance phases of therapy, was adopted to account for these differences
- Systematic review identified 11 placebo-controlled trials that were included in the NMA

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

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)
Infliximab 5mg/kg	0.11 (0.02; 0.48)	N/A	0.08 (0.01, 0.59)
Placebo	2.89 (1.95; 4.32)	3.12 (2.08, 4.68)	2.5 (1.60, 3.98)
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

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 feasible by the company
Table 21, company submission

Treatment sequence analysis

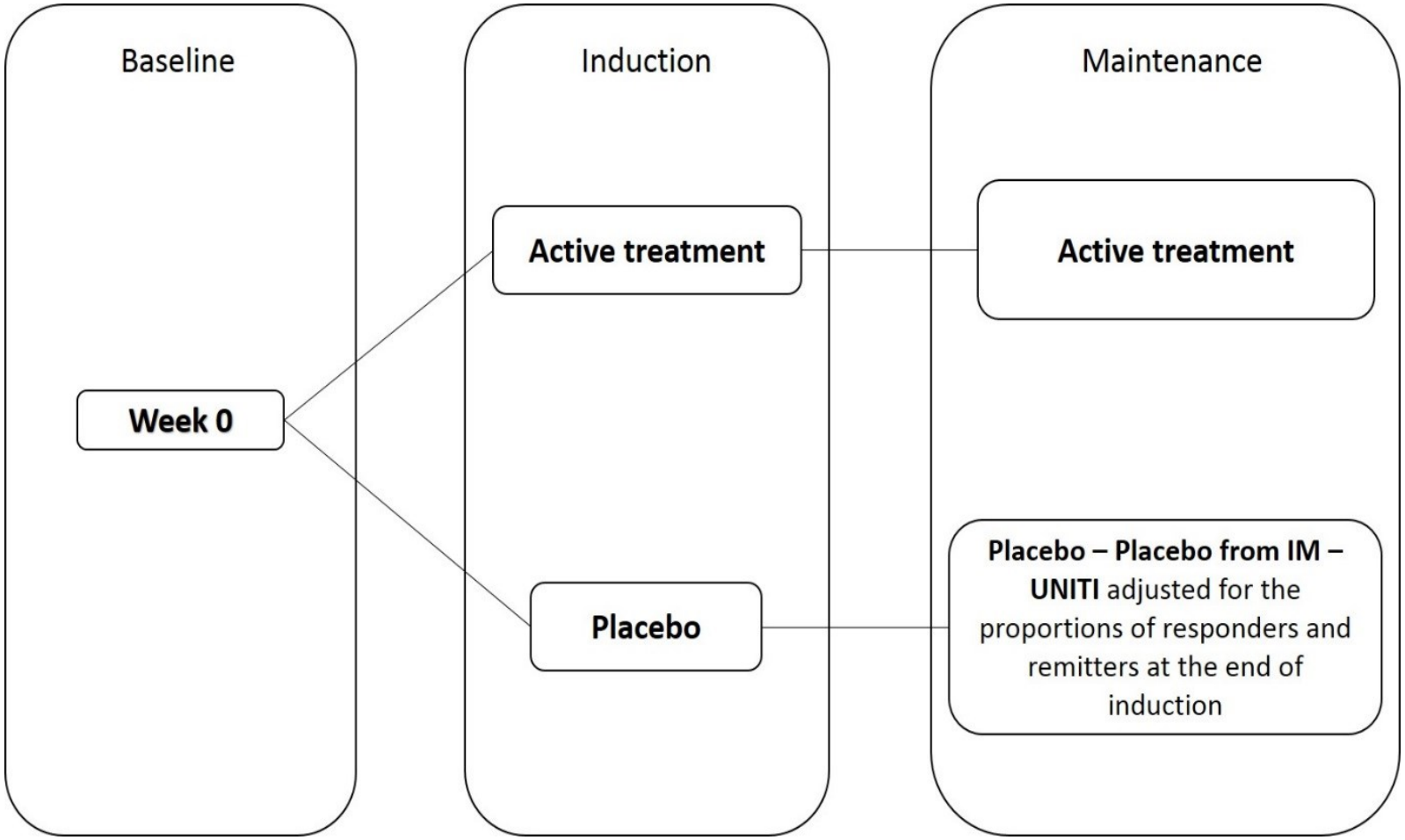

Figure 27, company submission

Summary of results of treatment sequence analysis

Conventional care failure subpopulation

- No statistically significant differences between ustekinumab and adalimumab in:
  - CDAI-100 response at 1 year (odds ratio [OR] for ustekinumab vs adalimumab 1.58, CrI 0.68 to 3.62)
  - Clinical remission at 1 year (OR 1.26, CrI 0.50 to 3.07)
- Infliximab was associated with the highest chance of clinical remission at 1 year (data not available for clinical response) but concerns of bias

TNF failure subpopulation

- No statistically significant differences between ustekinumab and vedolizumab in CDAI-100 response at 1 year (OR 1.77, CrI 0.91 to 3.45) or clinical remission at 1 year (OR 1.35, CrI 0.66 to 2.73)

Company believes that the conclusions of the treatment sequence analysis are limited and results should be interpreted with caution

Evidence Review Group (ERG) comments – UNITI-1 and UNITI-2

- Ustekinumab induction trials were generally well conducted with high internal validity, and reasonably generalisable to UK Crohn's disease population, but some issues:
  - short follow-up period for the primary (6 weeks) and secondary outcomes (8 weeks) based on only a single dose of study drug/placebo
  - the use of CDAI as the primary outcome does not reflect clinical opinion and practice in the UK, and is considered unreliable and subjective (outcomes based on the CDAI have been used in studies of other biologics in Crohn's)
  - excluded patients at the higher end of the CDAI spectrum (CDAI>450)
  - 20 to 30% of patients were not taking any background conventional medication for Crohn's disease
  - the conventional care failure trial (UNITI-2) included anti-TNF-alpha naïve and experienced patients (though none were anti-TNF-alpha failures). Unclear whether this reflects the NHS population eligible for ustekinumab

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

ERG comments – treatment sequence analysis

ERG identified a large number of issues with this analysis:

- Same comparability issues as in the induction NMA; in addition the maintenance trials varied in terms of re-randomisation criteria upon entry into maintenance phase
- The methods by which the control arm for all biologics was constructed using placebo-placebo IM-UNITI data introduces considerable potential for unobservable confounding of results because analysis is not based on randomised comparisons - may have inflated the relative effectiveness of ustekinumab
- Outcome measures (CDAI-70 and CDAI-100) and response rates (intention to treat and complete case response rates) between trials were inconsistent but were aggregated; such inconsistencies were likely to make ustekinumab appear better than its comparators
- ERG unable to replicate a number of inputs and believes the results are highly unreliable and do not represent a realistic long-term comparison of ustekinumab and its comparators

Key issues: clinical effectiveness

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- 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?
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