For public

NICE National Institute for Health and Care Excellence

Tofacitinib for ulcerative colitis
Lead team's presentation
Cost-effectiveness PART 1

1st appraisal committee meeting
Committee A
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Company: Pfizer

16.08.2018

Key cost effectiveness issues

- Are the comparators appropriate for each sub-group?
  - Company base case excludes ADA in TNFi-exposed group
- What is the committee's view on:
  - The most appropriate source of health-related quality of life data?
  - Patient characteristics (e.g. age) being different depending on TNFi exposure status?
  - Importance of stoma care costs and surgery costs ?
  - Application of stopping rules in the model vs. clinical practice
- What is the committee preferred scenario?

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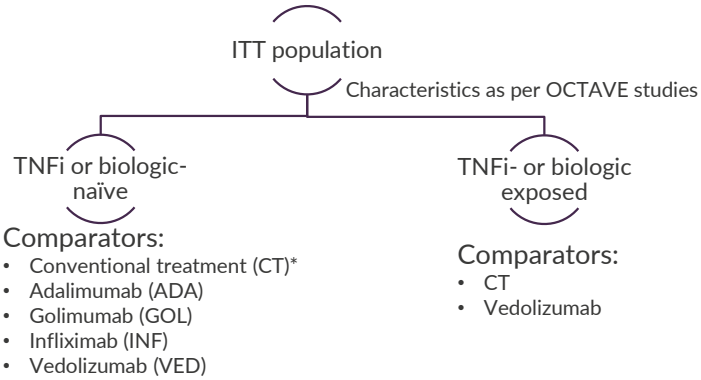
Company's model population and comparators



Treatment sequences:
- TOF and biologics are followed by CT in second line.
- CT modelled as single line therapy
- Model can compare treatment sequences.

[redacted]

*Conventional therapy defined as a combination of aminosalicylates (balsalazide, mesalazine, olsalazine and sulfalazine), corticosteroids (hydrocortisone and prednisolone) and the immunomodulator azathioprine

Company's model population and comparators - ERG critique

- **Subgroups by TNFi or biologics exposure:**
  - Company labelling by biologics exposure because:
    - prior exposure to biologics is an important treatment effect modifier
    - patient treatment history is a deciding factor in the treatment pathway
  - ERG agree but note that labelling is misleading, as NMA results are defined by prior exposure to TNFi alone (and not by prior biologic exposure)
- **Characteristics of the population**
  - Company: subgroups as per the OCTAVE trials
  - ERG: same gender, age and weight mix regardless of prior TNFi exposure
    => ERG explore impact of age and body weight in scenario analysis
- **Comparators**
  - Company did not include ADA in TNFi-exposed population
  - ERG considers ADA is a relevant comparator
    => ERG include ADA in their base case
- **Sequences**: *=> ERG explore effect of switching within or between classes and compare 'step-up' and 'step-down' strategies*

[redacted]

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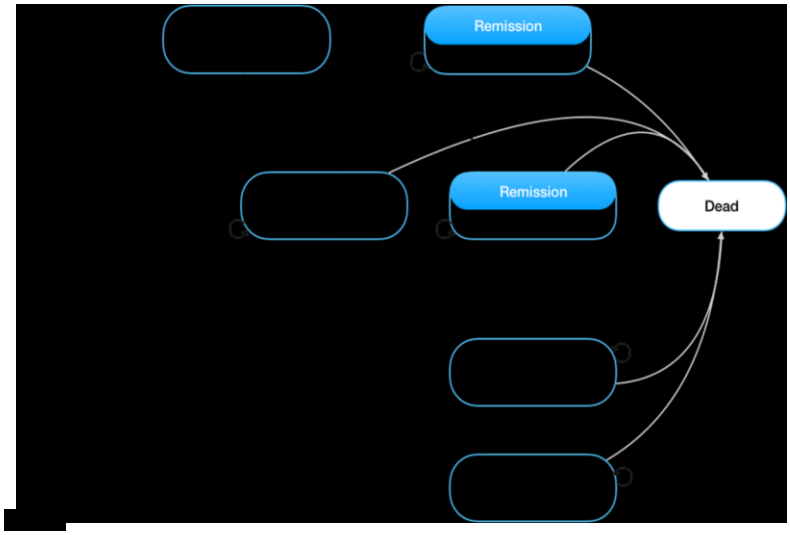
Company model structure



Key: CC, colectomy complications; UC, ulcerative colitis.

