NICE National Institute for Health and Care Excellence

SLIDES FOR PUBLIC OBSERVERS

Filgotinib for moderate to severe rheumatoid arthritis

Lead team presentation

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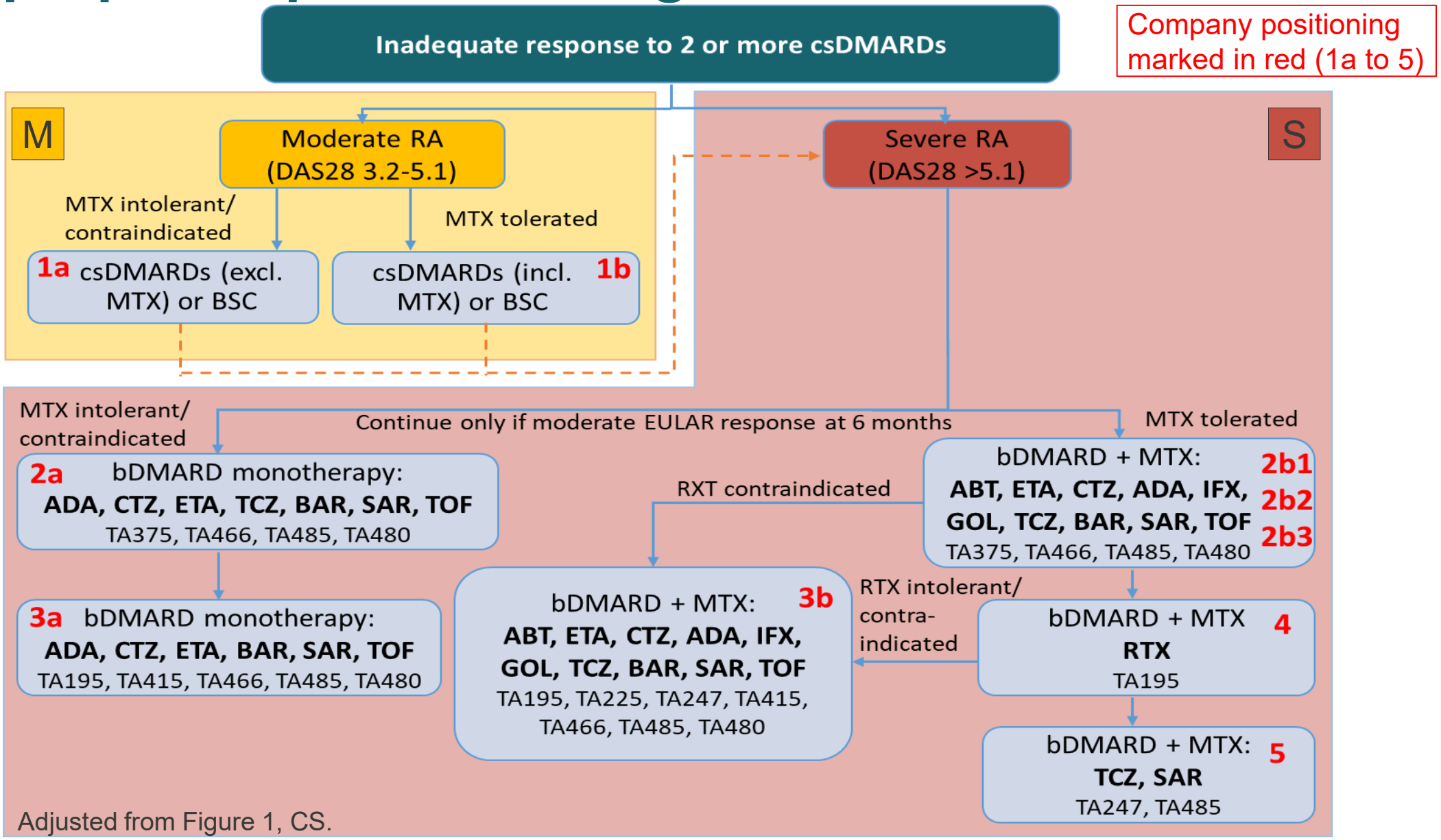
Rheumatoid arthritis (RA)

- Inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint.
- Causes swelling, stiffness, pain and progressive joint destruction.
- Severity of disease can be classified into 4 categories, based on the disease activity score (DAS-28) classification system.
  - DAS-28 >5.1: high disease activity or severe disease S
  - DAS-28 = 3.2 to 5.1: moderate disease activity M
  - DAS-28 <3.2: low disease activity
  - DAS-28 <2.6: disease remission

Filgotinib (Jyseleca, Gilead Sciences)

Description of technology	A Janus-kinase (JAK) 1 inhibitor that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory responses. It can be used as a monotherapy or in combination with methotrexate.
Marketing authorisation	Treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs (as monotherapy or in combination with methotrexate)
Dosage and administration	200 mg orally administered once daily
Proposed place in the RA treatment pathway	Filgotinib can be used in the moderate RA population after: • 2 or more csDMARDs (Company's target population) Filgotinib can be used in the severe RA population after: • 2 or more csDMARDs • 1 or more bDMARD Treatment options for RA differ by methotrexate and rituximab tolerance (see pathway diagram on next slide)

Treatment pathway for moderate-severe RA and proposed position of filgotinib



Adjusted from Figure 1, CS.

Proposed position of filgotinib: 10 populations

Pos #	Disease severity	Failed treatments	Methotrexate tolerant?	Rituximab tolerant?
1a	Moderate	≥2 csDMARDs	X	✓
1b	Moderate	≥2 csDMARDs	✓	✓
2a	Severe	≥2 csDMARDs	X	✓
2b1* 2b2* 2b3*	Severe	≥2 csDMARDs	✓	✓
3a	Severe	≥1 bDMARD	X	✓
3b	Severe	≥1 bDMARD	✓	X
4	Severe	≥1 bDMARD	✓	✓
5	Severe	Rituximab	✓	✓

*subdivided into 2b1, 2b2, 2b3 depending on the subsequent treatment

Patient perspectives

- Rheumatoid arthritis can be diagnosed early in teenage or adult life and can have a large impact on future plans such as starting a family or a new relationship
- Three of four people diagnosed with RA are of working age
- Patients living with RA stated that it has a large impact on mental and physical health and emotional well being causing fear, anxiety, stress, pain and fatigue
- RA also affects ability to work, everyday activities and relationships with children and other family members
- Young adults often feel less desirable, less confident and fear reduced fertility
- Advanced therapies can “give patients their life back” but the disease may relapse so patients need access to multiple biologics to treat or maintain the condition

We would like to thank the National Rheumatoid Arthritis Society (NRAS) and one patient expert for their submissions

NRAS survey: impact of living with RA in people not currently treated with advanced therapies

- Target population: people with RA, over the age of 16, with a disease duration of 2 years or more and living in the UK
- 612 respondents: mean age 59 years, 88% female:
  - Disease duration: 37.7%2 to 5 years; 27.9% 5 to 10 years; 34.2% 10+ years
  - 86.4% were taking at least one csDMARDs[a] and 15.4% were on corticosteroids
  - 90% had at least one RA flare and 23% had six or more flares in the past year
  - Average (range) disease activity score (e.g. DAS28) was not reported
- Key author's messages:
  - In established RA patients not on advanced therapies, patient-reported outcome measures indicate high levels of suffering
  - A patient acceptable state on the Rheumatoid Arthritis Impact of Disease (RAID)[b] tool is very uncommon (12.4% patients)
  - High levels of pain, physical disability, sleep difficulties and fatigue are prominent symptoms

Source: Nikiphorou et al. (in publication).
[a] as a monotherapy in 262 patients (42.8%) and as a combination therapy in 267 patients (43.6%);
[b] 7 domains: pain, functional disability, fatigue, sleep, physical well-being, emotional well-being, and coping; each domain is scored on a 10-item numerical rating scale, with zero being a good or low activity score and 10 a high or severe activity score. Patient acceptable state is defined as a RAID total score below 2.

