For public

NICE National Institute for Health and Care Excellence

Tofacitinib for ulcerative colitis

Lead team's presentation

Background and clinical

1st appraisal committee meeting
Committee A
Lead team: Mohit Sharma, Rita Faria
ERG: Southampton Health Technology Assessments Centre
NICE technical team: Aminata Thiam, Victoria Kelly
Company: Pfizer

16.08.2018

© NICE 2018. All rights reserved. Subject to notice of rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

Key Clinical Issues

- Where is tofacitinib used in the treatment pathway?
- Are the results of the OCTAVE trials generalisable to NHS clinical practice?
  - Are the subgroup results based on prior treatment with TNF alpha inhibitors appropriate?
- Is the ERG's use of a frequentist approach for the NMA of serious infections appropriate?
- Is tofacitinib associated with an increased risk of serious infections?

Disease background

Ulcerative colitis (UC)

- Most common inflammatory bowel disease
- Unknown cause; possible hereditary, infectious, immunological factors
- Approximately 146,000 people have UC in England, of whom about 52% have moderate to severe active disease
  - defined as Mayo score = 6 to 12
- Symptoms are bloody diarrhoea, colicky abdominal pain, urgency and tenesmus; extra-intestinal manifestations (joints, eyes, skin and liver)
- Onset of symptoms and diagnosis usually occurs between 15 and 25 years, and second peak of incidence between 55 and 65 years
- Symptoms can relapse and go into remission for months or even years:
  - 50% of people will have at least 1 relapse per year
- Complications of ulcerative colitis may include haemorrhage, perforation, stricture formation, abscess formation and anorectal disease
- High risk of surgery
- No increased mortality (only in more severe disease); increased risk of bowel cancer

[redacted]

3

Disease background

Total and partial Mayo score definition

Component	Description	Points
Stool frequency	Normal	0
	1–2 stools more than usual	1
	3–4 stools more than usual	2
	≥ 5 stools more than usual	3
Rectal bleeding	No blood	0
	Streaks of blood < 50% of time with stool	1
	Obvious blood most of time with stool	2
	Blood alone passed	3
Endoscopic findings	Normal/inactive disease	0
	Mild disease	1
	Moderate disease	2
	Erosions	3
Physician's global assessment	Normal	0
	Mild	1
	Moderate	2
	Severe	3

Partial Mayo

Total Mayo include all 4 subscores

[redacted]

- Moderate to severely active ulcerative colitis: total Mayo score of 6 to 12
- Remission: total Mayo score ≤ 2 with no individual sub-score exceeding 1

4

Relevant NICE guidance

Technology appraisal (TA)		
TA	Intervention	Population
TA329 (Feb. 2015)	Infliximab Adalimumab Golimumab (MTA)	Adults with moderately to severely active UC whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies
TA342 (Jun. 2015)	Vedolizumab	Adults with moderately to severely active ulcerative colitis
NICE clinical guideline (CG)		
CG166: Ulcerative colitis: management (2013, partially updated in 2017)		

[redacted]
MTA: multiple technology assessment

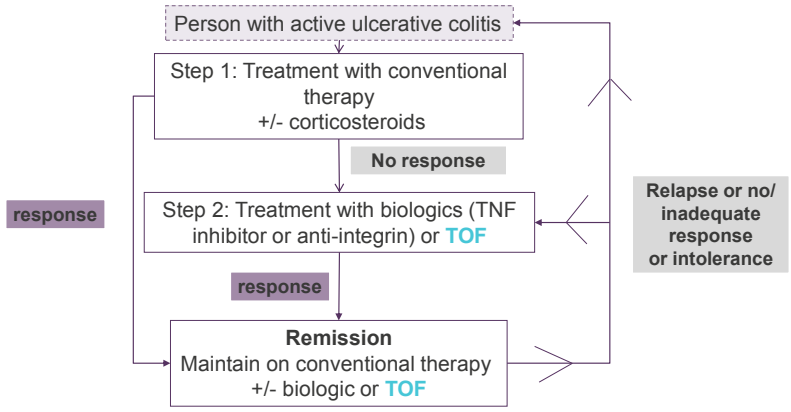
5

Tofacitinib citrate (Xeljanz)

