NICE National Institute for Health and Care Excellence

PART 1
AIC
Redacted

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

Lead team presentation

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Company: Galapagos
17th March 2022

Key issues

Issue No.	Description	ICER impact
1 3 7	**Precise line of therapy:** Which is the most appropriate line of therapy for filgotinib? **Sequence of biologics:** Does re-randomisation preclude an unbiased estimate of the long-term effectiveness of treatment sequence? **Third-line population not adequately modelled**	
5	**Conventional therapy:** Is conventional therapy an appropriate comparator?	
12	**Utility values:** Are the baseline utility values appropriate?	
11	**Health related quality of life:** Which are the most appropriate utility values?	
8	**Loss of response:** Given the lack of evidence, is assumption for equal loss of response acceptable?	
9	**Constant loss of response:** Is assuming constant loss of response appropriate?	
13	**Dose escalation**: Is dose escalation appropriate for comparators?	
6	**Treatment sequences**: Which is most appropriate treatment sequence for filgotinib?	
4	**Maintenance phase NMA**: Is the maintenance phase NMA appropriate?	
10	**Probability of pouchitis**: which is most appropriate to use acute or chronic?	

Key: Large impact Small/moderate impact Unknown impact

Background: Ulcerative colitis (UC)

- **Ulcerative colitis:**
  - Lifelong, progressive disease characterised by relapsing and remitting episodes of inflammation of the rectal and colonic mucosa.
  - Tiny ulcers develop on the surface of the lining of the colon (bleed and produce pus).
- **Epidemiology:**
  - Around 115,000 people in England have UC (52% moderate to severe disease - defined as Mayo clinic score - 6 to 12).
  - Incidence peaks between 15 and 25 years. Smaller peak between 55 and 65 years.
- **Risk factors:**
  - Unknown cause. Hereditary, infectious and immunological factors possible
- **Symptoms:**
  - Bloody diarrhoea, colicky abdominal pain, urgency and tenesmus; extra-intestinal manifestations (joints, eyes, skin and liver)
- **Complications:**
  - Haemorrhage, perforation, stricture formation, abscess formation and anorectal disease.
- **Treatments**:
  - Pharmacological: conventional therapy (aminosalicylates, corticosteroids or thiopurines) and biologics (adalimumab, golimumab, infliximab, vedolizumab, tofacitinib or ustekinumab).
  - Surgery: colectomy.

Filgotinib (Jyseleca, Galapagos)

Marketing authorisation	• 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 agent • Granted in January 2022 • Contraindications – hypersensitivity to active substance or excipients, active tuberculosis, active serious infections, pregnancy
Mechanism of action	• Next-generation Janus kinase (JAK) inhibitor that is a preferential and reversible inhibitor of JAK1. • Modulates the cytokine signalling pathway by preventing the phosphorylation and activation of signal transducers and activators of transcription by JAKs
Administration	• 200mg dose once daily indefinitely, until loss of response • 100mg dose for people with moderate or severe renal impairment (creatinine clearance 15 to <60 mL/min).
Price	• List price: £863.10 per bottle of 30, 200mg or 100mg tablets • Equivalent to £10,508.24 per year. • Patient access scheme (PAS) discount in place (confidential)

Source: table 2, CS

Patient experts perspective

Living with ulcerative colitis

- Ulcerative colitis has a profound and devastating impact on all aspects of a person's life
- Disease severity is wide raging and each individual has their own experience: people feel embarrassed, frustrated, sad and fear need of surgery or developing cancer
- Symptoms include frequent diarrhoea, abdominal pain and fatigue, anaemia, extra intestinal manifestation, ability to work, study and socialise

Unmet need for ulcerative colitis

- Range of treatments available but people who experience a lack of response face the prospect of surgery with considerable anxiety
- People feel dissatisfied with current treatments, side effects from steroids are extremely unpleasant and concerned about long-term safety profile of other treatments including biologics

Filgotinib

- Offers a novel and effective treatment option which would increase choice for clinicians and people with ulcerative colitis
- Gives greater personalised treatment options and has the potential significantly improve lives

"My life was terrible quality. I missed out on opportunities at work, very rarely went anywhere and people would comment on my features from the steroids, and they said I looked a strange green-yellow colour"

Source: patient expert submission

Clinical experts perspective

Aim of drug treatment for moderately to severely active ulcerative colitis

- Ulcerative colitis significantly impacts daily life due to bowel urgency and incontinence
- Main aim of the treatment is to induce clinical and endoscopic remission leading to normalisation of quality of life

Unmet need for ulcerative colitis

- Approximately 1/3rd people relapse during first 12 months on treatment
- Most people do not respond fully (response ~60%, remission 30-40%) to other biologics
- Infliximab is affected by loss of response while the performance of other anti-TNFs is suboptimal
- Tofacitinib (another JAK inhibitor) is associated with an increased cardiovascular risk

Filgotinib

- Filgotinib is targeted JAK1 inhibitor administered orally, more acceptable and people would welcome this treatment
- Rapid mechanism of action, lesser side effects and lower psychological barriers to treatment
- Easier to use with lower hospital resource requirement and less nursing time

◉ Are all JAK inhibitors associated with an increased cardiovascular risk?

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JAK: Janus Kinase; TNF: tumour necrosis factor

Source: clinical expert submission

Decision problem (1)

	Final scope issued by NICE	Company	ERG comment
Population	People with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response or were intolerant to conventional therapy, or a biologic agent	As per scope	As per scope **Issues regarding the precise line of therapy**
Intervention	Filgotinib	As per scope	As per scope
Comparator	• Conventional therapies • Infliximab, adalimumab and golimumab • Tofacitinib • Ustekinumab • Vedolizumab	As per scope	Conventional therapies, excluded from the network meta-analyses. But ERG questions relevance.

Source: ERG report table 2.1

Decision problem (2)

	Final scope issued by NICE	Company	ERG comment
Outcomes	• Mortality • Measure of disease activity • Rates of and duration of response, relapse and remission • Rates of hospitalisation • Rates of surgical intervention • Endoscopic healing (combines endoscopic and histological healing) • Corticosteroid-free remission • Achieving mucosal healing • Adverse effects of treatment • Health-related quality of life	• Aligned with scope except for mortality • SELECTION trial does not provide data on filgotinib's effect on mortality due to ulcerative colitis	As per scope

