Slides for public – no ACIC

NICE National Institute for Health and Care Excellence

Chair presentation: Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]

2nd Appraisal Committee meeting

Committee A

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Company: Janssen

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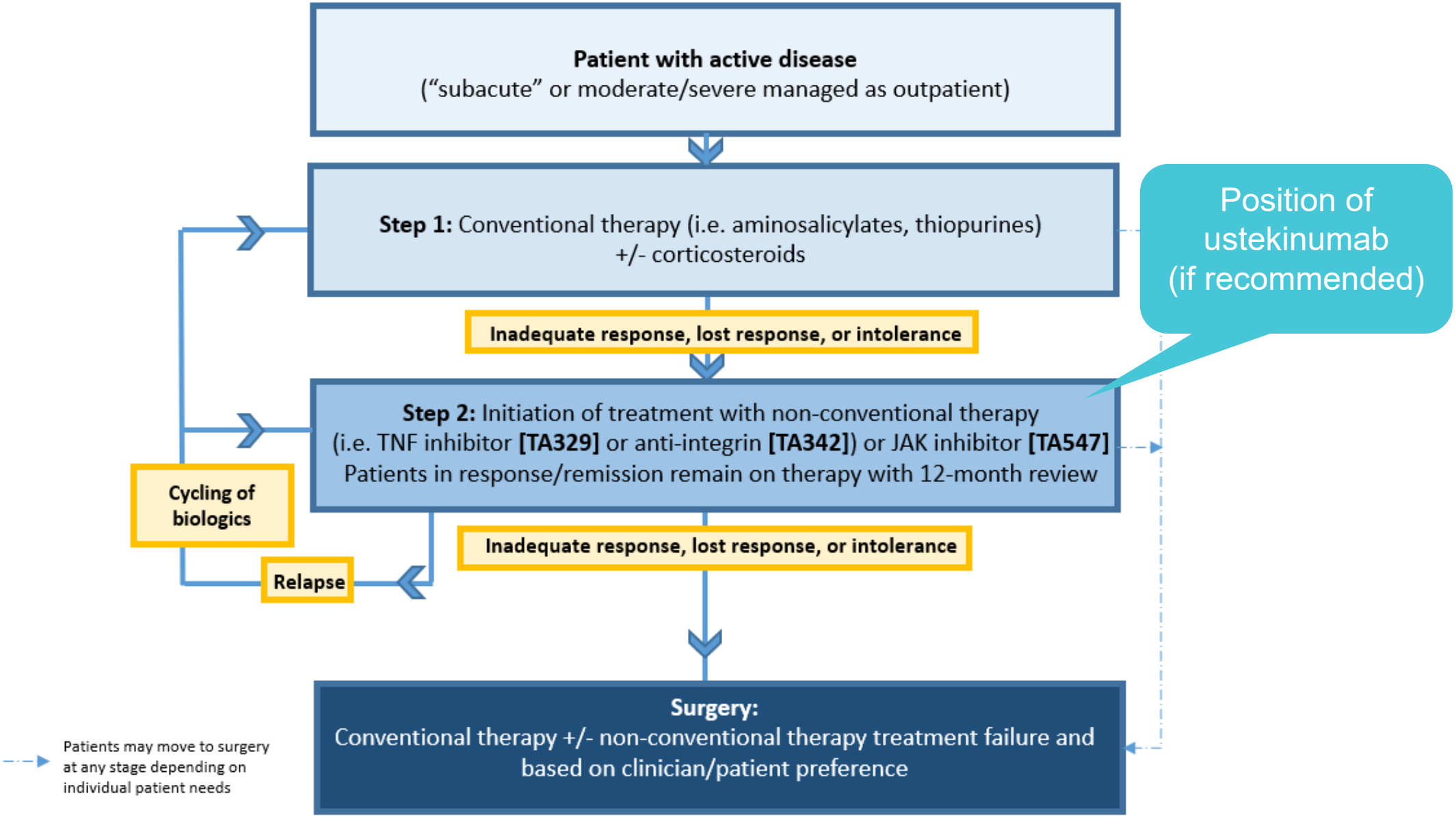
Ustekinumab (Stelara, Janssen)

Marketing authorisation	"Stelara is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies."
Administration	**Induction**: intravenous weight-based dose (aligns to a dose of approximately 6mg/kg) **Maintenance**: subcutaneous injection; fixed dose of 90mg • first dose given at week 8 following induction. After this, dosing every 12 weeks is recommended • Patients who have not shown adequate response 8 weeks after the first subcutaneous dose (week 16), may receive a second subcutaneous dose at this time to allow for delayed response • Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks • Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment
Acquisition cost	130mg vial concentrate for solution for infusion: £2,147; 90mg vial solution for injection: £2,147 (Annual treatment costs: induction year: £14,482; maintenance Year 2 and onwards: £9,304)