Impact on carers

- It can be very hard for carers and children to cope with seeing a family member in pain or seeing the rapid deterioration of the health of a parent with early RA
- Children may often become carers for parents living with RA or younger siblings. The parents worry about being a burden to their children or family

Benefits of filgotinib

- Filgotinib adds to the therapeutic options available to clinicians and patients in addressing inflammation and bone erosion
- An oral drug taken daily is preferable, especially for patients who are needle phobic or who have a significant hand disability
- Unlike injectables, filgotinib tablets need not be transported and stored at low temperatures

Clinician perspectives

Submission from a clinical expert:

- Despite a range of therapies available for RA, they fail to provide meaningful improvement for a sizeable proportion of patients
- “One size fits all” approach is not appropriate for patients with RA: heterogeneous disease and population (age, co-morbidity etc), drug safety and practical considerations important to consider
- NICE guidelines for managing RA recommend treatment target of remission or low disease activity – but currently patients with moderate disease have no access to advanced therapies (recommended only for patients with severe RA): suboptimal care, and unmet need
- Better treatment of RA is generally associated with improved quality of life and outcomes including co-morbidity and cardiovascular events
- Filgotinib could benefit patients across the pathway (prior failure of csDMARDs as well as bDMARD therapy)

Measuring response to treatment in RA

ACR responses

ACR20 is a composite measure defined as 20% improvement in the number of tender and number of swollen joints, and 20% improvement in three of the following five criteria:

- patient global assessment,
- physician global assessment,
- functional ability measure [most often Health Assessment Questionnaire (HAQ)],
- visual analog pain scale, and
- erythrocyte sedimentation rate or C-reactive protein (CRP).

ACR 50 and ACR70 define improvement levels as 50% and 70%.

EULAR responses

Dependent on the extent of change and the level of disease activity reached:

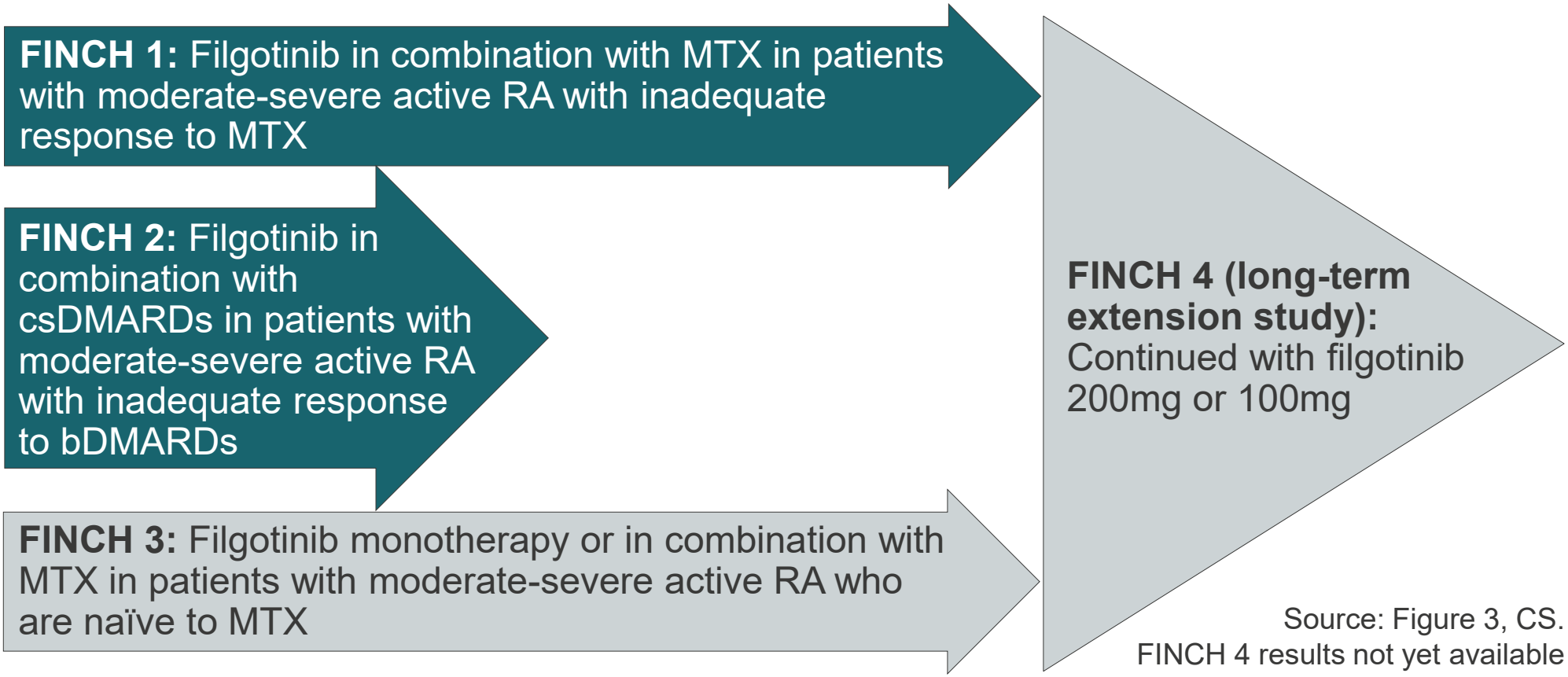
		Improvement in DAS28		
		>1.2	>0.6 and ≤1.2	≤0.6
DAS28 at endpoint	≤3.2 (LDA)	Good	Moderate	None
	>3.2 to ≤5.1 (moderate)	Moderate	Moderate	None
	>5.1 (severe)	Moderate	None	None