Source: ERG report table 2.1

Key issues after technical engagement

No	Summary of ERG's key issues considered at technical engagement	Status
1 3 7	**Precise line of therapy:** Which is the most appropriate line of therapy for filgotinib? **Sequence of biologics:** Does re-randomisation preclude an unbiased estimate of the long-term effectiveness of treatment sequence? **Third-line population:** not adequately modelled	For discussion
5	**Conventional therapy:** Is conventional therapy an appropriate comparator?	For discussion
12	**Utility values:** Are the baseline utility values appropriate?	For discussion
11	**Health related quality of life:** Which are the most appropriate utility values?	For discussion
8	**Loss of response:** Given the lack of evidence, is assumption for equal loss of response acceptable?	For discussion
9	**Constant loss of response:** Is assuming constant loss of response appropriate?	For discussion
13	**Dose escalation**: Is dose escalation appropriate for comparators?	For discussion
6	**Treatment sequences**: Which is most appropriate treatment sequence for filgotinib?	For discussion
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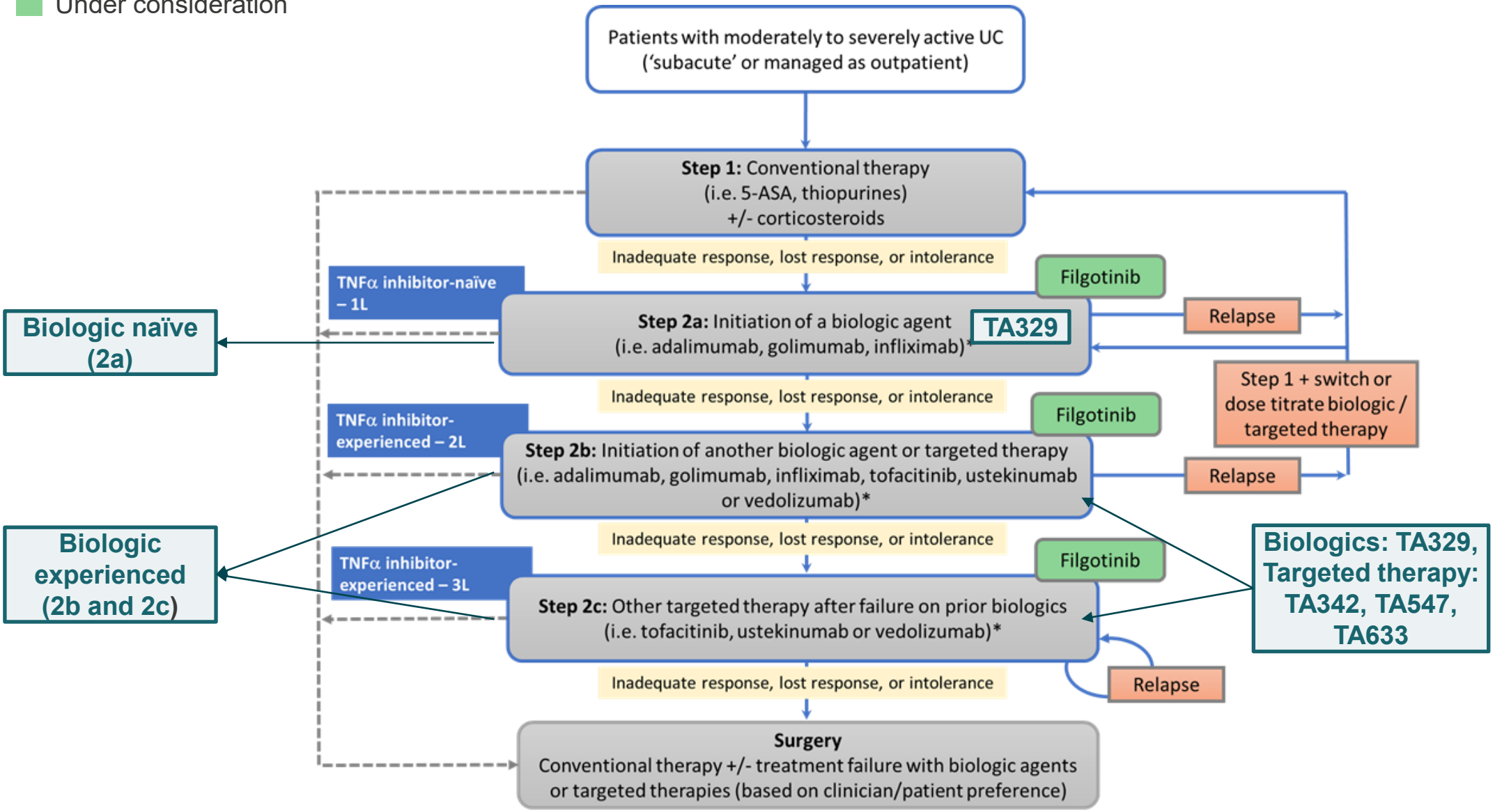
NMA: network meta-analyses

Ulcerative colitis treatment pathway

Under consideration



*Patients in response/remission remain on therapy with 12-month review

Where would filgotinib be used in the treatment pathway?

Source: Figure 2.1, ERG report

Existing guidance on ulcerative colitis

Guidance	Class	Intervention	Population	Pathway positioning
TA329 (2015)	Tumour necrosis factor [TNF] alpha inhibitor	Infliximab, Adalimumab, Golimumab	Adults with moderately to severely active ulcerative colitis after the failure of conventional therapy	Biologic naïve (2a), Biologic experienced (2b and 2c)
TA342 (2015)	Anti-integrin agent	Vedolizumab	Adults with moderately to severely active ulcerative colitis after the failure of conventional therapy or TNF alpha inhibitor	Biologic naïve (2a)*, Biologic experienced (2b and 2c)
TA547 (2018)	Janus kinase (JAK) inhibitor	Tofacitinib	Adults with moderately to severely active ulcerative colitis after the lack of toleration or inadequate response/failure of conventional therapy or biologic agent	Biologic naïve (2a)*, Biologic experienced (2b and 2c)
TA633 (2020)	Anti-interleukin	Ustekinumab	Adults with moderately to severely active ulcerative colitis after the failure of conventional therapy or biologic agent if TNF inhibitor has failed or cannot be tolerated	Biologic experienced (2b and 2c)

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* TA633 - “In current practice, most patients will be offered a tumour necrosis factor (TNF)-alpha inhibitor first when conventional therapy has failed. This is because biosimilars are available in this class, which have a lower price”

Issues 1, 3 & 7: Precise line of therapy of filgotinib

Background: Filgotinib at multiple positions in biologic experienced population (2b & 2c), but trial groups biologic experienced population together

Company

- NMA and CEA assess filgotinib at first-line treatment for biologic-naïve (2a) and biologic-experienced (2b & 2c) people at second and third-line
- Subgroup stratification (biologic-naïve [2a] and biologic-experienced [2b & 2c]) in line with NICE scope and TA633, TA547 and TA342
- Conduced scenario assuming same efficacy at second and third-line due to lack of data

Clinical experts

- Stratification by biologic exposure is not attempted before and likely impossible at this stage

ERG

- Decision problem could be restricted to second-line (2b) in biologic experienced
- Biologic experienced people achieving remission at 10 week decreases from 16.3% (2b) to 7.4% (2c) compared with placebo from 2% (2b) to 1.6% (2c)
- Estimates at third-line (2c) should informed by systematic review or by plausible assumptions where no efficacy estimates are available

◉ Which lines of therapy should filgotinib be considered at?
◉ Can results for biologic experienced be assumed to apply at 2nd (2b) and 3rd line (2c)?

NICE **2a: Biologic-naïve; 2b: biologic-experienced (2nd biologic); 2c: biologic-experienced (3rd or later biologic)**

NMA: network meta-analysis; CEA: cost-effectiveness analysis

Issue 5:Conventional therapy not appropriate comparator

Background:

- Comparators in NICE scope:
  - Biologics (infliximab, adalimumab and golimumab [2a, 2b & 2c])
  - Targeted therapies (tofacitinib, ustekinumab, vedolizumab [2b & 2c])
  - Conventional therapy

Company

- Consider conventional therapy as a relevant comparator (NICE scope and previous NICE technology appraisals in ulcerative colitis)
- Conventional therapies included in systematic reviews and NMAs with studies that only included conventional therapies without any biologic excluded

Clinical experts

- Not a relevant comparator. Filgotinib only used after conventional therapy

ERG

- Agree with experts and do not include in its base case

◉ Is conventional therapy a relevant comparator for filgotinib?