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ERG critique on the model structure

- Economic model of good quality
- Appropriate reflection of clinical practice, in line with previous UC models
- Includes risk of relapse and immediate cessation of treatment at each cycle
- Assumes a fixed duration of induction of 8 weeks, followed by cessation of treatment for patients whose disease does not show a response in this time
  - TOF SPC recommends assessment 8-16 weeks after initiation and annual reassessment
  - NICE MTA329 and NICE TA342 recommend assessment of response at 12 months. ERG's clinical experts agree that benefit is assessed annually.
  - NICE MTA329 and NICE TA342 recommend consideration of treatment withdrawal. ERG's clinical experts consider that withdrawal is unlikely in clinical practice.
- Adverse drug reactions only include serious infection, which in the model do not cause treatment discontinuation (although clinical advice is that TOF would be temporarily withheld)

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Clinical parameters in the model

	Efficacy	Safety	Complications
Parameters and rationale	Locally read clinical response/ remission; choice of NMA models based on DIC statistics, with preference for FE if no difference	Serious infections only included as model already accounts for UC related conditions (model health states are defined based on clinical response and clinical remission corresponding to Mayo scores)	Incidence and complication/mortality rates for surgery (perioperative complication and mortality, incidence of emergency and elective surgery)
Source	NMA (clinical) and assumption	NMA (safety) for serious infections	Literature and assumptions
ERG comments	• Prefer NMA results using RE models to better reflect uncertainty related to heterogeneity in efficacy outcomes => ERG test alternative NMA in scenario analysis • Safety: in clinical practice, patients would be temporarily withheld following serious infection so assuming no discontinuation due to serious infections or other AEs is unrealistic and likely to introduce bias		

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Key: DIC: Deviance information criterion

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Effectiveness in the model: TNFi-naïve

	Distribution by health state at end of induction			Response and remission given response (over 8 weeks)		
	Active UC	Response only	Remission		Probability of maintaining response	Percentage of responders in remission
ADA	[redacted]	[redacted]	[redacted]	ADA	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	GOL 50mg	[redacted]	[redacted]
				GOL 100mg	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	INF	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	TOF 5mg	[redacted]	[redacted]
				TOF 10mg	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	VED Q8W	[redacted]	[redacted]
				VED Q4W	[redacted]	[redacted]
CT	[redacted]	[redacted]	[redacted]	CT	[redacted]	[redacted]

[redacted]

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Effectiveness in the model: TNFi-exposed

	Distribution by health state at end of induction			Response and remission given response (over 8 weeks)		
	Active UC*	Response only	Remission		Probability of maintaining response	Percentage of responders in remission
ADA*	[redacted]	[redacted]	[redacted]	ADA*	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	TOF 5mg	[redacted]	[redacted]
				TOF 10mg	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	VED Q8W	[redacted]	[redacted]
				VED Q4W	[redacted]	[redacted]
CT	[redacted]	[redacted]	[redacted]	CT	[redacted]	[redacted]

*assumed same for INF and GOL

ERG comments:

- Assumption does not reflect clinical experience; clinical experience shows risk is greatest in first 6-12 months; and falls thereafter
- Likely to underestimate the duration of treatment and hence costs and QALYs of active treatments; unknown direction of bias in ICERs

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Safety outcomes in the model: Serious infections

- Probabilities of serious infections used in the company base case, with ranges for sensitivity analysis vs ERG preferred frequentist approach

Treatment	Company (Bayesian NMA RE)			ERG (Frequentist NMA RE)		
	Base case	Lower limit	Upper limit	Base case	Lower limit	Upper limit
Placebo	[redacted]	[redacted]	[redacted]	[redacted]		
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*By assumption, the company limits range for tofacitinib sensitivity analysis

ERG comments

- ERG frequentist estimates, give more plausible ranges of uncertainty
- Uncertainty associated with serious infections due to the rarity of events.