Pfizer

Marketing authorisation	Treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent (MA granted on 1 August)
Mechanism of action	Intracellular janus kinase inhibitor that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of creating new blood cells in the body (hematopoiesis) and immune cell function
Administration & dose	Oral; recommended dose: • induction: 10 mg twice daily for 8 weeks • maintenance: 5 mg twice daily *Patients who do not achieve adequate therapeutic benefit by week 8: extension of induction for 8 weeks, followed by maintenance. Patients who have failed prior TNF antagonist or those who experience a decrease in response on 5 mg can receive 10 mg for maintenance. If therapy is interrupted, restarting treatment can be considered. If there has been a loss of response, re-induction with 10 mg may be considered.*
Stopping rules	Induction should be discontinued if no evidence of benefit by week 16
List price and PAS discount	• List price: 5 mg x 56 tab: £690.03; 10 mg x 56 tab: £1,380.06 (average yearly treatment: £10,350.42 per patient; subsequent annual cost: £8,970.39 per patient) • Simple discount PAS approved

Positons of tofacitinib in the treatment pathway



[redacted]

Key: TOF, tofacitinib

8

Decision problem

	Final NICE scope	Company submission
Population	People with moderately to severely active UC who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy (oral corticosteroids and/or immunosuppressant) or a TNF-alpha inhibitor	
Comparator	• TNF-alpha inhibitors (infliximab, adalimumab, golimumab) • Vedolizumab • Conventional therapies	Same as final scope with addition of placebo
Outcome	• measures of disease activity, including rates and duration of response, relapse and remission • achieving mucosal healing • health-related quality of life • rates of surgical intervention • time to surgical intervention • rates of hospitalisation • adverse effects of treatment • mortality	Absence of 'time to surgical intervention'; company explained that it was not assessed in the OCTAVE trials

[redacted]

8

Clinician perspective

Tofacitinib

- First drug of this class offering an alternative treatment to patients whose disease has not responded to current treatment options (treatment-refractory or corticosteroid-dependent)
- Step-change in the management of ulcerative colitis (UC)
- Oral medication, does not require infusion facilities
- Increase chance of avoiding surgical intervention (e.g. colectomy, which can impact on education, relationships and pregnancy)
- Small molecule so reduced chance of immunogenicity and loss of response over time compared to monoclonal antibody therapies (biologics)
- Good safety profile
- OCTAVE trials reflect UK clinical practice (although excluded people with protitis*)
- Variability of access in England due to commissioners interpreting of NICE guidance differently
- Locally defined treatment pathways (commissioners /secondary care)

[redacted]

*Protitis: disease extent less than 15cm from anal verge

9

Patient perspective

Tofacitinib and current UC treatment

- Tofacitinib offers an additional treatment option with a different mechanism of action; reduced likelihood of loss of response
- Convenience of oral therapy
- Concerns with current available treatments
  - far from optimal due to lack of response and safety concern
  - surgery associated with considerable anxiety and potential complications; can interfere with religious and cultural belief
  - injections and infusions (at hospital or home) can impact significantly on patient's lives and work (e.g., travel/parking cost; cannot travel due to storage requirement)
- Profound and devastating impact of UC symptoms on all aspects of life: study, socialise, participate in leisure activities, have intimate relationships.
- Burden on carer as UC is (to some degree) an invisible condition, unpredictable symptoms, extremely uncomfortable to talk about