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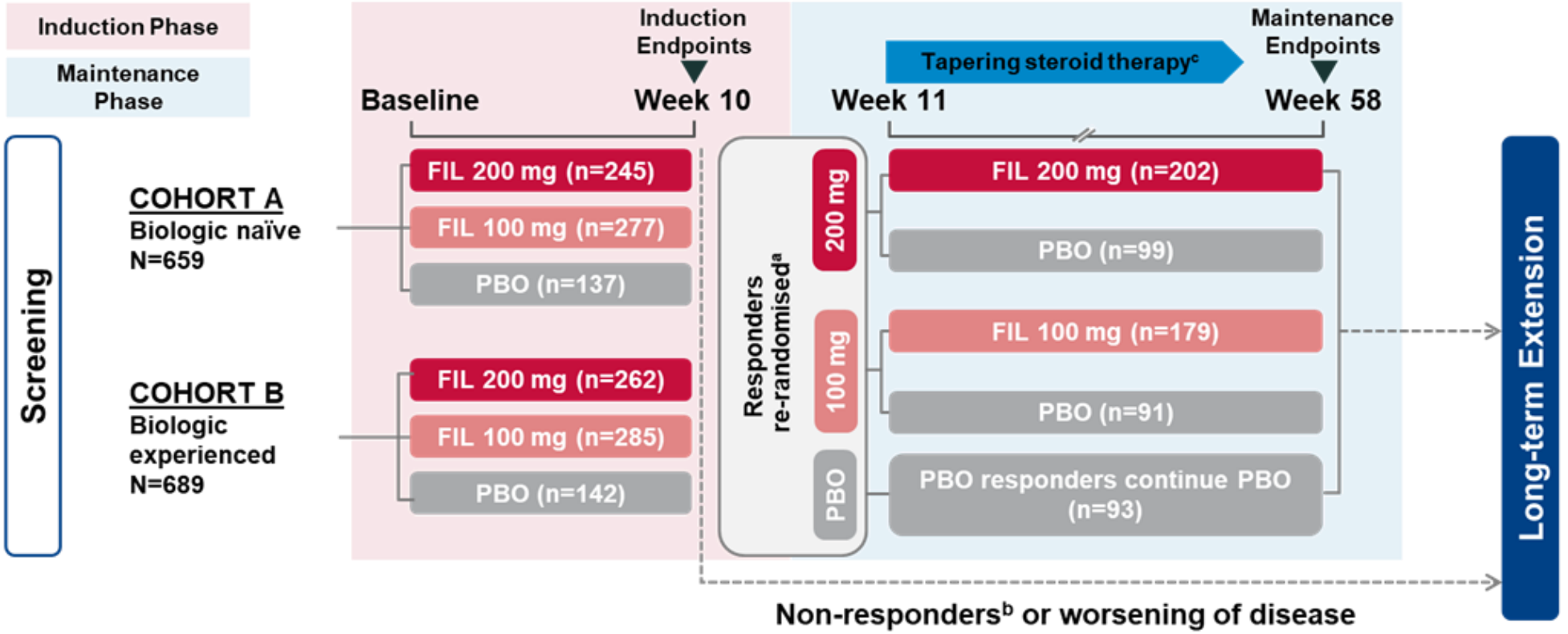
2a: Biologic-naïve; 2b: biologic-experienced (2nd biologic); 2c: biologic-experienced (3rd or later biologic)

NMA: network meta-analysis

SELECTION: trial schema



- **SELECTION trial:** is a combined phase 2b/3, double blinded, randomised trial designed and analysed as three separate studies: two induction studies and a maintenance study
- **Induction studies** (10 weeks): biologic-naïve (cohort A, 2a) and biologic-experienced (cohort B, 2b+)
- **Maintenance study** (weeks 11-58): people on active treatment, completed induction studies, and achieved either EBS remission or MCS response were re-randomised

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EBS: endoscopy/bleeding/stool frequency; MCS: Mayo clinic score

Source: Figure 5, CS

Mayo clinic score (MCS) for ulcerative colitis

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

- Each part is rated from 0 to 3, giving a total score of 12
- Moderate to severely active ulcerative colitis: total Mayo score of 6 to 12

◉ ***What is a clinically meaningful improvement in Mayo clinic score?***

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UC: ulcerative colitis

Outcomes from SELECTION

Endpoints	Definition
Primary endpoint (induction and maintenance)	
Proportion of people achieving EBS remission	Endoscopic sub score of 0 or 1, RB sub score of 0, and at least one-point decrease in SF from baseline to achieve a sub score of 0 or 1
Secondary endpoints (induction and maintenance)	
MCS response	MCS reduction of ≥3 points, at least 30% from baseline with decrease in RB sub score of ≥1 point or an absolute RB sub score of 0 or 1
MCS remission	MCS of 2 or less and no single sub score higher than 1
MCS remission*	RB, SF, and PGA sub scores of 0 and an endoscopic sub score of 0 or 1; overall MCS of ≤1
Mucosal healing	An endoscopic sub score of 0 or 1
Endoscopic sub score of 0	Endoscopic sub score of 0
Geboes histologic remission	Grade 0 of ≤0.3, Grade 1 of ≤1.1, Grade 2a of ≤2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0
Secondary endpoints (maintenance)	
Sustained EBS remission	EBS remission at both weeks 10 and 58
6-months CS-free remission	EBS remission with no CS use for the indication of for at least 6 months prior to week 58 among subjects who are on corticosteroid at re-baseline

* Alternative definition

NMA outcomes

CS: corticosteroids; EBS: endoscopy/bleeding/stool frequency; MCS: Mayo clinic score; PGA: Physician's Global Assessment; RB: rectal bleeding; SF: stool frequency

Source: table 14, CS

SELECTION: Baseline characteristics

Not evenly distributed at induction for biologic naïve (2a) but evenly distributed biologic experienced induction (2b+) and maintenance

Baseline characteristics	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo
Induction study cohort A (biologic naive)			
Age, mean (SD)	42 (13.1)	42 (13.3)	41 (12.9)
Sex at birth, Female, n (%)	122 (49.8%)	120 (43.3%)	50 (36.5%)
Geographic region			
United states	14 (5.7%)	33 (11.9%)	19 (13.9%)
Non-US	231 (94.3%)	244 (88.1%)	118 (86.1%)
Concomitant use of systemically absorbed corticosteroids and immunomodulators			
Systemic corticosteroids	54 (22.0%)	67 (24.2%)	34 (24.8%)
Immunomodulators	53 (21.6%)	63 (22.7%)	33 (24.1%)
Systemic corticosteroid and immunomodulators	20 (8.2%)	19 (6.9%)	8 (5.8%)

ERG comment

- Filgotinib 200 group has more women (49.8%) than the placebo group (36.5%)
- Filgotinib 200 group has more non-US patients (94.3%) than the placebo group (86.1%)
- Baseline differences might have caused an overestimate of the treatment effect

Do these differences in baseline characteristics impact on validity?

Source: CS, table 9

SELECTION results: induction phase

Endpoint % [95% CI]	Cohort	Filgotinib 200 mg A: n= 245; B: n=262	Placebo A: n= 137; B: n=142	Difference % [95% CI]
EBS remission	2a	26.1% (20.4% - 31.8%)	15.3% (8.9% - 21.7%)	10.8% (2.1% -19.5%)
	2b+	11.5% (7.4% -15.5%)	4.2% (0.6% - 7.9%)	7.2% (1.6% - 12.8%)
MCS response	2a	66.5% (60.4% - 72.6%)	46.7% (38.0% - 55.4%)	19.8% (9.0% - 30.6%)
	2b+	53.1% (46.8% - 59.3%)	17.6% (11.0% - 24.2%)	35.4% (26.2% - 44.7%)
MCS remission	2a	24.5% (18.9% - 30.1%)	12.4% (6.5% - 18.3%)	12.1% (3.8% - 20.4%)
	2b+	9.5% (5.8% -13.3%)	4.2% (0.6% - 7.9%)	5.3% (-0.1% - 10.7%)
Mucosal healing	2a	33.9% (27.7% - 40.0%)	20.4% (13.3% - 27.6%)	13.4% (3.9% - 23.0%)
	2b+	17.2% (12.4% - 21.9%)	7.7% (3.0% - 12.5%)	9.4% (2.5% - 16.3%)
Endoscopic sub score 0	2a	12.2% (7.9% to 16.6%)	3.6% (0.1% - 7.2%)	8.6% (2.9% - 14.3%)
	2b+	3.4% (1.0% - 5.8%)	2.1% (0.0% - 4.8%)	1.3% (-2.5% - 5.1%)
Geboes Histologic	2a	35.1% (28.9% - 41.3%)	16.1% (9.5% - 22.6%)	19.0% (9.9% - 28.2%)
	2b+	9.8% (14.8% - 24.9%)	8.5% (3.5% - 13.4%)	11.4% (4.2% - 18.6%)
MCS remission*	2a	12.2% (7.9% - 16.6%)	4.4% (0.6% - 8.2%)	7.9% (1.9% - 13.8%)
	2b+	3.8% (1.3% - 6.3%)	2.1% (0.0% - 4.8%)	1.7% (-2.2% - 5.6%)