[redacted]

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Surgical complication parameter
Sources

	Value	Source
Colectomy rates	Elective colectomy: 0.058% per cycle; emergency colectomy: 0.021% per cycle	Misra et al. (2016), HES analysis; ERG scenario analysis: Chhaya et al. (2015)
Perioperative complications and mortality	2.8% mortality risk per operation	UK IBD audit 2008-2014
Post-surgery complications	1.5% per cycle	Ferrante et al. (2007); ERG scenario analysis: Japanese study by Arai et al. (2010)
All-cause mortality	Same as general population, adjusted for age and gender-mix	

[redacted]

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Health-related quality of life

- Company used utilities for pre and post-surgical states from Woehl *et al.* 2008; and the background utility ('no disease') is based on EQ-5D by age and gender in the general population (Ara *et al*. 2010):

Health state	Woehl *et al.* 2008 (company base case)	OCTAVE trials		Swinburn *et al.* 2012
		8 weeks	52 weeks	
Active UC	0.47	[redacted]	[redacted]	0.6317
Response	0.87	[redacted]	[redacted]	0.8944
Remission	1.00	[redacted]	[redacted]	1.0000
Post-surgery	0.82	NA	NA	0.6596

ERG comments:

- Utilities from OCTAVE trials are problematic because of the re-randomisation design and lack of intermediate assessments between week 8 and 52. ERG agrees that utilities by Woehl *et al.* provide a more appropriate source for base case parameters and also, are consistent with previous NICE TAs for UC.
- ERG use these estimates in ERG preferred analyses, and test scenarios based on the company's OCTAVE analyses and published sources (Swinburn et al.).

[redacted]

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Resource use and costs

Items	Company assumption	ERG comments
Drug acquisition	• TOF: confidential patient access scheme (PAS) discount • GOL: PAS discount assume 50 and 100 mg dose at same cost • INF: biosimilar cost included	• ERG analysis also include VED confidential PAS discount (results in part 2) • INF: biosimilar cost included
Conventional therapy	Assumed equal usage for balsalazide, mesalazine, olsalazine and sulfalazine	• Does not reflect UK practice; mesalazine is prescribed more • Update cost of CT with correct NHS price
Outpatient visit	Assumed 2 outpatient visits for patients in remission on maintenance treatment and 4.5 visits/ year for patients with a response but no remission	Monitoring and follow-up costs might not reflect clinical practice whereby treatment can be withdrawn within 8 weeks of a relapse => ERG explore scenario with additional costs for outpatient visits to enable treatment cessation within 8 weeks of a relapse (6.5 visits/year)
Drug administration	Assumed no administration cost for self-administered sub-cutaneous injections (golimumab, adalimumab)	ERG explore impact of assuming an initiation of self-administration
Stoma care	Company model omits ongoing costs of stoma care for post-colectomy health states (£426.36 per person in post-surgery assuming 40% have a stoma)	ERG include these costs in their base case and explore variation in scenario analysis

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Company's base case results *(with TOF PAS)*

TNF-i naïve

Strategy	ICER (£/QALY) fully incremental
Conventional Therapy (CT)	-
Adalimumab	Dominated
Golimumab	Dominated
Infliximab	Dominated
Tofacitinib	£8,554
Vedolizumab*	£615,057

TNF-i experienced

Strategy	ICER (£/QALY) fully incremental
CT	-
Tofacitinib	£10,302
Vedolizumab*	£7,838,238

[redacted]

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*Vedolizumab has a confidential PAS and results incorporating this are presented in part 2

Company's scenario analysis

Company scenarios	Brief rationale/assumption	ICERs for Tofacitinib vs CT (£/QALY)	
		TNFi-naïve	TNFi-exposed
Company base case		£8,554	£10,302
Tofacitinib maintenance dose mix *	[redacted] of patients receiving 5mg; [redacted] of patients receiving 10mg	£12,628	£13,947
OCTAVE trial utilities	EQ-5D data were collected in Tofacitinib Phase III clinical trials	£15,508	£18,276

ERG comments: company do not explore impact of key assumptions such as inclusion of costs associated with stoma care, cost-effectiveness results from alternative NMA models. ERG extend the range of scenario analyses in ERG additional analyses.