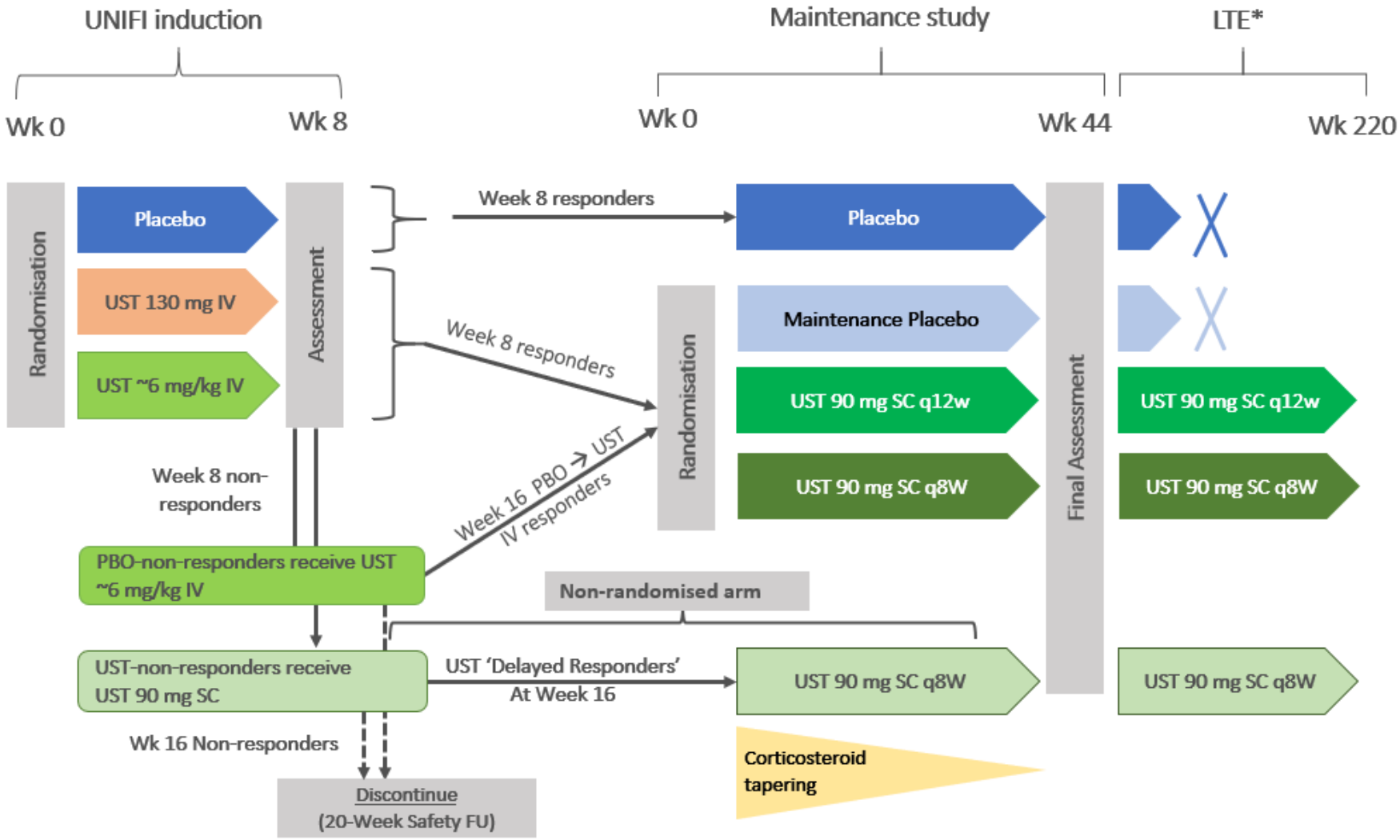
Treatment pathway



Source: CS, section B.1.3.3, figure 9

Abbreviations: JAK = janus kinase; TA = technology appraisal; TNF = tumor necrosis factor

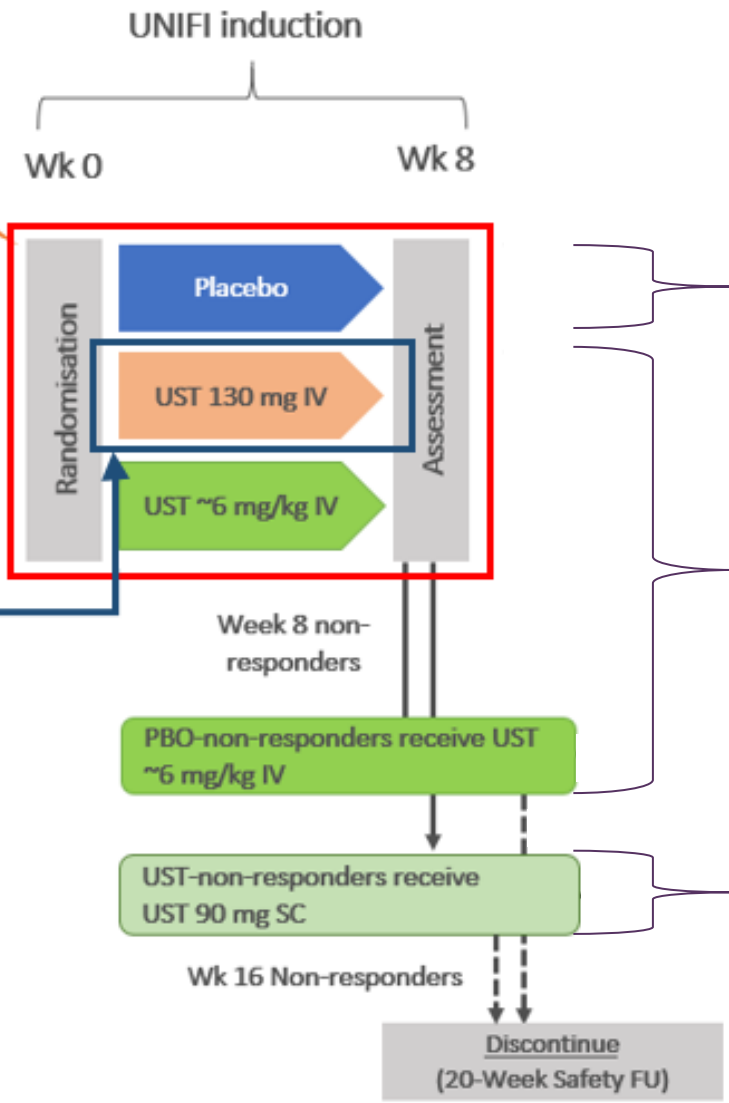
UNIFI trial design



*Patients will continue to receive the same treatment regimen during the LTE that they were receiving at the end of the maintenance study
Note: Conventional therapy is the background treatment for patients on placebo and ustekinumab.

UNIFI trial design (induction)

Induction study ITT population



Dose not covered by draft SPC but patients who responded to it were included in maintenance ITT

Responders progress to maintenance as a non-randomized, non-ITT population treated with placebo

Responders progress to maintenance and become ITT population; patients are re-randomized to either UST 90 mg q8w, UST 90 mg q12w or placebo

Responders progress to maintenance as a further, non-randomized non-ITT population of 'delayed responders'; all patients receive 90 mg q8w

Key trial results (induction ITT)

Included in company model via induction NMA

	Overall population (induction ITT)			Non-biologic failure population			Biologic failure population		
End point	**PBO N=319**	**6mg/kg (p-value)[a] N=322**	**130mg (p-value) N=320**	**PBO N=158**	**6mg/kg (p-value)[a] N=156**	**130mg (p-value) N=156**	**PBO N=161**	**6mg/kg (p-value)[a] N=166**	**130mg (p-value) N=164**
Clinical remission	5.3%	15.5% (<0.001)	15.6% (<0.001)	9.5%	18.6% (0.022)	19.9% (0.009)	1.2%	12.7% (<0.001)	11.6% (<0.001)
Clinical response[b]	31.3%	61.8% (<0.001)	51.3% (<0.001)	35.4%	66.7% (<0.001)	57.7% (<0.001)	27.3%	57.2 (<0.001)	45.1% (<0.001)

Source: CS, section B.2.6.1.1 figure 12, table 12, section B.2.7.1, table 17 | Abbreviations: PBO, Placebo | a Weight-range based UST doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), and 520 mg (weight > 85 kg), b Patients who had a prohibited change in concomitant UC medication or an ostomy or colectomy prior to the Week 8 visit were considered not to be in clinical remission; patients who had all 4 Mayo subscores missing at Week 8 were considered not to be in clinical remission or response

