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

Cost effectiveness

1st Appraisal Committee meeting

9th March 2017

Committee A

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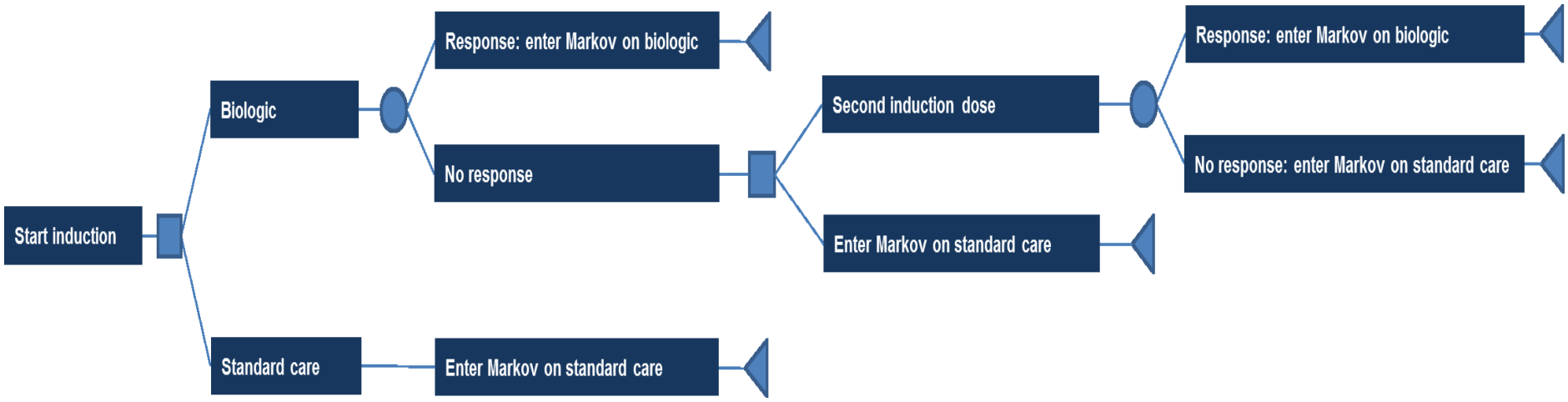
Key issues: cost effectiveness

- The ERG raised concerns about the structure of the company's model. What is the committee'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?

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)

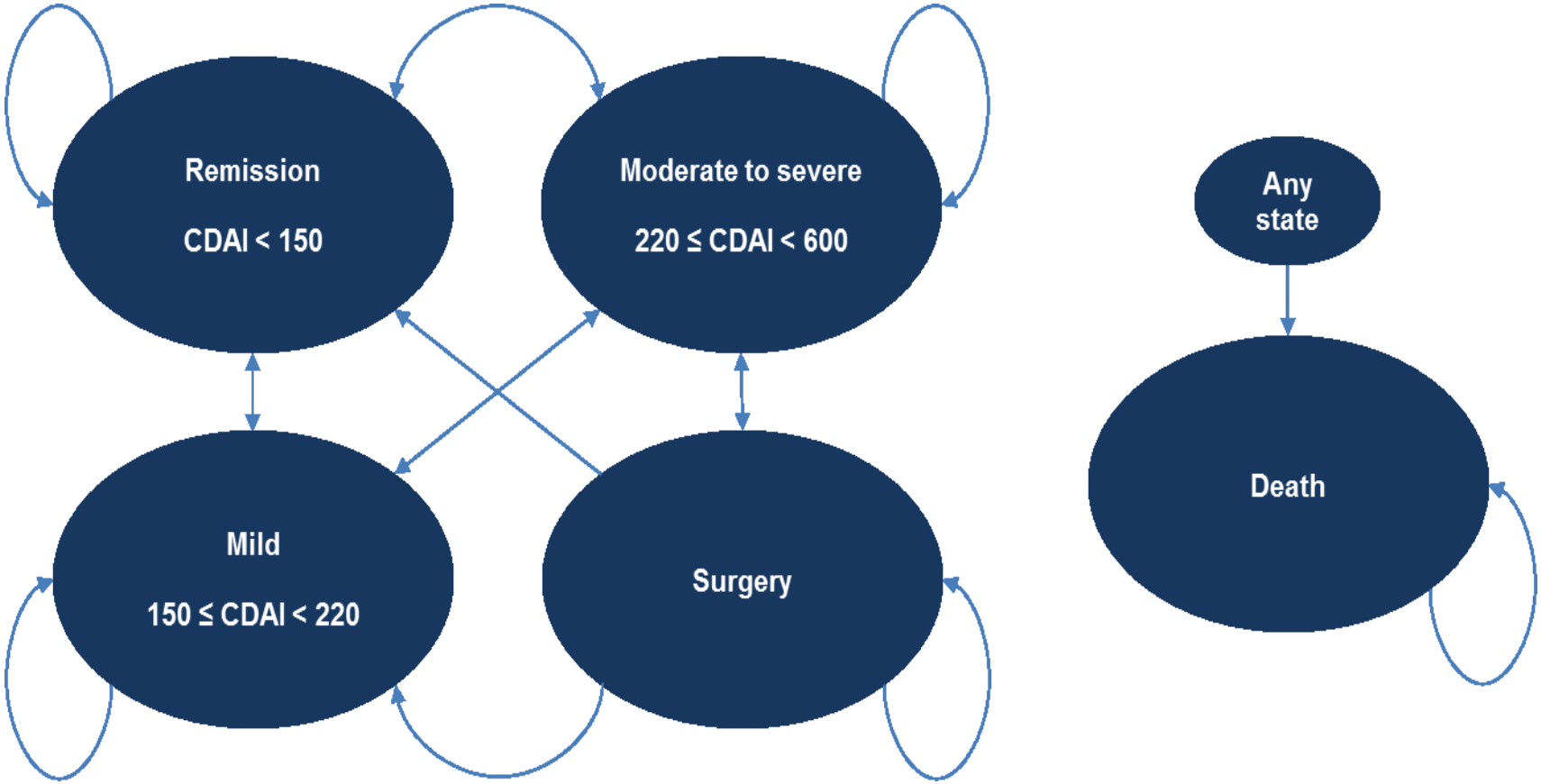
Induction phase (decision tree)