Disease activity score (DAS)28 is based on tender joint count, swollen joint count (based on assessment of 28 joints), ESR or CRP and assessment of global patient health

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; LDA=low disease activity

Filgotinib clinical trial programme

Study duration		
24 weeks	52 weeks	>52 weeks



Source: Figure 3, CS.
FINCH 4 results not yet available

FINCH 1&2 (key trials for target population): randomised, double-blind, multicentre phase 3 trials:

- Primary outcome: proportion of patients achieving an ACR20 response at week 12
- Key secondary outcomes: disease activity (ACR20, ACR50, ACR70), EULAR response, DAS28, HAQ-DI at weeks 12 and 24.

Clinical evidence from FINCH trials

Outcomes: % patients	FINCH 1 (cDMARD-IR population)			FINCH 2 (bDMARD-IR population)	
	FIL 200mg + MTX (n=475)	ADA + MTX (n=325)	PBO + MTX (n=475)	FIL 200mg + cDMARDs (n=147)	Placebo + cDMARDs (n=148)
12-week results					
ACR20	76.6%* [†]	70.5%	49.9%	66.0%*	31.1%
ACR50	47.2%* [†]	35.1%	19.8%	42.9%*	14.9%
ACR70	26.1%* [†]	14.2%	6.7%	21.8%*	6.8%
EULAR	51.4%	44.8%	24.6%	42.6	18.0
Remission	34.1%* [†]	23.7%	9.3%	18.8%*	6.7%
Low disease activity	49.7%* [†]	43.4%	23.4%	40.8%*	15.5%
24-week results					
ACR20	78.1%*	74.5%	59.2%	69.4%*	34.5%
ACR50	57.9%*	52.3%	33.3%	45.6%*	18.9%
ACR70	36.2%* [†]	29.5%	14.9%	32.0%*	8.1%
EULAR	68.4%	58.0%	41.8%	57.9%	35.2%
Remission	48.4%*[†]	35.7%	16.2%	30.6%*	12.2%
Low disease activity	NR	NR	NR	48.3%*	20.9%