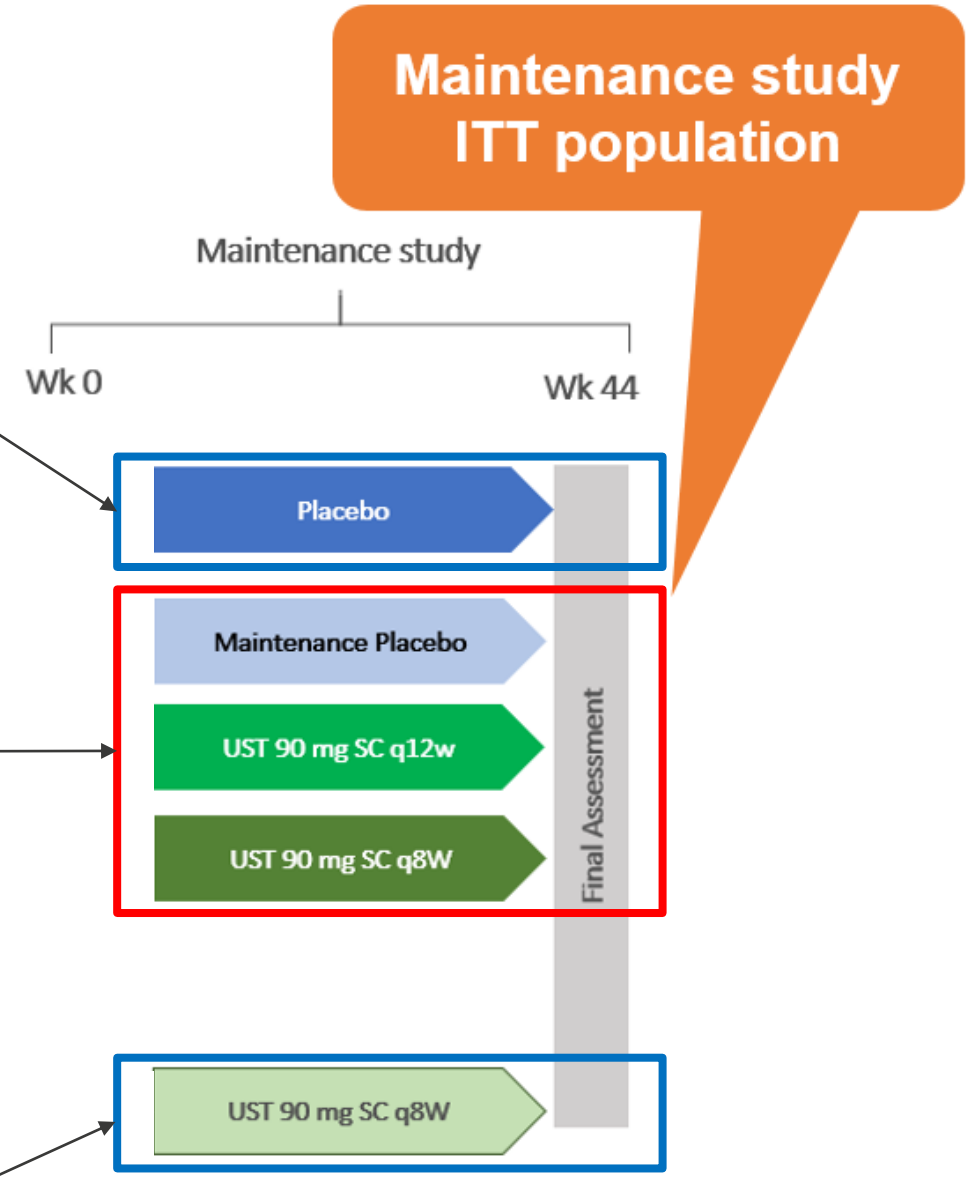
UNIFI trial design (maintenance)

Non-randomised group consisting of patients who were randomised to placebo group at induction and were in response at week 8

Re-randomised population consisting of:

- patients who had been randomised to UST 130 mg IV or UST ~6mg/kg IV during induction and were in response at week 8 PLUS
- patients who were randomised to placebo group at induction and did not respond, then were given ~6 mg/kg UST IV at week 8 and were in response at week 16

Non-randomised group consisting of 'delayed responders' i.e. patients who were in response at week 16 having received an additional 90 mg UST SC at week 8 following non-response to active treatment during weeks 0-8 of induction phase



Key trial results (maintenance ITT)

Pooled results included in company model directly (pooling = simple mean of two regimens with 30% assumed to have escalated regimen)

Un-pooled results included in company model directly

	Overall population (maintenance ITT)			Non-biologic failure population			Biologic failure population		
End point	**PBO[a] N=175**	**90mg SC q8w (p-value) N=176**	**90mg SC q12w (p-value) N=172**	**PBO[a] N=87**	**90mg SC q8w (p-value) N=85**	**90mg SC q12w (p-value) N=102**	**PBO[a] N=88**	**90mg SC q8w (p-value) N=91**	**90mg SC q12w (p-value) N=70**
Clinical remission	24%	43.8% (<0.001)	38.4% (0.002)	31.0%	48.2% (0.024)	49.0% (0.020)	17.0%	39.6% (<0.001)	22.9% (0.044)
Clinical response[b]	44.6%	71% (<0.001)	68% (0.001)	50.6%	77.6% (<0 .001)	76.5% (<0 .001)	38.6%	64.8% (<0 .001)	55.7% (<0 .001)

Source: CS, section B.2.6.2.1 figure 14, section B.2.7.2, table 18, figures 19 and 20 | Abbreviations: PBO, Placebo; UST, ustekinumab; q12w, every 12 weeks; q8w, every 8 weeks | a Patients who were in clinical response to ustekinumab IV induction dosing and were randomised to maintenance placebo SC on entry into this maintenance phase, b Maintenance of clinical response through end of maintenance

Indirect treatment comparisons (1)

Differences in trial designs (treat-through versus re-randomised) meant NMAs that included maintenance trial data could not be carried out using standard methods. Consequently different ITC methods were explored by the company and ERG

Name	Company 1-year NMA conditional on response	Company direct trial loss of response analyses	ERG maintenance only NMA
Description	Data from re-randomised trials recalculated to correspond to treat-through designs. Data for induction non-responders excluded	Absolute data on clinical remission and response from individual trial arms included in economic model directly (data effectively become observational in nature)	Data from treat through trials re-calculated to correspond to re-randomised design (assumes number of induction responders is a proxy for entering maintenance)
Company base case	No	Yes	No
Company scenario	Yes	No	No
ERG base case	Yes	No	No
ERG scenario	No	No	Yes

Committee concluded that all ITCs are uncertain but maintenance-phase NMAs provide more robust estimates of relative effectiveness than company's unadjusted ITC

Indirect treatment comparisons (2)

Committee preferred 1-year NMA conditional on response or ERG maintenance only NMA

The company scenario analysis - 1-year NMA conditional on response – was used as ERG base-case and has been used as company's updated base-case