- Statistically significant proportion of people achieved EBS remission at week 10 compared to placebo in both cohorts

* Alternative definition; EBS: endoscopy/bleeding/stool frequency; MCS: Mayo clinic score

2a: Biologic-naïve; 2b: biologic-experienced (2nd biologic); 2c: biologic-experienced (3rd or later biologic)

NMA outcomes

Source: table 3.11 and 3.12, ERG report

SELECTION results: maintenance phase

Endpoint % [95 % CI]	Maintenance phase		
	Filgotinib 200 mg (n=199)	Placebo (n=98)	Difference Endpoint %
EBS remission	37.2% (30.2% - 44.2%)	11.2% (4.5% -18.0%)	26.0% (16.0% - 5.9%)
Sustained EBS remission	18.1% (12.5% - 3.7%)	5.1% (0.2% - 0.0%)	13.0% (5.3% to 20.6%)
MCS response	66.8% (60.0% - 73.6%)	32.7% (22.9% - 42.4%)	34.2% (22.1% - 46.3%)
MCS remission	34.7% (27.8% - 41.5%)	9.2% (3.0% - 15.4%)	25.5% (16.0% - 35.0%)
Mucosal healing	40.7% (33.6% - 47.8%)	15.3% (7.7% - 22.9%)	25.4% (14.8% - 36.0%)
Endoscopic sub score 0	15.6% (10.3% - 20.9%)	6.1% (0.9% -11.4%)	9.5% (1.8% - 17.1%)
Geboes Histologic	38.2% (31.2% - 45.2%)	13.3% (6.0% - 20.5%)	24.9% (14.6% - 35.2%)
MCS remission*	22.1% (16.1% - 28.1%)	6.1% (0.9% - 11.4%)	16.0% (7.8% - 24.2%)
6-months CS-free remission	27.2% (17.5% - 36.8%)	6.4% (0% - 14.4%)	20.8% (7.7% - 33.9%)

- Statistically significant proportion of people achieved EBS remission at week 58 compared to placebo

Would only those responding to treatment continue to maintenance?

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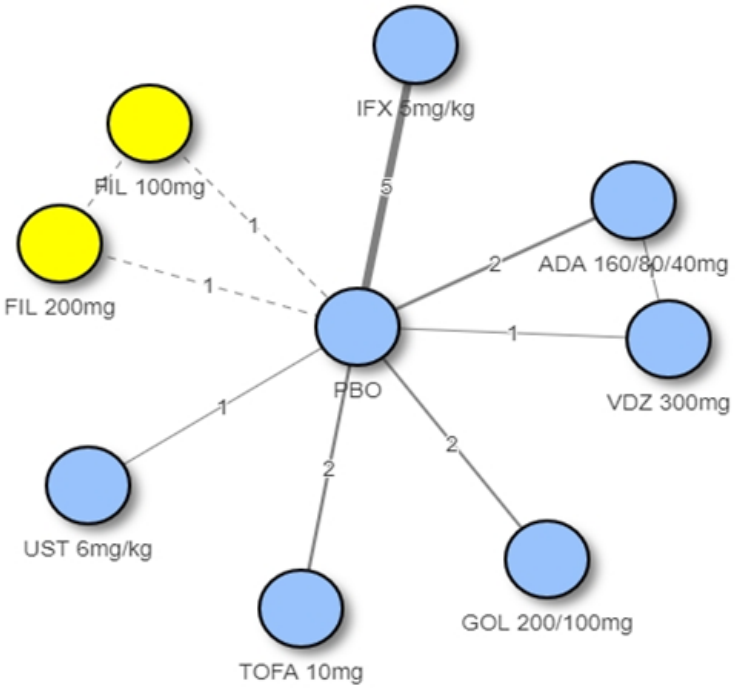
* Alternative definition; CS: corticosteroids; EBS: endoscopy/bleeding/stool frequency; MCS: Mayo clinic score

NMA outcomes

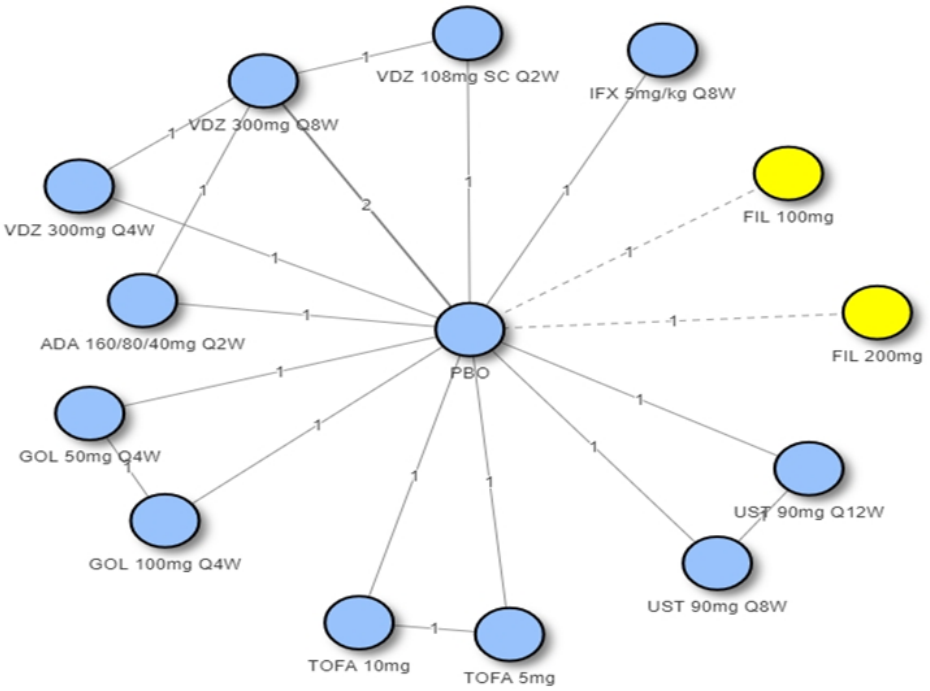
Source: table 3.13, ERG report

Company's NMA: Biologic-naïve (2a)

Induction (MCS response and remission)



Maintenance (MCS response and remission)



ERG comments

- Induction phase NMA informs effectiveness of filgotinib for response and remission
- Maintenance phase NMA not valid:
  - No decision on treatment switching to be made at this point
  - Population is heterogeneous. Will vary according to response to each treatment during induction
  - Estimates from maintenance phase required to inform model

◉ Is the company's approach for maintenance NMAs appropriate?

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ADA: adalimumab; FIL: filgotinib; GOL: golimumab; IFX: infliximab; PBO, placebo TOFA: tofacitinib; UST: ustekinumab; VDZ: vedolizumab Q4W, every 4 weeks; G8W, every 8 weeks: Q12W: every 12 weeks

Source: Figures 8 & 9, CS

NMA results: biologic-naive – 2a (induction)

Filgotinib 200mg [redacted]

*On the probit scale a negative coefficient indicates that filgotinib 200mg is more effective than the comparator at increasing the probability of response. Zero is the point of no difference

ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; TOF: tofacitinib; UST: ustekinumab; VDZ: vedolizumab

Source: table 25, CS

NMA results: biologic-naïve – 2a (maintenance)