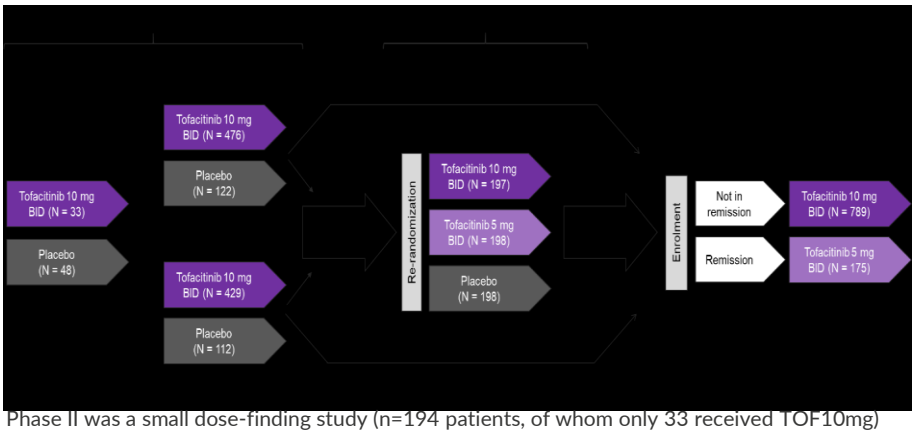
"Tofacitinib has completely changed my life…. I am now in my 4th year of taking tofacitinib and it is like I am a new person"

[redacted]

10

CONFIDENTIAL

Overview of company tofacitinib trial programme



- Phase II was a small dose-finding study (n=194 patients, of whom only 33 received TOF10mg) therefore company submission only focuses on Phase III OCTAVE trials (although included in NMA because it met inclusion criteria)
- **ERG comments**: reasonable; each study included UK patients although number was low ([redacted])

11

Summary of OCTAVE trials

	Induction cohort		Maintenance cohort
	OCTAVE Induction 1	OCTAVE Induction 2	OCTAVE Sustain
N (n prior TNF exposed)	598 (319)	541 (299)	593 (283)
Design	Phase III	Phase III	Phase III
Duration	9 weeks	9 weeks	52 weeks
Population	Patients with moderate to severe active UC **(results are presented by prior TNFi exposure)**		Patients who achieved clinical response in OCTAVE Induction 1 or 2 **(results are presented by prior TNFi exposure)**
Intervention	TOF 10mg BID	TOF 10mg BID	TOF 5mg & 10mg BID
Comparator	placebo	placebo	placebo
Endpoints	1° remission (central & local read)* 2° mucosal healing; clinical response; clinical remission; IBDQ; SF-36; EQ-5D (all outcomes measured at 8 wk)		1° remission (central & local read)* 2° mucosal healing; sustained steroid-free remission** (24 wk); clinical response; clinical remission (all outcomes measured at 52 wk)

[redacted] BID, twice daily; EQ-5D, 5-dimension EuroQol questionnaire; IBDQ, Inflammatory Bowel Disease Questionnaire; SF-36, 36-Item Short Form Survey
*Remission is measured based on centrally & locally assessment of endoscopic subscores; only locally read included in NMA; **although corticosteroids used for induction of remission, because of their side-effect profile they are not typically used for long-term management of UC, making corticosteroid-free remission an important goal

12

Definition of clinical endpoints

Endpoints		Definition		
Primary	Remission	Mayo score of ≤ 2, no individual subscore exceeding 1 point	+	rectal bleeding subscore = 0
Secondary	Clinical Remission			
	Clinical Response	Decrease from baseline Mayo score of ≥ 3 points and ≥ 30%, with a decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1		
	Mucosal Healing	Mayo endoscopic subscore of ≤ 1		
	Endoscopic Remission	Mayo endoscopic subscore of 0		

- Definition of clinical remission and remission are almost identical and results are very similar; only the outcomes of clinical remission and clinical response contribute to the economic model *(clinical remission is included in clinical response)*

- Mucosal healing and endoscopic remission are measured using endoscopy via 2 routes :
  - Locally assessed by study site investigator; used in clinical practice and therefore used in in **base case network meta-analysis and cost-effectiveness model**
  - Centrally assessed by central reader; requested by EMA; results could have been confounded by local assessment; used in **sensitivity analysis**

13

CONFIDENTIAL

Results by subgroup: Proportion of patients in clinical remission & response (1)

OCTAVE 1 & 2 pooled data at week 8 (locally read scores)