Company 1-year NMA conditional on response (preferred by ERG)	**ERG maintenance only NMA (ERG scenario analysis)**
Within trial randomisation preserved	
Assumes that the placebo-placebo arms are similar (there are some differences in terms of response rates and these rates are low leading to a weak evidence base)	Post-re randomisation placebo arm data included (meaning more observations contribute to final estimates) BUT assumes re-randomised placebo arms are similar (not supported by evidence)
Imputation required – imputation method not used in previous UC appraisals	Imputation required – imputation method accepted (despite limitations) in previous UC appraisals
Results very uncertain – see ERG report table 36. Some of these uncertainties are reflected in the large credible intervals around point estimates. Impact of other uncertainties cannot be estimated statistically	
Does not use the post-re-randomisation placebo arm data and is therefore not prone to carry-over effects BUT relative treatment effects are based on data from a small subset of placebo arms which may not be representative	

Comparison of NMA results: Non-biologic failure

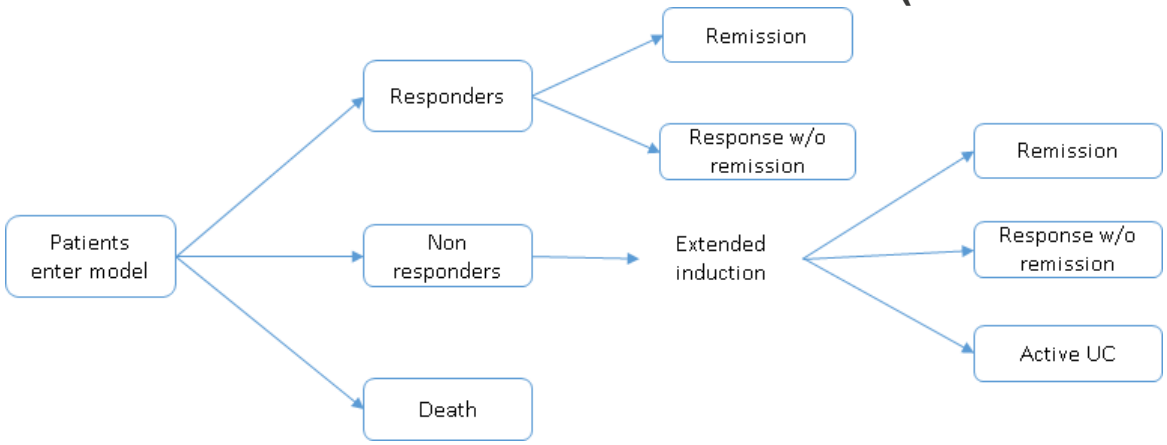
Comparator		Median OR [CrI], comparator vs. PBO	
		Clinical response	
Induction	Maintenance	1 year NMA conditional on response	ERG maintenance only NMA
VED 300mg	VED 300mg pooled	4.18 [1.82; 10.68]	4.34 [1.83; 10.43]
INF pooled	INF pooled	3.82 [2.18; 7.06]	2.29 [0.91; 5.85]
GOL 200/100mg	GOL pooled	2.47 [1.58; 3.85]	2.08 [0.98; 4.40]
ADA 160/80/40mg	ADA 40mg EOW	2.11 [1.21; 3.74]	1.31 [0.52; 3.31]
TOF 10mg	TOF pooled	3.46 [2.00; 6.31]	4.67 [2.08; 10.58]
UST 6mg/kg	UST 90mg pooled	6.21 [3.59; 11.05]	3.30 [1.44; 7.59]

Comparison of NMA results: Biologic failure

Comparator		Median OR [CrI], comparator vs. PBO	
		Clinical response	
Induction	Maintenance	1 year NMA conditional on response	ERG maintenance only NMA
VED 300mg	VED 300mg q8w	2.99 [0.75; 12.24]	NR
VED 300mg	VED 300mg q4w	2.64 [0.61; 11.43]	NR
VED 300mg	VED 300mg pooled	NR	4.53 [1.46; 15.58]
ADA 160/80/40mg	ADA 40mg EOW	2.98 [1.13; 9.01]	2.85 [0.80; 10.98]
TOF 10mg	TOF 5mg	3.43 [1.68; 7.77]	NR
TOF 10mg	TOF 10mg	5.07 [2.57; 11.26]	NR
TOF 10mg	TOF pooled	NR	6.59 [2.69; 16.83]
UST 6mg/kg	UST 90mg q12w	5.21 [2.33; 11.65]	NR
UST 6mg/kg	UST 90mg q8w	5.24 [2.64; 10.54]	NR
UST 6mg/kg	UST 90mg pooled	NR	2.50 [1.10; 5.71]

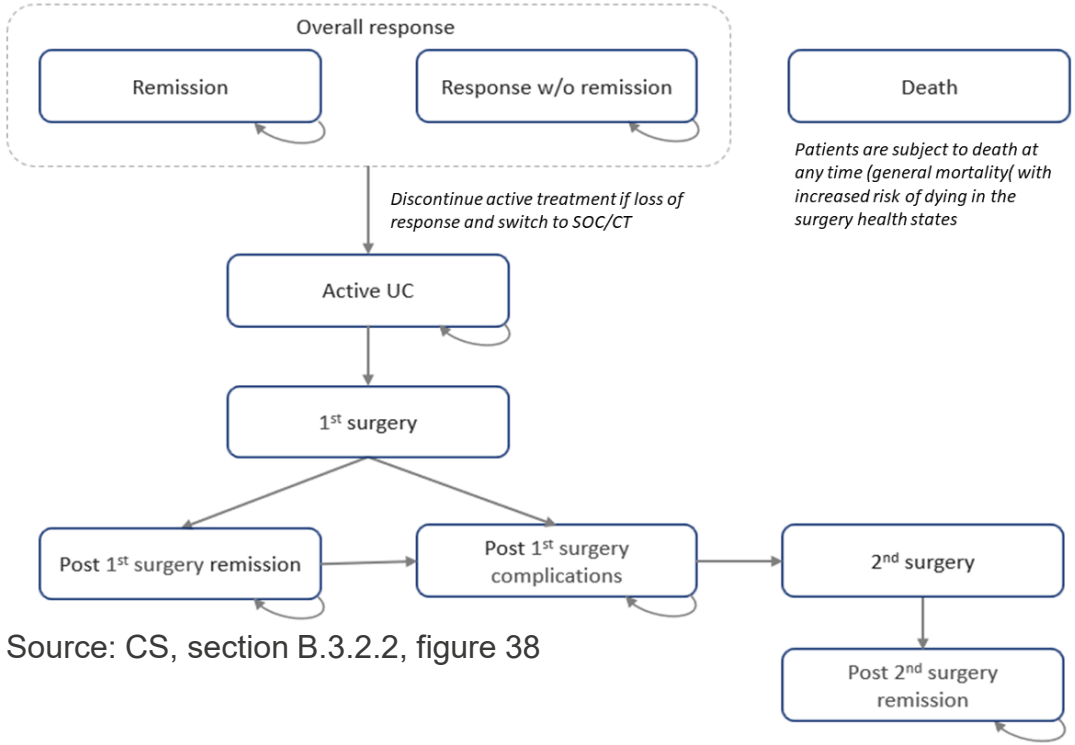
Company model structure – updated base case