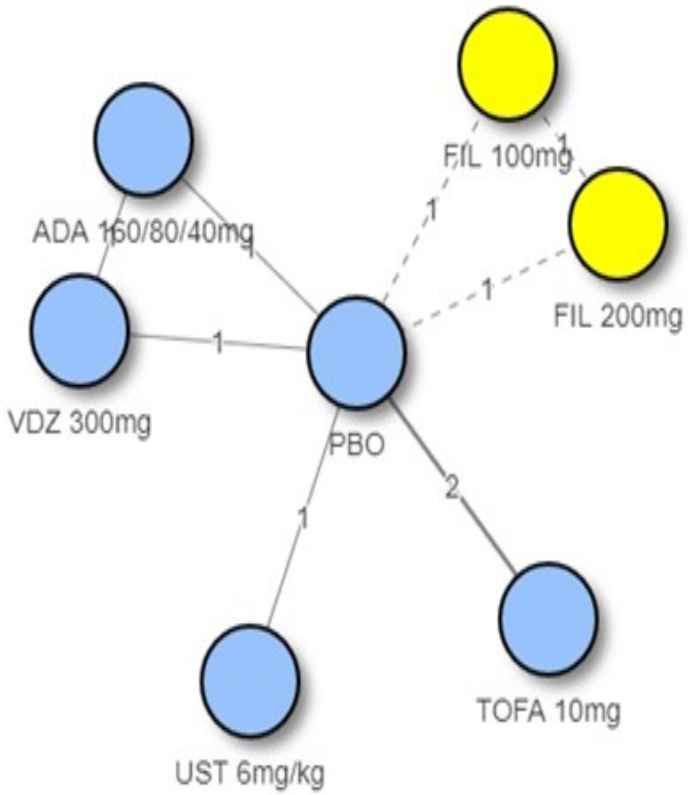
Filgotinib 200 mg [redacted]

NICE *On the probit scale a negative coefficient indicates that filgotinib 200mg is more effective than the comparator at increasing the probability of response. Zero is the point of no difference

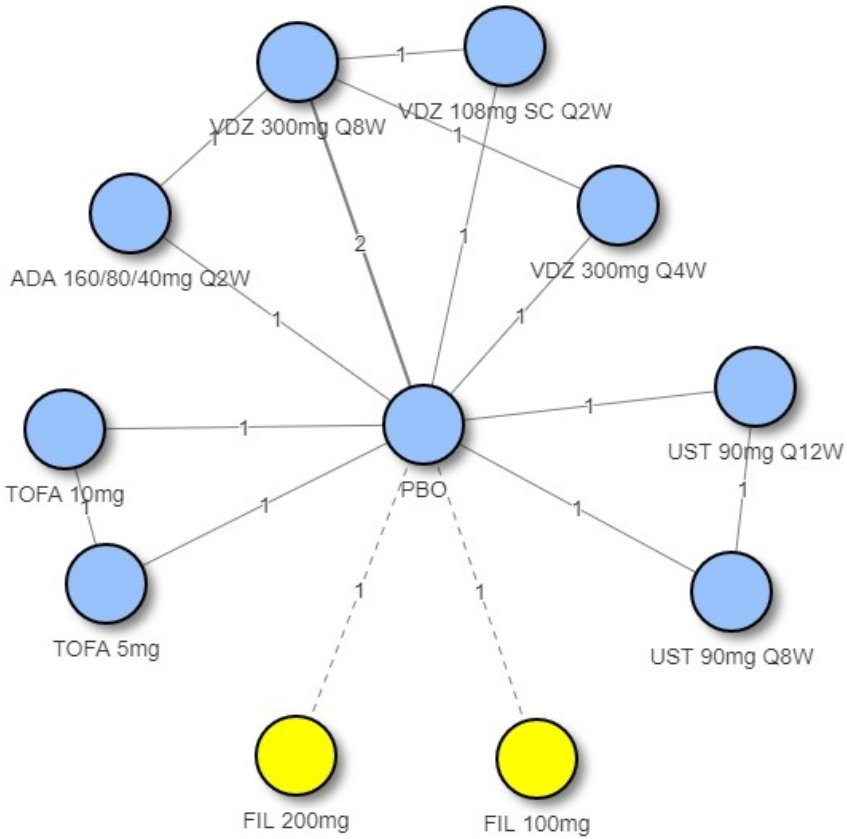
Source: Table 26, CS

Company's NMA: Biologic-experienced (2b+)

Induction



Maintenance



ERG comments are as per biologic-naïve (2a) population

ADA: adalimumab; FIL: filgotinib;; IFX: infliximab; PBO, placebo TOFA: tofacitinib; UST: ustekinumab; VDZ: vedolizumab Q4W, every 4 weeks; G8W, every 8 weeks: Q12W: every 12 weeks

Source: Figures 10 &11, CS

NMA results: biologic-experienced (induction)

Filgotinib 200 mg [redacted]

*On the probit scale a negative coefficient indicates that filgotinib 200mg is more effective than the comparator at increasing the probability of response. Zero is the point of no difference

Significantly superior

ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; TOF: tofacitinib; UST: ustekinumab; VDZ: vedolizumab

Source: table 25, CS

NMA results: biologic-experienced – 2b (maintenance)

Filgotinib 200mg [redacted]

*On the probit scale a negative coefficient indicates filgotinib 200 mg is more effective. Zero is point of no difference

NICE

ADA: adalimumab; CrI: credible interval; FIL: filgotinib; GOL: golimumab; IFX: infliximab; MCS: Mayo clinic score; TOF: tofacitinib; UST: ustekinumab; VDZ: vedolizumab; Q4W: every 4 weeks; G8W: every 8 weeks.

Cost-effectiveness evidence

Key issues

Issue No.	Description	ICER impact
1, 3 7	**Precise line of therapy:** Which is the most appropriate line of therapy for filgotinib? **Sequence of biologics:** Does re-randomisation preclude an unbiased estimate of the long-term effectiveness of treatment sequence? **Third-line population not adequately modelled**	
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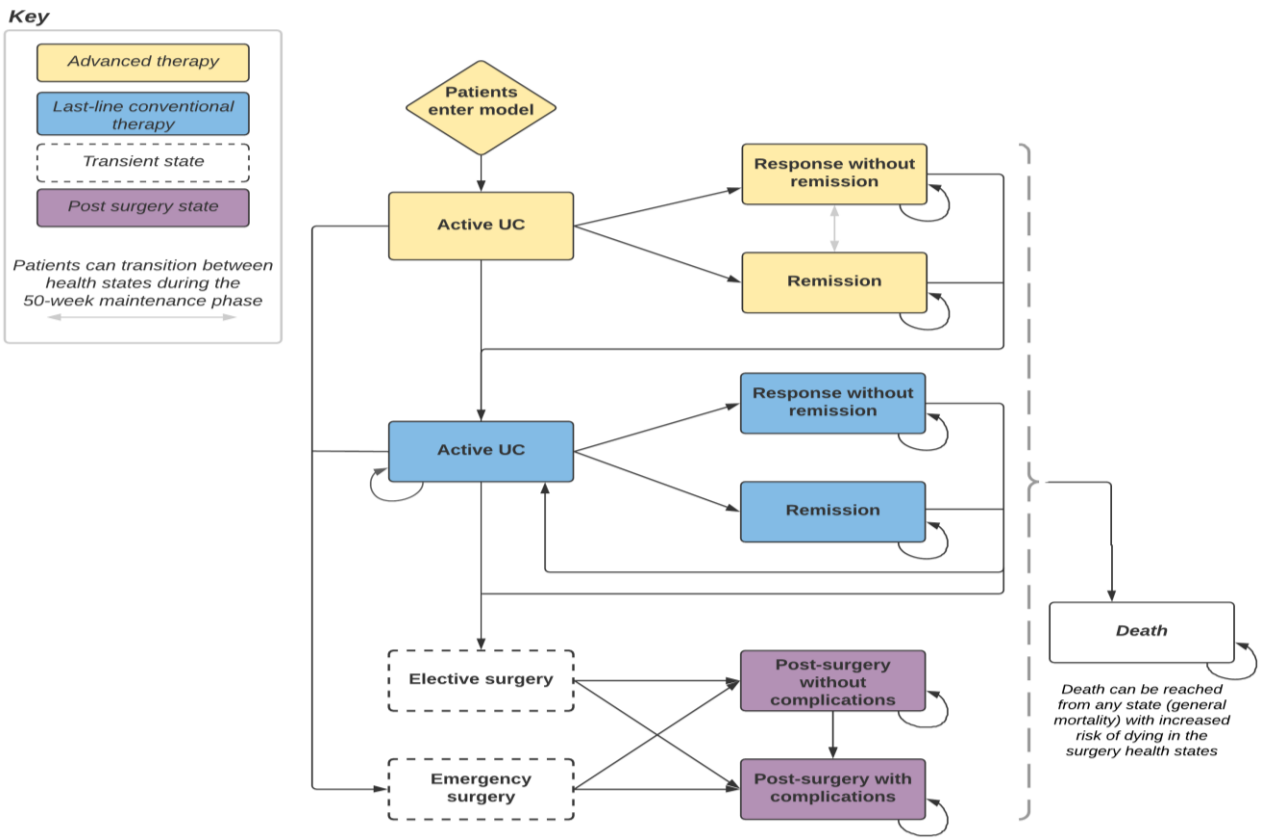
Key: Large impact  Small/moderate impact  Unknown impact 