[redacted]

* This scenario accounts for the differences in costs as well as effectiveness of tofacitinib maintenance dose of 5mg and 10 mg

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Modelled QALYs

Study name (time horizon)	QALYs	
	TNFi- naive	TNFi-exposed
Current appraisal (lifetime)	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
MTA329 (lifetime, AG model)	Moderate to severe UC who failed at least 1 prior therapy	
	Ada: 10.82	
	Inf:10.81	
	Gol: 10.63	
	CT: 10.47	

ERG comments: QALY differences could be due to different methods used to calculate transition probabilities

[redacted]

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ERG additional analyses: TNFi Naïve (*with PAS for TOF*)

- ERG made some corrections* to company base case and developed a preferred base case (results including the PAS for VED presented in part 2)
- ERG ran several scenario analyses with results presented in part 2 to incorporate VED PAS

ICER TOF vs conventional	ICER TOF vs ADA	ICER TOF vs GOL	ICER TOF vs INF	ICER TOF vs VED
Company base case corrected by ERG				
£8,564	TOF dominant	TOF dominant	TOF dominant	£615,077 (SW)
Average age: 41 years				
£8,562	TOF dominant	TOF dominant	TOF dominant	£614,916 (SW)
+ ERG preferred NMAs for remission and response				
£8,584	TOF dominant	TOF dominant	TOF dominant	£590,046 (SW)
+ Frequentist NMA for serious infections				
£7,886	TOF dominant	TOF dominant	TOF dominant	£607,571 (SW)
*+ Cost of stoma-care = **ERG base case***				
£7,815	**TOF dominant**	**TOF dominant**	**TOF dominant**	**£607,571 (SW)**

SW: south-west

[redacted]

*ERG corrected 3 main errors: Error in cost calculation for elective surgery and conventional therapy, Error in estimation of weight – wastage, Error in incremental cost & QALY **Vedolizumab has a confidential PAS and results incorporating this are presented in part 2

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ERG additional analyses: TNFi exposed (*with PAS for TOF*)

ICER TOF vs CT	ICER TOF vs ADA	ICER TOF vs VED
Company base case corrected by ERG		
£10,311	TOF dominant	£7,838,381 (SW)
Average age: 41 years		
£10,304	TOF dominant	£7,798,892 (SW)
+ ERG preferred NMAs for remission and response		
£10,148	TOF dominant	TOF dominant
+ Frequentist NMA for serious infections		
£9,458	TOF dominant	TOF dominant
*+ Cost of stoma-care = **ERG preferred***		
£9,389	**TOF dominant**	**TOF dominant**

SW: south-west

[redacted]

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Equality issues

- No potential equality issues raised during scoping or by the company
- Patient perspective: Potential equality issues that should be considered are:
  - women who have not yet completed their family
  - people who consider surgery to be unacceptable due to cultural or religious factors
  - cost may also be a factor associated with lower income.

[redacted]

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Innovation (Company)

- First therapy in its class; offers a new mechanism of action in ulcerative colitis
- Oral therapy given as monotherapy; alternative to current parenteral treatments
- Small molecule that should not be associated with issues relating to immunogenicity
- Opportunity to stop treatment and restart with similar efficacy
- Rapid improvements in ulcerative colitis symptoms

[redacted]

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Key cost effectiveness issues

- Are the comparators appropriate for each sub-group?
  - Company base case excludes ADA in TNFi-exposed group
- What is the committee's view on:
  - The most appropriate source of health-related quality of life data?
  - Patient characteristics (e.g. age) being different depending on TNFi exposure status?
  - Importance of stoma care costs and surgery costs ?
  - Application of stopping rules in the model vs. clinical practice
- What is the committee preferred scenario?

[redacted]

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