Decision Tree for the Induction Phase (ERG's illustration)



Source: ERG report, section 4.3.3, figure 13

Markov model for the Maintenance Phase

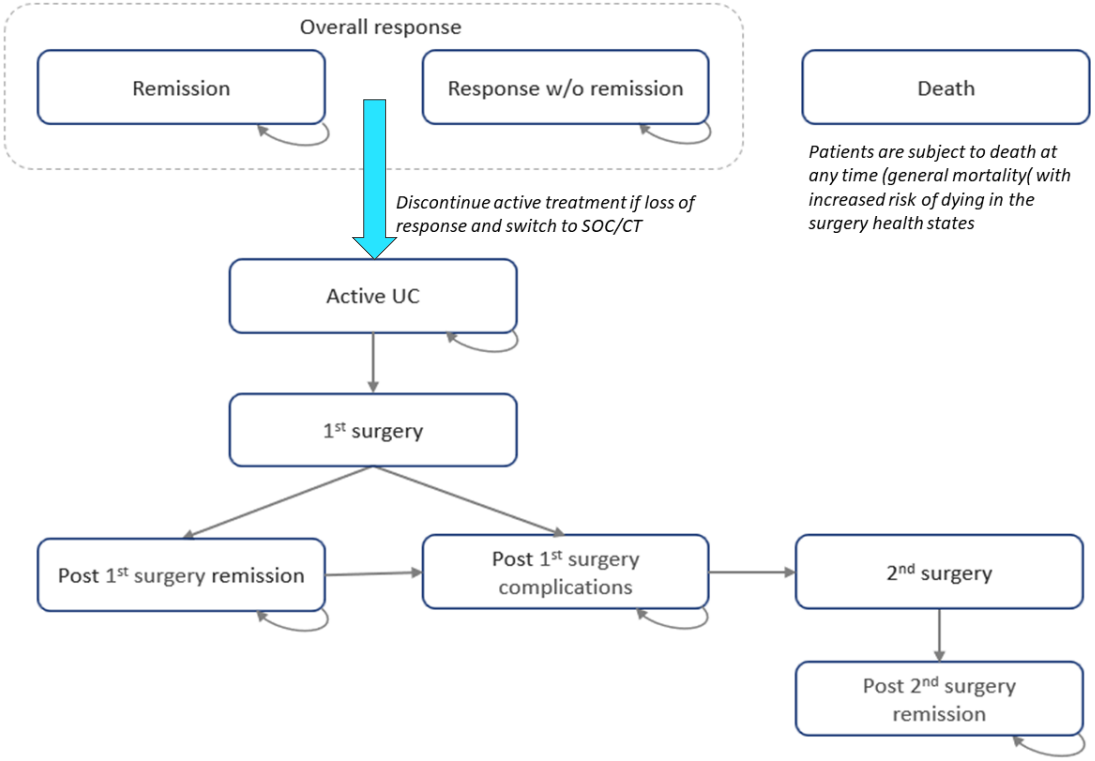


Source: CS, section B.3.2.2, figure 38

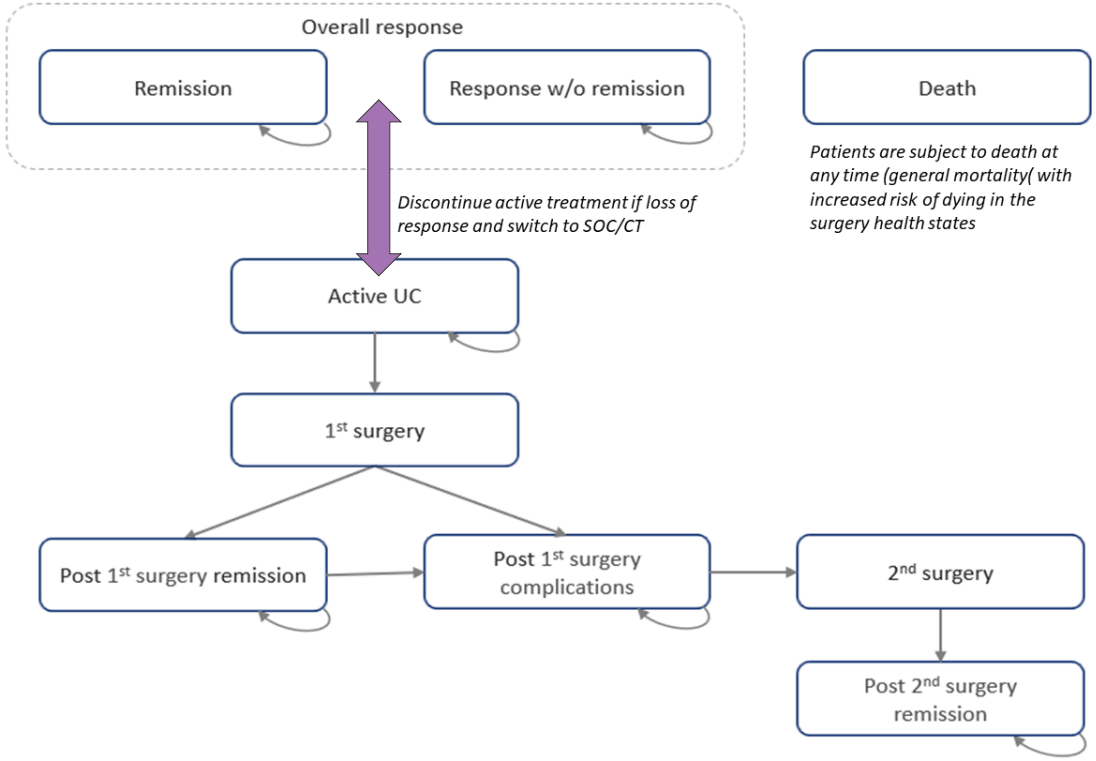
- Conventional design for UC, but with some changes to previous TA models
- Hybrid - decision tree (for the induction phase) / Markov model (for maintenance and ongoing care)
- Markov has a cycle length = 2 weeks, designed to accommodate induction periods of different lengths
- 50-year time horizon (effectively lifetime from a starting age of 41 years), with a half-cycle correction
- Costs and QALYs are discounted at an annual rate of 3.5%

Response and remission rates for patients that do not respond or who lose response to therapy

Company model



ERG model



Response and remission rates are uncertain in people with disease that does not respond or loses response to initial therapy: committee considered response rate is likely to be near to 0 to 1%

Choice of utility values for response and remission health states

- Important driver of cost effectiveness; using UNIFI data instead of Woehl 2008 increases company base case ICER vs. CT by £55,344 and £61,651 per QALY for the non-biologic failure and biologic failure groups respectively
- In both company and ERG base case, utilities for the 'Remission', 'Response without remission' and 'Active UC' health states are all derived from Woehl et al. (2008) UK EQ-5D-3L study of 180 UC patients
- Utilities from EQ-5D data collected in the UNIFI trial also presented by the company and used in a scenario analyses

	Woehl et al. (2008) values	Values estimated from the UNIFI trial using EQ-5D-3L			
Health state	Based on total sample size of N=180	Average (sample size)	Standard deviation	Minimum	Maximum
Remission	0.87	[redacted]	[redacted]	[redacted]	[redacted]
Response without remission	0.76	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	**0.41**	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report section 4.3.5 tables 45 and 46

Choice of utility values for response and remission health states cont.