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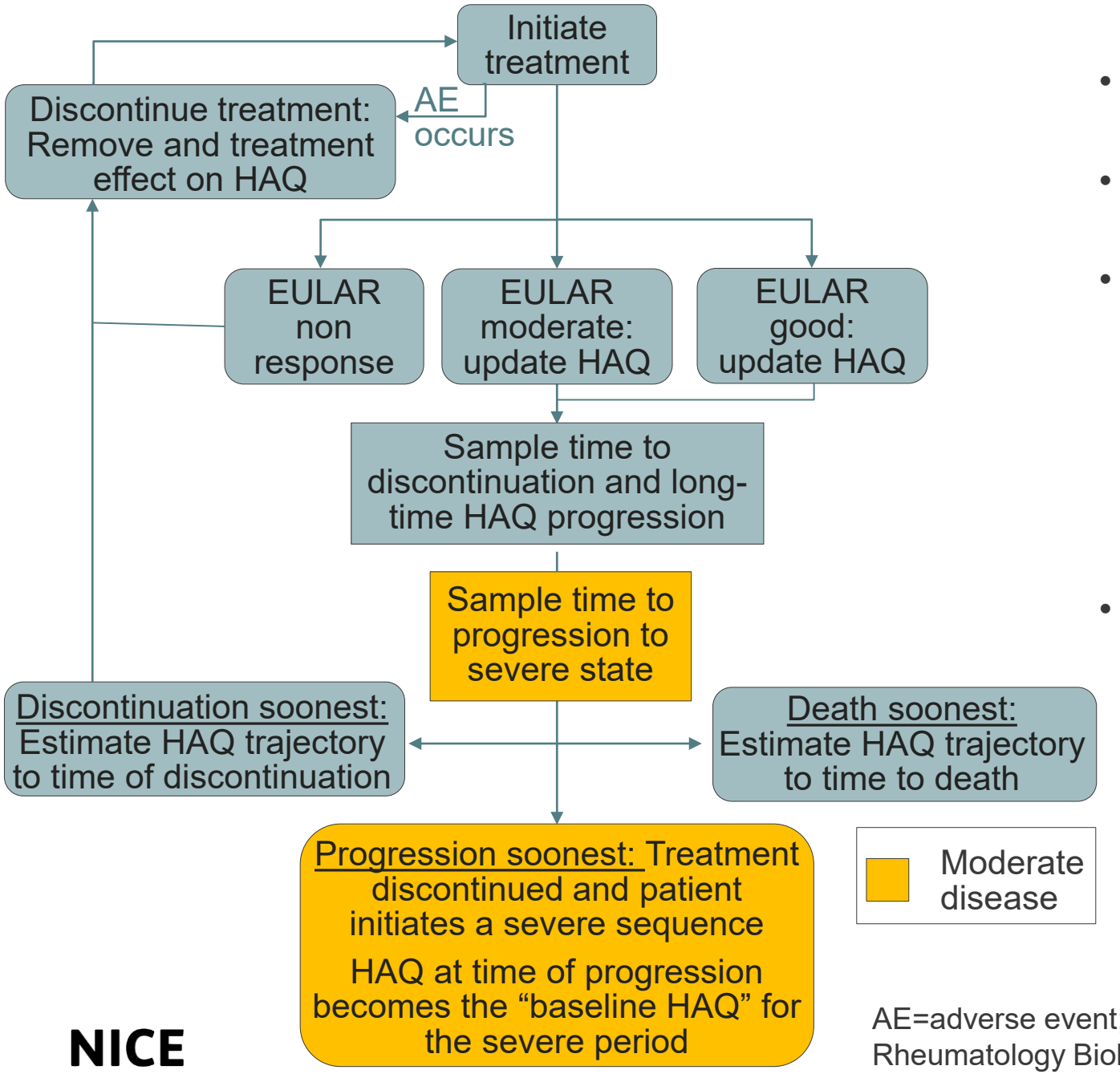
*P<0.05; versus placebo. †P<0.05; versus adalimumab; Remission = DAS28-CRP <2.6; Low disease activity = DAS28-CRP ≤3.2. ADA=adalimumab; CRP=C reactive protein value; FIL=filgotinib; IR = inadequate response; MTX=methotrexate. Source: ERG report Table 4.6.

Filgotinib model structure: discrete event simulation



- Model structure in line with previous submissions to NICE
- Moderate RA disease activity can progress to severe states
- The ERG was satisfied that the model performs as expected but highlighted model complexity and low number of patient profiles (1,000 profiles, drawn from 10,000 times; likely under-estimated heterogeneity) and PSA iterations
- Long-term HAQ-DI progression based on:
  - bDMARDs: BSRBR dataset (as in MTA375)
  - csDMARDs: Norton et al. 2014 (ERAS and NOAR cohorts)

AE=adverse event; BSRBR=British Society of Rheumatology Biologics Register for Rheumatoid Arthritis; ERAN=Early RA Network; NOAR=Norfolk Arthritis Register