Cost effectiveness model



Structure	Markov model
Horizon	Lifetime (100 years)
Cycle length	10 weeks
Discount rate	3.5% for both health and cost outcomes
Perspective	NHS and PSS
Stopping rule	None in base case

ERG comments

- Considered company's approach of using Markov model instead of hybrid is appropriate
- Absence of relapse state may introduce some bias: but broadly agreed with company's approach
- Company's choice of 10-week cycle length appropriate with minimal bias

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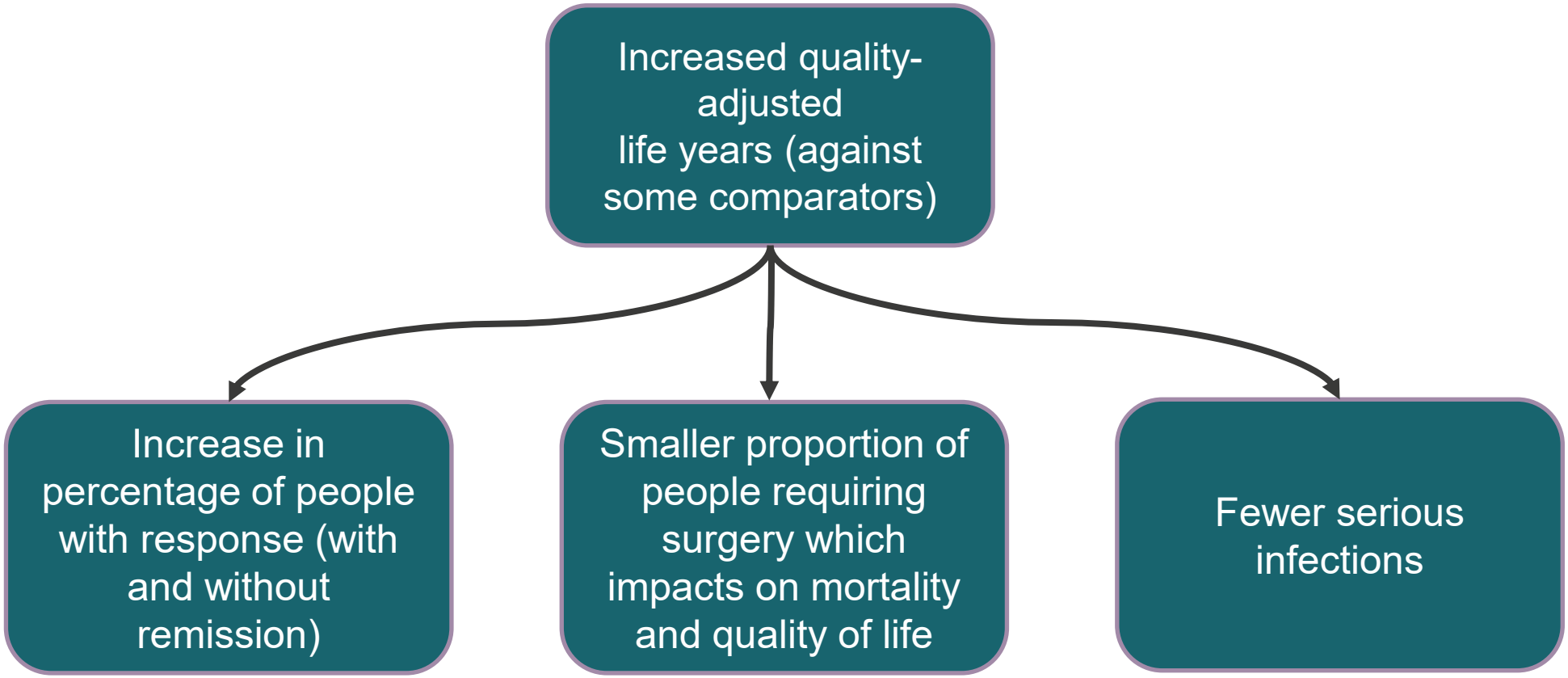
◉ Is the company's model acceptable for decision making?

Source: CS Figure 15

Where do the QALY gains come from in model?



QALY, quality-adjusted life year

Company model inputs

Input	Company	ERG comment
Baseline characteristics	SELECTION	Agrees with approach
Transition probabilities	NMA for induction and maintenance phase relapse/remission HES data for surgery	Uses individual trial results for maintenance phase. Otherwise generally aligned
Treatment waning and discontinuation	Treatment maintained until loss of response and transition to active UC state	Agrees with approach, but not values used for loss of response. Alternative scenarios presented.
Utilities	Pre-surgical states – SELECTION Post-surgical states – Arseneau et al. 2006	Uncertainty in values used. Alternative scenarios presented.
Costs	MIMS for drug costs, NHS reference costs 2018/19	Uncertainty in dose escalation and health state costs. Alternative scenarios presented.
Resource use	Tsai et al. 2008	
Adverse events	Serious infections only	Agrees with approach
Mortality	All-cause mortality and perioperative mortality associated with colectomy	Agrees with approach

NICE

HES: hospital episode statistics; MIMS: Monthly Index of Medical Specialities: NMA: network meta-analysis

Source: table 35, CS

Adverse events included in the model

ERG: Only serious infections were modelled

Treatment	Probability from safety NMA	10-week probability base-case	10-week probability scenario
Filgotinib	[redacted]	[redacted]	3.8%
Adalimumab	[redacted]	[redacted]	0.9%
Golimumab	[redacted]	[redacted]	0.1%
Infliximab	[redacted]	[redacted]	0.4%
Tofacitinib	[redacted]	[redacted]	3.8%
Ustekinumab	[redacted]	[redacted]	0.2%
Vedolizumab	[redacted]	[redacted]	0.2%
Conventional therapy	[redacted]	[redacted]	0.9%

ERG comments

- Company's approach for incorporating adverse events appropriate
- Only serious infection are modelled while other infections were quite prevalent for filgotinib but have small impact on cost-effectiveness results

◉ Is it appropriate to only model serious infections?
◉ Should cardiovascular events be included in model?

NICE

NMA: Network meta-analyses

Source: table 4.9, ERG report

Issue 12: Appropriateness of baseline utility values

Background: Uncertainty in the utility values used for the active UC health state

- Lower utility values 0.41 and 0.47 for active UC states were used in TA633 (ustekinumab) and TA547 (tofacitinib) respectively

Base case	Utility value	Source	Rationale
Company	[redacted]	SELECTION - baseline	• Baseline utility value is more conservative than 10-week for active UC • Scenarios presented show results are robust to either value
ERG	[redacted]	SELECTION – 10 week	• 10-week values used for other health states • Baseline value doesn't capture improvements during induction • Baseline value includes non-responders • Area of uncertainty

◉ Which utility value is most representative of active UC health state?