Subgroup: prior-TNFi treatment	TOF 10 mg n/N (%)	PBO n/N (%)	Difference (95% CI); p-value
Clinical remission			
TNFi-naive	[redacted]	[redacted]	[redacted]
TNFi-exposed	[redacted]	[redacted]	[redacted]
Clinical response			
TNFi-naive	[redacted]	[redacted]	[redacted]
TNFi-exposed	[redacted]	[redacted]	[redacted]

- [redacted]

14

CONFIDENTIAL

Results by subgroup: Proportion of patients in clinical remission & response (2)

OCTAVE Sustain at week 52 (locally read scores)

Subgroup: prior-TNFi treatment	TOF 5 mg n/N (%)	PBO n/N (%)	Difference vs PBO (95% CI)	TOF 10 mg n/N (%)	Difference vs PBO (95% CI)
Clinical Remission					
TNFi-naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNFi-exposed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Response					
TNFi-naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNFi-exposed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- [redacted]

15

Adverse events

OCTAVE trials

Adverse event (AE)	Phase II trial		OCTAVE Induction 1		OCTAVE Induction 2		OCTAVE Sustain		
	TOF 10 mg (N=33)	PBO (N=48)	TOF 10 mg (N=476)	PBO (N=122)	TOF 10 mg (N=429)	PBO (N=112)	TOF 5 mg (N=198)	TOF 10 mg (N=196)	PBO (N=198)
Serious AE, n (%)	2 (6)	4 (8)	16 (3)	5 (4)	18 (4)	9 (8)	10 (5)	11 (6)	13 (7)
Serious infection, n (%)	2 (6)	0	6 (1)	0	1 (0.2)	0	2 (1)	1 (1)	2 (1)

- 5 deaths occurred, 1 was related to tofacitinib (in OCTAVE Open)
- **ERG comments**: Overall, and in comparison with evidence from the use of tofacitinib in patients with rheumatoid arthritis, no new safety signals were identified.

[redacted]

16

Company's network meta-analysis (NMA)

Description

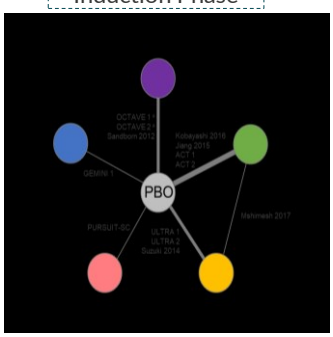
- Company performed a Bayesian network meta-analysis (NMA) to estimate the relative efficacy and safety between tofacitinib [TOF] (5mg and 10mg) and
  - TNF-alpha inhibitors: adalimuab [ADA] (40/80/160mg); golimumab [GOL] (200/100mg and 100 mg); infliximab [INF] (5mg/kg)
  - vedolizumab [VED] (300mg Q4W and Q8W)
  - conventional therapies (placebo)
- 2 evidence networks for each induction and maintenance cohort, to match OCTAVE trials
  - ***TNFi naïve/ TNFi experienced***
- Used a **multinomial probit model** for clinical response and clinical remission-this modelled clinical response and remission jointly to avoid impossible predictions such as more patients experience clinical remission than experience clinical response.
- **Efficacy endpoints**: clinical response, clinical remission, mucosal healing *(only clinical response, clinical remission were included in the economic model)*
- **Safety endpoints**: discontinuations due to adverse events, serious adverse events, and serious infections *(only serious infections were included in the economic model).*

[redacted]

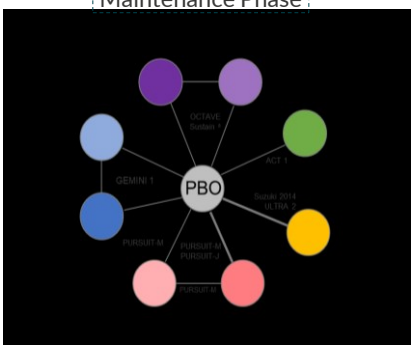
17

Company's network for TNFi Naïve

Induction Phase



Maintenance Phase



[a] Local read

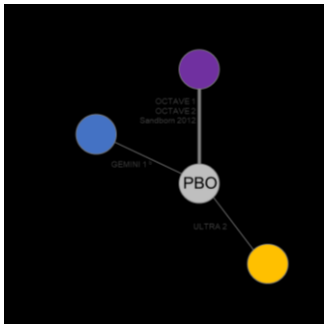
Abbreviations: PBO, placebo; Q4W, every 4 weeks; G8W, every 8 weeks.