Source: Figure 40, company's submission

Model structure – maintenance phase (Markov state-transition model)

- Patients remain on biologic treatment if they have responded to induction treatment (defined in base case as a decrease in CDAI score >100 points [CDAI-100]).
- Non-responders are eligible for the first maintenance dose to assess delayed response



Source: Figure 41, company's submission

Clinical data used in company's model

Induction phase

- Efficacy data for ustekinumab derived from UNITI-1 & UNITI-2 (~6mg/kg dose)
- Data for comparators derived by applying odds ratios calculated in the induction NMA to ustekinumab induction results

Maintenance phase

- The model uses data from the treatment sequence NMA to calibrate a fixed 2-week maintenance transition matrix for each treatment (this is a major issue of uncertainty)

Summary of treatment costs (lower dose)

		Induction		Maintenance year 1		Average maintenance year 2 +	
[redacted]							
Ustekinumab	£2,147	1	XXX	4	£8,588	4.35	£9,339
[redacted]							
Adalimumab	£352.14	2	£2,113	25	£8,804	26.09	£9,187
[redacted]							

* Excludes Vedolizumab Patient Access Scheme: XXX discount on the NHS list price

Tables 53 and 54, company submission

Summary of treatment costs (higher dose)

			Induction	Maintenance year 1		Average maintenance year 2 +	
[redacted]							
Ustekinumab	£2,147	1	XXX	6	£12,882	6.52	£13,998
[redacted]							
Adalimumab	£352.14	2	£2,113	49	£17,255	52.12	£18,375
[redacted]							

* Excludes Vedolizumab Patient Access Scheme: XXX discount on the NHS list price

Tables 53 and 54, company submission

Utility values used in company's model

Health state	Utility value*
[redacted]	
Mild	0.680
[redacted]	
Surgery	As for moderate to severe

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

Decrements in QALYs due to adverse events**	
[redacted]	
Tuberculosis	-0.55
[redacted]	
Acute hypersensitivity reactions	-0.11
[redacted]	

**Taken from TA352 based on published literature

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
[redacted]					

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
[redacted]					

Tables 46 and 47, company response to clarification

*Ustekinumab also dominates other treatment options in the probabilistic analysis

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
[redacted]					
Infliximab – Remsima	278,693	12.8208	15,640	-0.2292	Dominated
[redacted]					
Adalimumab	283,762	12.9022	20,709	-0.1479	Dominated

Table 67, company submission

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
[redacted]					
Infliximab – Remicade	265,930	13.1388	1454	0.0000	Dominated
[redacted]					
Adalimumab	286,251	12.8766	21,776	-0.2622	Dominated

Table 68, company submission

Company's cost minimisation analysis

Company suggested that since ICERs are unstable due to small differences in QALYs between treatments, a cost minimisation analysis may be more appropriate

Conventional care failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
	XXX		XXX	
Adalimumab	£13,486	£0	£13,486	XXX