NICE

UC: ulcerative colitis

Issue 11: Health-related quality of life source (1)

Company: Lack of consistency between SELECTION, previous TA guidance and published values
- Base case uses pooled population values (2a and 2b+) measured at 10 weeks except for active UC health state

Topic	Source		Active UC	Response w/out remission	Remission
Filgotinib	SELECTION	Company (BC)	[redacted]	[redacted]	[redacted]
		ERG (BC)	[redacted]		
TA633 (ustekinumab)	Woehl et al. 2008		0.41	0.76	0.87
TA547 (tofacitinib)	Woehl et al. 2008		0.47*	0.87	1

ERG: Value in active UC state likely overestimated. Used 10-week pooled population utility values. Requested 3 scenarios from the company:

Scenario 1 (population stratified):

- Using biologic-naïve (2a) and biologic-experienced (2b+) specific utility values where 10-week data are used for all pre-surgery health states
- **Company:**
  - no utility values stratified by population were provided
  - conducted scenario analysis, but appeared to misunderstand ERG request
- **ERG**: impact of utility values stratified by population not analysed and uncertainty remains

BC: base case: TA: technology appraisal * Based on patient experts' experience of active disease

Source: Table 5, company TE response

Issue 11: Health-related quality of life impact (2)

Scenario 2 (26-week SELECTION utility data for pre-surgery response and remission):

- **Company:**
  - 26-week data not comparable with baseline, week 10 and 58 (due to definition of remission used)
  - Scenario using 26-week utilities was not conducted, but utility values provided
- **ERG:** used 26-week SELECTION data in a scenario

Scenario 3 (differential utilities for the induction and maintenance phase):

- **Company:**
  - provided a scenario using differential values for the active state only with values from Swinburn et al. 2012
  - SELECTION not used due to sample size at 58 weeks (n=38) and overestimation of utility value due to adaptation to disease and those feeling less well not completing questionnaire
- **ERG:** data not provided by company, so couldn't assess. Scenario provided does not address the full impact of differential utility values by phase

ERG conclusion:

- Uncertainty remains about utility values that reflect ulcerative colitis, particularly per population (biologic-naïve [2a] and –experienced [2b/2c])

◉ What are the committee's preferred utility values?

Issue 8: Equal loss of response for response/remission

Background: Model assumes loss of response to be equal for remission and response

Company

- Long-term loss of response over time was estimated from NMA and rates do not differ by health states (e.g. response without remission vs. remission)
- Clinical experts agreed when people are considered to be in response or remission and their response to treatment would not wane over time

Clinical experts

- Loss of response is less likely to occur in people remission in comparison to responders

ERG

- Assuming equal loss of response rates in response and remission favours filgotinib
- Remission is more difficult to attain than response but once attained people are more stable and stay in remission longer
- Suggest scenario based on SELECTION to estimate of loss of response for each health state
- Company's model does not permit testing the scenarios with differential loss of response

TA633: patients in remission and patients in response (without remission) had different loss of response probabilities which was included in model

TA547: assumed equal loss of response for response (without remission) and remission

◉ Is company's approach to model equal loss of response appropriate?

NMA: network meta-analyses

Issue 9: Constant loss of response

Background: In addition to assuming equal loss of response company's model also assume loss of response to be constant over lifetime

Company

- Due to lack of evidence it assumed constant loss of response and in line with TA547 (tofacitinib) and TA633 (ustekinumab)
- Provided a scenario where loss of response was lowered by 25% after 1st year of maintenance in line with TA633
- Maintained its assumption of constant loss of response is conservative

Clinical experts

- Disagreed with constant loss of response assumption
- Scenario with 25% reduction in loss of response is reasonable

ERG

- No evidence or expert opinion for treatment-specific long-term loss of response
- Uncertainty on true reduction
- Scenario with 25% reduction in loss of response provided for consistency
- Constant loss of response rates would favour treatments with lower observed non-response

◉ What is expected to happen to loss of response over time?

NICE

Issue 13 : Application of dose escalation

Company

- Applied costs of dose escalation to most comparators, but not clinical benefit of dose escalation
- Included for all comparators expect vedolizumab SC in maintenance
- Dose escalation for filgotinib judged not appropriate as only 200 mg and 100 mg are approved doses

Clinical experts

- Agreed dose escalation is routinely used in NHS practice

ERG

- Excludes dose escalation in base case
- NG130 does not recommend dose escalation (even immediately before surgery)
- Approximately 5.0% to 70.8% people undergo dose escalation after anti-TNFs and time to escalation varies from 16% at 6 months to 44% at 36 months
- Disagreed with the company that dose escalation occurs immediately prior to surgery but normally used for a partial, absence, or loss of response
- Inconsistent to model only the increased cost for comparators with dose escalation but not prolonged response (clinical benefit)
- Dose escalation should be only applied in a clinically plausible way with an increase in effectiveness and did not consider appropriate to include in its base case

◉ Should dose escalation be applied in the model and how should this be modelled?

TNF: tumour necrosis factor; UC ulcerative colitis: SC: subcutaneous

Issue 6: Inclusion of uncertainty of treatment sequences

Company

- Treatment sequences informed by clinical experts and represents NHS clinical practice
- Explored additional treatment sequences in its scenario analyses

Initial treatment	Biologic-naïve (2a) Subsequent treatments
Filgotinib	**ADA → VDZ IV**
Golimumab	**VDZ IV → UST**
Adalimumab	**VDZ IV → UST**
Infliximab	**VDZ IV → UST**
Tofacitinib	**ADA → VDZ IV**
Vedolizumab SC	**TOFA → UST**
Vedolizumab IV	**TOFA → UST**

Initial treatment	Biologic-experienced (2b+) Subsequent treatment
Filgotinib	**VDZ IV**
Adalimumab	**VDZ IV**
Tofacitinib	**VDZ IV**
Ustekinumab	**VDZ IV**
Vedolizumab SC	**UST**
Vedolizumab IV	**UST**

Clinical experts: Comprehensive sequences included and multiple scenarios are possible

ERG : Agreed with company's selection of subsequent treatments some variability in NHS. Scenarios:

- biologic naïve (2a): **ADA→ VDZ IV→ TOFA**
- biologic experienced (2b+): **VDZ IV → TOFA**

◉ Do these represent subsequent treatments to be used in NHS clinical practice?

NICE

ADA: adalimumab; IV: intravenous; TOFA: tofacitinib; UST: ustekinumab; VDZ: vedolizumab, SC: subcutaneous

Source: table 4.6, ERG report

Issue 4: Validity of maintenance phase NMA

Background: values on effectiveness of treatments during maintenance phase required to populate model

Company

- Uses maintenance NMA results and considers this conservative

ERG

- Use of maintenance NMA is not clinically plausible nor methodologically correct (see clinical section)
- Calculated 50-week probabilities conditional on response at 10 weeks based on individual trial of same intervention at the end of the maintenance for its base case
- Used these values in model and notes limited impact on ICER

◉ How should efficacy be estimated during the maintenance phase?

NICE

NMA: Network meta-analyses; RCT: randomised controlled trial

Issue 10: Probability of pouchitis not aligned with utility

Background: Severity of pouchitis utility value is for chronic pouchitis, but probability of event for acute pouchitis

Company

- Post-surgery complications were taken from Ferrante et al. 2008 (6.5 year follow-up):
  - 46% developed at least one episode of acute pouchitis
  - 19% developed chronic pouchitis
- Used 46% to calculate 10-weekly probability of developing post-surgery complications to a lower utility score for remainder of lifetime
- Considers its assumption is conservative and consistent with TA547

ERG

- Company model is inconsistent approach is not conservative colitis
- ERG used probability of chronic pouchitis in its base case

◉ Should the probability of pouchitis included in the model be restricted to chronic pouchitis only?

Innovation

Company

- Filgotinib is a second generation JAK inhibitor that is preferential and reversible inhibitor of JAK1
- Oral treatment offers a more convenient option compared with subcutaneous treatment options
- Potential for drug-drug interactions is low

Equality

- For certain religious groups impact of active disease and effects of surgery may interfere with religious practices and cause distress

◉ Is filgotinib for treating moderately to severely active ulcerative colitis innovative and are there any additional benefits that have not been captured?
◉ Are there any equality issues that should be taken into account?