[redacted]

18

Company's network for TNFi Exposed

Induction Phase



Maintenance Phase

[b] TNFi failures

Abbreviations: PBO, placebo; Q4W, every 4 weeks; G8W, every 8 weeks.

[redacted]

19

CONFIDENTIAL

Company's NMA Results: TNFi Naïve (1)

- In the Induction phase for TNFi naïve [redacted]

Random effects model used	Treatment effect (probit scale*) Median (95% CrI)	Proportion of patients in		SUCRA**
		Clinical response	Clinical remission	
Induction Phase				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]

*On the probit scale a negative coefficient indicates treatment is more effective than placebo

**The surface under cumulative ranking curve (SUCRA) value is used to rank treatments based on their probability of ranking first through to last among the treatment options. If the SUCRA probability is 0% the treatment always ranks last and if it is 100% the treatment always ranks first

[redacted]

20

CONFIDENTIAL

Company's NMA Results: TNFi Naïve (2)

- In the maintenance phase for TNFi naïve, TOF 10 mg had the largest treatment effect on clinical remission and clinical response compared with PBO

Fixed effects model used	Treatment effect (probit scale) Median (95% CrI)	Proportion of patients in		SUCRA
		Clinical response	Clinical remission	
Maintenance Phase				
PBO	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10 mg	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]

ERG comments: Preferred Random effects model. Results of this analysis showed wider credible intervals *=> ERG used this model in its preferred base case*

[redacted]

21

CONFIDENTIAL

Company's NMA results: TNFi Exposed

- In both the induction and maintenance phase for TNFi exposed, TOF had the largest treatment effect on clinical remission and clinical response compared with PBO

Fixed effects model used	Treatment effect (probit scale) Median (95% CrI)	Proportion of patients in		SUCRA
		Clinical response	Clinical remission	
Induction Phase				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Phase				
PBO	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10 mg	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
VED Q8W	[redacted]	[redacted]	[redacted]	[redacted]
VED Q4W	[redacted]	[redacted]	[redacted]	[redacted]

ERG comments: Preferred Random effects model for induction phase. Results of this analysis showed wider credible intervals *=> ERG used this model in its preferred base case*

[redacted]

22

CONFIDENTIAL

Company's Serious Infections NMA *(induction phase only)*

Comparator	Treatment effect vs placebo, median (95% CrI), odds ratios	
	Company base-case (random effects)	ERG alternative model selection (fixed effects)
TOF	[redacted]	[redacted]
INF	[redacted]	[redacted]
ADA	[redacted]	[redacted]
GOL	[redacted]	[redacted]
VED	[redacted]	[redacted]
AZA	[redacted]	[redacted]

ERG comments:

- ERG replication of company fixed effect model showed high level of uncertainty with very wide credible intervals which persisted in a fixed effect model
- ERG noted this is probably caused by the lack of any serious infections across placebo arms in the 3 TOF studies (in the other studies included in the NMA only 1 trial had 0 events)
- ERG ran a frequentist NMA to adjust for this *(added 0.5 to zero events)*. Results showed a **non-significant** increased risk of serious infection with TOF [redacted]

=> ERG used this analysis in its preferred base case

[redacted]

23

Key Clinical Issues

- Where is tofacitinib used in the treatment pathway?
- Are the results of the OCTAVE trials generalisable to NHS clinical practice?
  - Are the subgroup results based on prior treatment with TNF alpha inhibitors appropriate?
- Is the ERG's use of a frequentist approach for the NMA of serious infections appropriate?
- Is tofacitinib associated with an increased risk of serious infections?

[redacted]

24