TNF failure population

Technologies	Treatment acquisition costs	Administration costs	Total costs	Incremental cost
	XXX		XXX	
Vedolizumab	£20,307	£5,138	£25,445	XXX

Health state/AE costs excluded under assumption that all treatments have equal efficacy and comparable safety profiles

Tables 80 and 81, company submission

ERG comments

Minor corrections

- Some errors were identified in the company's model. On correction of the results by the ERG, ustekinumab remained dominant in both the conventional care failure and TNF failure populations compared with conventional care

General weaknesses of model structure

- Model does not fully characterise the chronic life-long relapsing-remitting nature of Crohn's disease - fails to capture that patients cycle through multiple biologic therapies to combat relapses in disease
- Impact of surgery on future prognosis (including the need for further surgery) and HRQL not appropriately incorporated
- Impact of these structural failures on the cost-effectiveness of ustekinumab is unclear

ERG comments

Clinical data

Substantial concerns regarding data, assumptions and methods used to calculate the transition probabilities in the maintenance phase

- Method is based on treatment sequence analysis, which company describes as “limited”, while ERG has concerns over its interpretation and reliability
- Algorithm to calculate transition probabilities requires specification of a set of initial values; changing the initial values results in a different set of probabilities (i.e. no unique solution)
- Implausible predictions from model:
  - Data from company suggest ~60% of ustekinumab patients who achieve remission will stay in remission during maintenance phase; model predicts this to be over 90%
  - CHARM trial: adalimumab more effective than placebo during maintenance phase; model predicts conventional care more effective than adalimumab

ERG comments

Duration of treatment with biologic therapy

- ERG highlights the substantial uncertainty around this - the company's base case assumes a maximum duration of 1 year but evidence from the Inflammatory Bowel Disease Audit suggests 90% of patients continue on therapy for more than a year

Costs and utilities

- ERG is largely satisfied with company's approach to estimating utility values for the different health states but considers that EQ-5D data from the GEMINI studies of vedolizumab are theoretically superior as they are directly elicited
- Concern that the health state costs (derived using a modified Delphi panel approach including 12 clinicians and nurses) are very high and are significantly greater than those used in TA352
- Concern that the cost of injection site reactions (£5,240) is an overestimate and is far in excess of the £1,363 value used in TA352

ERG's exploratory analyses

The ERG conducted a number of exploratory analyses to explore uncertainty in model assumptions and inputs:

1. Inclusion of the CERTIFI phase II ustekinumab trial to estimate treatment efficacy during the induction phase for the anti-TNF failure population
2. Alternative health state utility values from the vedolizumab GEMINI studies (0.82 for remission, 0.73 for mild disease, 0.57 for moderate to severe disease, and 0.57 for surgery)
3. An alternative cost for injection site reactions using NHS reference costs (£1,621)
4. Alternative starting values in the valuation of the transition probabilities used during the maintenance phase
5. Alternative assumptions regarding time horizon (5 and 10 years)
6. Alternative assumptions for the maximum duration of biologic treatment (5 years, 10 years and lifelong)

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. Suggests substantial weakness in the modelling

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)

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

Company base case (corrected)				ERG preferred base case			
[redacted]							
Ustekinumab	263,292	13.08	-	Conventional care	107,150	13.11	-
[redacted]							
Infliximab-Inflectra	278,730	12.85	Dominated	Infliximab-Inflectra	116,756	13.17	Dominated
[redacted]							
Infliximab-Remicade	279,739	12.85	Dominated	Infliximab-Remicade	117,767	13.17	Dominated
[redacted]							

Table 107 ERG report

*Probabilistic analysis showed ICERs minimally different from deterministic analysis

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

Company base case (corrected)				ERG preferred base case			
[redacted]							
Ustekinumab	287,780	12.99	-	Conventional care	123,303	12.46	-
[redacted]							
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

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

Key issues: cost effectiveness

- The ERG raised concerns about the structure of the company's model. What is the committee'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?

Additional slides

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

Company base case (corrected)				ERG preferred base case			
[redacted]							
Ustekinumab	263,292	13.08	-	Conventional care	107,097	13.12	-
[redacted]							
Infliximab-Inflectra	278,730	12.85	Dominated	Infliximab-Inflectra	120,188	13.19	705,040
[redacted]							
Infliximab-Remicade	279,739	12.85	Dominated	Infliximab-Remicade	120,838	13.22	Dominated
[redacted]							

Table 107 ERG report

*Probabilistic analysis showed ICERs minimally different from deterministic analysis

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

Company base case (corrected)				ERG preferred base case			
[redacted]							
Ustekinumab	287,780	12.99	-	Conventional care	123,259	12.46	-
[redacted]							
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