Company and ERG preferred base-case assumptions

Issue	Company	ERG
Conventional therapy	Relevant comparator (Included)	Not relevant comparator (Not included)
Dose escalation	Filgotinib: No Comparators: Yes	Filgotinib: No Comparators: No
Maintenance network meta-analyses	Used maintenance network meta-analyses	Used trial data
Utility values	Baseline utility value for active ulcerative colitis [redacted]	10 week utility value for active ulcerative colitis [redacted]
Probability of pouchitis	Acute pouchitis (1.8%)	Chronic pouchitis (0.62%)

Cost-effectiveness results

All ICERs are reported in PART 2 slides because of confidential agreements

Back up slides

Description of model health states

Health state	Definition
Remission	Mayo score of ≤ 2 points and no individual sub score > 1 point
Response without remission	• Not meeting remission definition, and • Decrease from baseline in Mayo score of ≥ 30% and ≥ 3 points, and • Decrease from baseline in the rectal bleeding sub score ≥ 1, or an absolute rectal bleeding sub score of 0 or 1
Active ulcerative colitis	• Remission and response without remission not achieved. • People enter the model here, defined as total Mayo score between 6 and 12 and the following sub scores: endoscopy score and Physician's Global Assessment score ≥2, rectal bleeding score and stool frequency score ≥1
Emergency surgery	Emergency colectomy due to acute exacerbation
Elective surgery	Elective colectomy which can be undergone by patients with active ulcerative colitis
Post-surgery with complications	Chronic complications after undergoing surgery
Post-surgery without complications	No chronic complications after undergoing surgery

NICE

Source: table 34, CS

Dosing regimen for filgotinib and comparators

Treatment	Dose escalation	Standard dose	Escalated dose (maintenance)
Filgotinib	No	200mg qd	N/A
Adalimumab	Yes	40mg q2w	40mg qw
Golimumab	Yes	50mg q4w	100mg q4w
Infliximab	Yes	5mg/kg q8w	5 mg/kg q4w
Tofacitinib	Yes	5mg bid	10mg bid
Ustekinumab	Yes	90mg q12w	90mg q8w
Vedolizumab IV	No	300mg q8w	300mg q4w
Vedolizumab SC	Yes	108mg q2w	N/A

[a] Based on the baseline weight for the biologic-naïve subgroup

[b] Based on the baseline weight for the biologic-exposed subgroup

[c] Induction dose is 2 doses (initially and at week 2)

NICE

Bid: twice per day; IV: intravenous; kg: kilogram; mg: milligram; qd: once daily; qw: once per week; q2w: once every two weeks; q4w: once every four weeks; q8w, once every eight weeks; q12w, once every twelve weeks; SC :subcutaneous

Source: table 36, CS

ERG's results: biologic-naïve – 2a (maintenance)

Trial	Treatment	No response n (%)	Response without remission n (%)	Response with remission n (%)
ACT	PBO	28 (23.1%)	7 (5.8%)	10 (8.3%)
	IFX 5 mg/kg Q8W	32 (57.1%)	10 (17.9%)	14 (25.0%)
GEMINI	PBO	58 (73.4%)	6 (7.6%)	15 (19%)
	VDZ 300 mg Q8W	25 (34.7%)	14 (19.4%)	33 (45.8%)
	VDZ 300 mg Q4W	32 (43.8%)	6 (8.2%)	35 (47.9%)
OCTAVE SUSTAIN	PBO	82 (75.2%)	15 (13.8%)	12 (11%)
	TOF 5 mg	50 (43.5%)	17 (14.8%)	48 (41.7%)
	TOF 10 mg	37 (35.6%)	21 (20.2%)	46 (44.2%)
PURSUIT-M	PBO	106 (68.8%)	14 (9.1%)	34 (22.1%)
	GOL 100 mg Q4W	80 (53%)	21 (13.9%)	51 (33.8%)
	GOL 50 mg Q4W	76 (50.3%)	24 (15.9%)	50 (33.1%)
SELECTION	PBO	32 (59.3%)	15 (27.8%)	7 (13%)
	FIL 200 mg QD	27 (25.2%)	31 (29%)	49 (45.8%)
	PBO	26 (48.1%)	19 (35.2%)	9 (16.7%)
	FIL 100 mg QD	44 (41.9%)	35 (33.3%)	26 (24.8%)
ULTRA 2	PBO	32 (57.1%)	10 (17.9%)	14 (25.0%)*
	ADA 160/80/40 mg Q2W	45 (50.6%)	16 (17.9%)	28 (31.5%)
UNIFI	PBO	43 (49.4%)	17 (19.5%)	27 (31%)
	UST 90 mg Q12W	24 (23.5%)	28 (27.5%)	50 (49%)
	UST 90 mg Q8W	19 (22.4%)	25 (29.4%)	41 (48.2%)
VARSITY	ADA/160/80/40 mg Q2W	53 (25.0%)	55 (25.9%)	104 (49.1)
	VDZ 300 mg Q8W	53 (35.1%)	24 (15.9%)	74 (49.0%)
VISIBLE	PBO	30 (81.1%)	NR	7 (18.9%)
	VDZ 108 mg SC Q2W	31 (46.3%)	NR	36 (53.7%)
	VDZ 300 mg Q8W	15 (46.9%)	NR	17 (53.1%)

ERG's results: biologic-experienced – 2b+ (maintenance)

Trial	Treatment	No response n (%)	Response without remission n (%)	Response with remission n (%)
GEMINI 1	PBO	32 (84.2%)	4 (10.5%)	2 (5.3%)
	VDZ 300 mg Q4W	26 (60.5%)	6 (14.0%)	16 (37.2%)
	VDZ 300 mg Q8W	20 (50%)	1 (2.5%)	14 (35%)
OCTAVE SUSTAIN	PBO	76 (85.4%)	3 (3.4%)	10 (11.2%)
	TOFA 5 mg	46 (55.4%)	17 (20.5%)	20 (24.1%)
	TOFA 10 mg	38 (40.9%)	21 (22.6%)	34 (36.6%)
SELECTION	PBO	34 (77.3%)	8 (18.2%)	2 (4.5%)
	FIL 200 mg QD	39 (42.4%)	33 (35.9%)	20 (21.7%)
	PBO	28 (80%)	4 (11.4%)	3 (8.6%)
	FIL 100 mg QD	41 (61.2%)	13 (19.4%)	13 (19.4%)
ULTRA 2	PBO	23 (79.3%)	3 (10.3%)	3 (10.3%)
	ADA 160/80/40 mg Q2W	21 (58.3%)	7 (19.4%)	8 (22.2%)
UNIFI	PBO	54 (61.3%)	19 (21.6%)	15 (17%)
	UST 90 mg Q12W	31 (44.3%)	23 (32.9%)	16 (22.9%)
	UST 90 mg Q8W	32 (35.2%)	23 (25.3%)	36 (39.6%)
VISIBLE	PBO	NR	NR	1 (5.3%)
	VDZ 108 mg SC Q2W	NR	NR	13 (33.3%)
	VDZ 300 mg Q8W	NR	NR	6 (27.3%)
VARSITY	VDZ 300 mg Q8W	20 (45%)	8 (18%)	16 (36%)
	ADA 160/80/40 mg Q2W	13 (50%)	0 (0%)	13 (50%)

ADA: adalimumab ;FIL: filgotinib; GOL: golilumab; PBO: placebo; TOFA: tofacitinib; UST: ustekinumab; VED: vedolizumab

Source: table 3.30, ERG report

Issue 2: Lack of data analysis for filgotinib 100 mg

Background: Two recommended two doses for filgotinib 200 mg (ulcerative colitis) and 100 mg (ulcerative colitis with moderate or severe renal impairment)

Company

- 100 mg dose is approved for people with estimated CrCL 15 to < 60 mL/min based on clinical pharmacology study
- Due to lack of the data in people with renal impairment for both filgotinib and comparators it is not included in economic analysis

Clinical experts

- Renal impairment is relatively rare so this issue may not be clinically relevant
- Efficacy data for 100 mg dosage is relatively suboptimal
- Decision problem could be restricted to 200mg dose

ERG

- Restrict decision problem and exclude people on 100 mg dose
- No efficacy or cost-effectiveness analysis was included for 100 mg dose in people with renal impairment

Conclusion from technical engagement

- Restrict decision making to 200mg dose

NICE

CrCL : creatinine clearance