Woehl et al. utilities	U0NIFI EQ-5D utilities
Has been used in previous appraisals (TA329, TA324, TA547)	Insufficient duration of trial follow up to assess change in utilities over time
Patient perspective heard in ACM1 may support utility value of 0.41 (Woehl et al. utility for active UC)	Committee to consider plausibility of active UC being associated with a health state of **** (UNIFI utility for active UC)
Only available as abstract – methodology cannot be appraised	Methodological limitations to UNIFI EQ-5D data collection: • data collected at multiple timepoints • imputation used for missing health states • potential reporting bias • potential selection bias
Population included unknown – may be less or more sick than UNIFI patients	Patients in UNIFI continue to receive ustekinumab but in model they switch to CT on loss of response
Smaller sample size: total of 180 across 3 health states	Larger sample size: total 1,976 across 3 health states
	EQ-5D-5L scores from UNIFI cross-walked to the 3L scale using a published algorithm (van Hout et al. 2012 - recommended by NICE)

ACD: preliminary recommendation

1.1 Ustekinumab is not recommended, within its marketing authorisation, for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment.

Committee considerations (1)

- Living with moderately to severely active UC is physically and emotionally challenging
- There is unmet need for new treatments that reduce the need for corticosteroids or surgery
- UNIFI trial showed ustekinumab is more effective than placebo at inducing and maintaining remission and response
- Exclusion of studies conducted in Asia from NMAs has little effect on the cost-effectiveness estimates
- Company's induction-phase NMAs were methodologically robust
- Maintenance-phase NMAs have limitations and results are very uncertain
- Response and remission rates are uncertain in people with disease that does not respond or loses response to initial therapy: committee considered response rate is likely to be near to 0 to 1%

Committee considerations (2)

- The utility values are uncertain and the choice of inputs has a large effect on the cost-effectiveness estimates
- Fully incremental ICERs for all the key scenarios, across both subgroups ('biological failure' and 'non-biological failure'), using utility values from Woehl et al. 2008, are all above £30,000 per QALY gained compared with the next most cost-effective therapy; ICERs are between £24,849 and £35,512 per QALY gained compared with conventional therapy in pairwise analysis
- Using the UNIFI utility data instead of Woehl et al. 2008 increases the company base-case ICER compared with CT by £55,344 and £61,651 per QALY gained for the non-biologic failure and biologic-failure groups respectively
- The cost-effectiveness estimates are sensitive to changes in the 3 parameters, all of which are very uncertain

ACD consultation responses

- Consultee comments from:
  - Company
  - Crohn's and Colitis UK
  - Patient expert

- Web comments

Comments from Crohn's and Colitis UK (1)

- There is a significant unmet need - new treatments are needed, especially for people with co-morbidities and ability to be treated at home is important
- Untreated and uncontrolled disease is associated with high risks and mortality
- For people with moderate to severe UC, the condition is frequently overwhelming and detrimentally life altering and associated with impact on social functioning:
  - "I have become isolated and really hid myself away from society"
  - "Your life is on hold and all normality is replaced by a 'new normal' of pain, distress and sickness"
- Corticosteroids have diminishing returns, harsh side effects and risk of dependency
- Stopping rules mitigate against inappropriate use of biologics

Comments from Crohn's and Colitis UK (2)

- Avoidance of surgery is highly valued; with more treatment options available, surgery is more likely to be avoidable:
  - "Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life."
  - "Surgery was on the cards, but my mum, dad and I begged the surgeon not to do it."
- Concerns that not all post-surgery costs and utilities have been considered
- Consideration of equalities issues – regarding surgery as an option for people below child bearing age and some religious groups

Comments from patient expert (1)

- “In its severe form… ulcerative colitis can also be life-altering, i.e. ‘normal functioning’ (socially, emotionally and economically) is on hold indefinitely. This is all encompassing and created significant disability”
- “I may have described going to work and leaving the house with severe symptoms, but…I was doing so while in constant pain and distress, suffering fatigue, nausea, heart palpitations, shortness of breath walking from the station to my office and anxiety about the location of toilets”

Comments from patient expert (2)

- “Whilst a person living with quite severe disease can ‘self-manage’ with the right support in place, i.e. they can develop resilience and coping methods to help them tolerate certain symptoms or employ strategies such as avoiding social activities, taking adequate rest, relaxation techniques, working from home, mapping local toilets etc, the severity of their symptoms and their disease activity itself cannot be moderated without effective treatment”

Web comments

- Multiple treatment options are highly beneficial in this population
- There isn't a '1 size fits all' approach to UC so different treatments are effective (or ineffective) in different people
- Current treatments are associated with high rates of treatment failure, and although they may be effective for a time, they can become ineffective meaning further treatment options need to be considered for these people
- Treatment options available can be reduced by the presence of co-morbidities
- Ustekinumab provides a different mechanism of action to TNF-alpha inhibitors
- Evidence of ustekinumab being more effective in biological-failure patients vs vedolizumab and adalimumab (recent NMA)
- Avoidance of surgery is highly valued; with more treatment options available, surgery is more likely to be avoidable

Company comments – fully incremental vs pairwise analysis

- Previous appraisals (TA329, TA342 and other immunology appraisals) have concluded that fully incremental analyses are problematic and pair-wise ICERs versus CT should be used for decision making
- Positive ACD *[Jan 2020]* for upadacitinib for RA based on pairwise analysis – upadacitinib not cost effective in fully incremental analysis
- In this appraisal, fully incremental analysis are problematic due to uncertainty in the long-term relative effectiveness of treatments
- TA329 MTA: committee concluded that all 3 anti-TNFs considered cost effective, although 2/3 were dominated or extendedly dominated and all 3 anti-TNFs had pair-wise ICERs versus CT exceeding £50,000 per QALY

ERG response – fully incremental vs pairwise analysis

Judgement has been made on the interpretation of fully incremental analysis in previous appraisals:

- TA329: committee chose not to distinguish between TNF-alpha inhibitors due to uncertainty of the NMA and shortcomings of the cost-effectiveness models
- TA342: applied judgement to allow for uncertainties in utility values, costs of surgery and post-surgery care and impact of stopping rules
- TA547: both fully incremental and pairwise analysis discussed

Both incremental and pairwise analysis are informed by NMAs with inherent uncertainty

Head-to-head comparisons in pairwise analysis reduce uncertainty, but conventional therapy may not be the most relevant comparator – market share is biggest for anti-TNFs

Company comments on ACD – limitations of ERG's NMA

- Assumption of placebo arm similarity across studies does not hold
- It includes an inappropriate population of people who were given an unlicensed dose of ustekinumab in induction
- The ERG NMA has not been incorporated appropriately in the economic model

ERG response:

- Placebo arm similarity: this was an assumption underlying an ERG scenario which is justified
- Maintenance outcome data reported in the CS combines induction doses; outcome data reported by 6mg/kg and 130mg induction doses is not reported
- CT arm in the model should reflect real-world outcomes through both induction and maintenance, alongside active treatment arms. Given the ERG assumptions in the maintenance-only NMA that placebo arms are equivalent, baseline comparator of placebo-placebo is valid as a proxy for CT-CT.

Company comments on ACD – long-term effectiveness of ustekinumab

- Company 1-year NMA provides the most complete and comprehensive evidence base for considering relative effectiveness of treatments: shows that ustekinumab has high probability of being better than other comparators over a year of treatment
- Data from UNIFI show that partial Mayo remission scores are maintained to week 92
- Real-world data in psoriasis shows minimal discontinuations of ustekinumab, with 80% of people still on treatment at 2 years; data from people with Crohn's shows median time of treatment is >2 years
- There is an underestimation of treatment effect at 2 years in the models shown by comparison with real-world data

ERG response – long-term effectiveness of ustekinumab

- 1-year NMA cannot be used to inform the model because it does not reflect real-world practice
- Company has not reported methods of their LTE study therefore ERG cannot comment on validity
- Psoriasis and UC are different conditions which may have different issues relating to compliance; the dose of ustekinumab in psoriasis may be lower than in UC
- Unclear on validity of using long-term data in Crohn's disease as proxy for UC
- Unclear which outcome is referred to in comparison of model and real-world data

Company's updated base case

- Company have updated their base-case including: modelled relative effectiveness in maintenance from the company NMA; 0% rate for spontaneous remission and response; utility values from Woehl et al.

	ICER; Ustekinumab versus CT	
Scenario	**Non-biologic failure**	**Biologic failure**
Updated base-case (1-year NMA, 0% response)	**£24,849**	**£28,348**
Updated base-case (1-year NMA, 1% response)	**£26,359**	**£29,920** (corrected by ERG from £29,290)

- Company suggest their updated base case is conservative because:
  - benefits of corticosteroid-free remission hasn't been modelled
  - safety concerns and limited real-world use with tofacitinib wasn't modelled
  - UNIFI data for biological failure includes people who failed anti-TNF and vedolizumab compared with other studies which included people who failed anti-TNF only

ERG analysis of company's updated base case and scenario analysis versus CT

ERG investigated 4 key scenarios (KS) as described in the ACD
Company updated base case is KS1, and company scenario is KS2

Key scenarios	Maintenance phase NMA	Response or remission after initial treatment failure	Source of utilities
1	1-year conditional on response NMA	0%	Woehl et al. (2008)
2	1-year conditional on response NMA	1%	Woehl et al. (2008)
3	Maintenance-only NMA	0%	Woehl et al. (2008)
4	Maintenance-only NMA	1%	Woehl et al. (2008)

	ICER; Ustekinumab versus CT	
Key scenario	**Non-biologic failure**	**Biologic failure**
3 (maintenance-only NMA, 0% response)	**£29,681**	**£33,624**
4 (maintenance-only NMA, 1% response)	**£31,512**	**£35,512**

ERG analysis of company's updated base case and scenario analysis versus active therapies

- ICERs for ustekinumab compared with the lowest-cost TNF-inhibitor are above £30,000 per QALY gained for all scenarios presented, both for patients who have, and have not previously had a biologic.

The fully incremental and individual comparator ICERs including cPAS will be shown in part 2

Company comments on ACD – issues with UNIFI utility data

- Utility values from Woehl et al. 2008 have been used in previous appraisals
- It may be implausible that the health state of active UC would have a utility value of **** (UNIFI EQ-5D), and the patient perspective heard in ACM1 supports using utility value of 0.41 (Woehl et al. 2008). This is further supported by consultee comments from Crohn's and Colitis UK and a submission by the patient expert which suggested the wording in the ACD did not describe how debilitating UC can be.
- There are methodological limitations to the UNIFI EQ-5D data collection:
  - data were collected at multiple timepoints, meaning the same person may have contributed multiple times
  - imputation was used for missing health states when Mayo scores were missing for an EQ-5D assessment
  - there is a potential reporting bias based on the ability of the person to adapt to their condition
  - potential selection bias as people who are too unwell may be less likely to complete the EQ-5D

ERG response – issues with UNIFI utility data

- There are (avoidable and unavoidable) methodological issues with UNIFI utility data collection – but there are also methodological and reporting issues with Woehl et al.
- Other NICE appraisals for UC have used various sources of utilities:
  - Swinburn et al. 2012 for scenario analysis, judged equally plausible as Woehl et al. in TA329 and TA342
  - Vaizey et al. 2013 cited in TA329, but not used because it did not report post-surgery outcomes
- No basis to distinguish between Woehl, Swinburn and Vaizey on methodology or reporting quality, generalisability or applicability
- Cost-effectiveness is very sensitive to the source of utility

ERG analysis for alternative utility sources (1)

Cost-effectiveness for ustekinumab versus CT by key scenario and utility source:

	ICER; Ustekinumab versus CT	
Scenario	Non-biologic failure	Biologic failure
Woehl et al. (2008) pre-surgery utility estimates: remission 0.87, response 0.76, active 0.41		
KS1	£24,849	£28,348
KS2	£26,359	£29,920
KS3	£29,681	£33,624
KS4	£31,512	£35,512
Swinburn et al. (2012) pre-surgery utility estimates: remission 0.91, response 0.80, active 0.55		
KS1	£32,664	£37,722
KS2	£34,617	£39,758
KS3	£39,349	£44,860
KS4	£41,757	£47,316

ERG analysis for alternative utility sources (2)

Cost-effectiveness for ustekinumab versus CT by key scenario and utility source:

	ICER; Ustekinumab versus CT	
Scenario	Non-biologic failure	Biologic failure
Vaizey et al. (2013) pre-surgery utility estimates: remission 0.86, response 0.77, active 0.66		
KS1	£54,026	£64,079
KS2	£57,148	£67,329
KS3	£66,291	£76,663
KS4	£70,274	£80,622
UNIFI trial (CS 2019) pre-surgery utility estimates: remission [redacted], response [redacted], active [redacted]		
KS1	£82,643	£93,836
KS2	£87,665	£99,029
KS3	£98,424	£110,804
KS4	£104,490	£116,992

Company's response to ACD – cost comparison with vedolizumab

- In a simple cost-comparison analysis, the efficacy of ustekinumab and vedolizumab has been assumed equivalent.
- Analysis by company (using list price for vedolizumab) suggests a cost saving with ustekinumab compared with vedolizumab
- Vedolizumab chosen by company because:
  - it has a different mechanism of action compared with TNF-alpha inhibitors (as ustekinumab does)
  - is only comparator in scope that's shown head-to-head superior efficacy versus an anti-TNF (vedolizumab vs adalimumab)
  - has the biggest market share after anti-TNFs (~30%)

Results of cost-comparison including cPAS for vedolizumab will be shown in part 2

ERG response – cost comparison with vedolizumab

- This approach ignores uncertainty – health benefits of UST vs VED estimated from uncertain NMAs and direct data for VED vs ADA only available as 2 brief abstracts
- Is the comparison with vedolizumab alone appropriate? Other comparators are also available:
  - TNF-inhibitors are routinely used for initiation of biologic treatment and so are an important and relevant comparator for NHS practice.
  - Tofacitinib is associated with safety concerns, but is still an option for some people.
- In most scenarios, estimated QALYs are greater for ustekinumab than vedolizumab

Company's response to ACD - stopping rules

- Stopping rules should be considered in cost-effectiveness analysis
- Stopping rules are considered in TA329 and TA342 and have influenced committee decision making
- Company have provided ICERs (UST vs CT) including stopping at 1, 2, 3 or 5 years based on their updated base-case, and company NMA with 1% spontaneous remission/response
- Stopping rules (and detail on pathway position and dose escalation) would also be beneficial for clinicians if approved, to aid understanding of how this would be given in practice

ERG response – stopping rules

- Stopping rules are inherited from NICE guidance on Crohn's disease, not UC
- There is variation in use of stopping rules in practice
- Stopping rule in model is applied to patients with sustained response with or without remission – but TA329 and TA342 stopping criteria only apply to patients in sustained remission
- Unclear if estimated rates for loss of response after treatment withdrawal are realistic – inferred from trial data on proportion of induction responders re-randomised to placebo who were in response at the end of the maintenance trial ([redacted]% for biologic failure and [redacted]% for non-biologic failure)

Key issues

- Is the ‘company 1-year NMA conditional on response’ used in the company’s updated base-case the most appropriate NMA to use?
- What is the most appropriate source of utility data?
- Is fully incremental or pairwise analysis more appropriate for decision making?
- Would conventional therapy be the appropriate comparison for all patients, given the number of active treatments now recommended?
- Is a cost-comparison with vedolizumab valid for decision making?
- Which patients would currently receive vedolizumab (‘non-biologic failure’, ‘biologic failure’, or all patients)?
- Should stopping rules be considered?

Back up slides

Utilities used in previous appraisals

TA329:

- Infliximab and golimumab: utilities from 2 clinical trials not appropriate because made different assumptions for same decision problem
- Adalimumab: clinical trial utilities not used by company and deemed inappropriate; company used Swinburn et al. and Tsai et al.
- Woehl et al. used as base-case and Swinburn et al. as sensitivity analysis by assessment group

TA342:

- Company used clinical trial data for pre-surgery utilities, but used published data for surgery and post-surgery utilities – resulting in post-surgery remission utilities lower than mod-severely active UC (considered implausible)
- ERG used Woehl et al and Swinburn et al. (Woehl utilities post-surgery similar to mild UC; Swinburn utilities post-surgery similar to mod-severe UC) – committee agreed that QoL might be improved after surgery but the magnitude was unclear. Both sets of utilities were used.

Alternative sources for health utilities

					Health state, utility (decrement vs. Remission)					
	n	*Setting*	*Utility*	Severity	Remission	Response (without remission)	Active UC	Surgery (6 months)	Post surgery	Post surgery complications
Sources of utility estimates										
Woehl 2008	180	UK	EQ5D	SCCAI	0.87	0.76 (0.11)	0.41 (0.46)		0.715	
Swinburn 2012	230	UK	EQ5D	pMayo	0.91	0.80 (0.11)	0.55 (0.36)		0.59	
Vaizey 2013	173	UK	EQ5D	pMayo	0.86	0.77 (0.09)	0.66 (0.20)			
UNIFI 2019		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Arseneau 2006	48	US	TTO		0.79		0.32	0.614		0.34

[redacted]

IBDQ; SCCAI Simple Clinical Colitis Activity Index; pMAYO Partial Mayo (remission 0-2, response decrease ≥2 from induction baseline)

Health outcomes by utility source

(conventional therapy, non-biological failure from updated company base case)

Outcome	Remission	Response w/o remission	Active UC	Surgery, post-surgery & AE	Total
Life years (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Woehl et al. 2008 pre-surgery utilities (0.87, 0.76, 0.410)					
QALYs (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Swinburn et al. 2012 pre-surgery utilities (0.91, 0.80, 0.55)					
QALYs (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vaizey et al. 2013 pre-surgery utilities (0.86, 0.77, 0.66)					
QALYs (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UNIFI trial pre-surgery utilities ([redacted], [redacted], [redacted])					
QALYs (undiscounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Meta-analysis of utilities in ulcerative colitis

Malinowski et al. 2016 – meta-analysis of published utility data for UC

Did not include Woehl, Swinburn or Vaizey – unclear if excluded or not identified

State	Utility
Remission	0.87 (0.85 to 0.90)
Active	0.70 (0.58 to 0.81)
Mild	0.78 (0.73 to 0.84)
Moderate	0.70 (0.40 to 1.0)
Moderate to severe	0.80 (0.70 to 0.90)
Severe	0.71 (0.51 to 0.91)

NICE methods guide – cost comparison

- “A cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication.” (Paragraph 1.2)

- “For the acceptance of a cost comparison case, evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes, must be presented in the company’s evidence submission.” (Paragraph 2.5)

Company's updated base case with stopping rules

	ICER; Ustekinumab versus CT	
Scenario	**Non-biologic failure**	**Biologic failure**
Updated base-case	**£24,849**	**£28,348**
Updated base-case and stopping rule at 5 years	**£23,020**	**£27,610**
Updated base-case and stopping rule at 3 years	**£20,428**	**£25,844**
Updated base-case and stopping rule at 2 years	**£17,476**	**£23,388**
Updated base-case and stopping rule at 1 year	**£11,148**	**£17,189**

Company's scenario (assuming 1% spontaneous remission/response)

	ICER; Ustekinumab versus CT	
Scenario	**Non-biologic failure**	**Biologic failure**
Company NMA, 1%	**£26,359**	**£29,920**
Company NMA, 1% and stopping rule at 5 years	**£24,445**	**£29,155**
Company NMA, 1% and stopping rule at 3 years	**£21,733**	**£27,319**
Company NMA, 1% and stopping rule at 2 years	**£18,642**	**£24,762**
Company NMA, 1% and stopping rule at 1 year	**£12,004**	**£18,293**

Stopping rules from previous appraisals

TA329:

Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:

- *They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.*
- *They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.*

TA342:

Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.