Summary of key issues considered at technical engagement	Status	Population
1. Relevant population: Is study population representative of the company's target population (number of prior DMARDs failed)?	Resolved	M
2. Relevant comparators and treatment sequences (severe RA): Is company selection of comparators and treatment sequences appropriate?	For discussion	S
3. Generalisability of FINCH trials: Are FINCH trials generalisable to the decision problem and UK clinical practice?	For discussion	M S
4. Network meta-analysis: Is company's network meta-analysis suitable for decision-making?	Partially resolved	M S
5. Rate of progression from moderate to severe RA: Has the rate of progression been modelled appropriately?	For discussion	M
6. Treatment sequence upon progression from moderate to severe RA: What is the most appropriate treatment sequence after progression?	For discussion	M
7. Modelling best supportive care (BSC) in the moderate population: Has the BSC been modelled appropriately?	Partially resolved	M
8. Utility values: Which mapping approach should be used to estimate utility values?	Partially resolved	M S

Issue 1: Relevant population (moderate RA)

Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
The company limited their submission in moderate RA to patients for whom 2 or more csDMARDs have failed. The technical team agreed with the target population but raised concerns about discrepancy between the target population and trial population (only 49% of FINCH 1 patients with moderate RA had 2 or more prior csDMARDs; 51% had only 1 prior csDMARD).	The company provided: 1) pairwise comparison of baseline characteristics and clinical efficacy data for patients with moderate RA who had 1 prior csDMARD and ≥2 prior csDMARDs (exploratory post-hoc analyses based on small patient numbers). 2) exploratory cost-effectiveness analyses for patients with ≥2 prior csDMARDs, showing no major impact on ICERs compared to the overall moderate population*.	The technical team: 1) noted estimates of clinical and cost-effectiveness seem to be aligned for these two groups. 2) noted this is aligned with GID-TA10389 (upadacitinib) 3) agreed clinical data from the overall moderate population from FINCH 1 trial should be used in base case analysis, supported by data from patients with 2 or more csDMARDs exposures in scenario analyses.	Yes (original and updated base case)

*Both analyses based on head-to-head FINCH 1 trial data for both filgotinib and BSC (placebo)

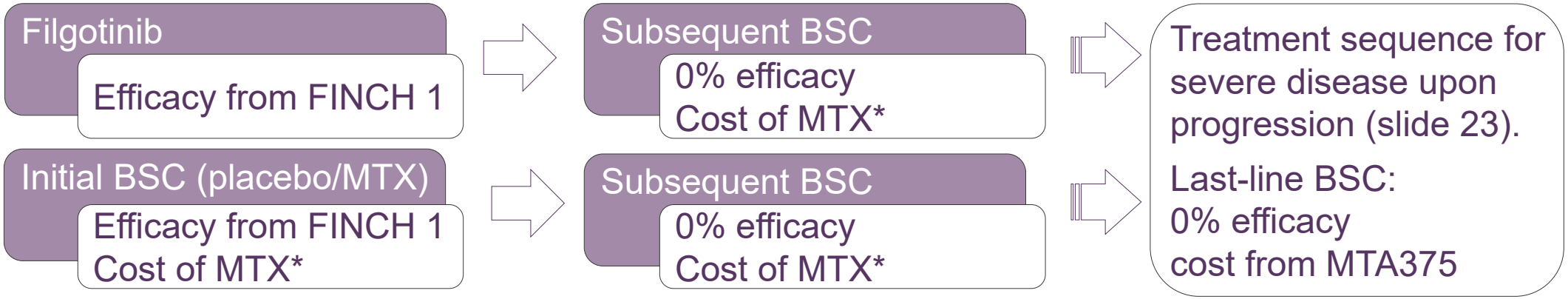
Issue 4: Network meta-analysis

Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
Company NMA may not be appropriate for the moderate RA population - it was not possible to separate it by severity. The technical team preferred using direct head-to-head trial data from FINCH 1 for moderate RA population.	The company provided revised base case analysis using head-to-head trial data to model efficacy of both filgotinib and BSC (methotrexate). The company also provided scenario analyses using data from a subset of patients who had 2 or more prior csDMARDs exposures.	The technical team considers analyses based on head-to-head trial data more appropriate for decision-making, in agreement with the guide to the methods of technology appraisal 2013. This approach is aligned with GID-TA10759.	Yes

Further discussion (slide 20):
Is company's network meta-analysis suitable for decision-making for severe RA population?

Issue 7: Modelling BSC in the moderate population

Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
BSC (further csDMARDs) used after failure of 2 or more csDMARDs is unlikely to have any effect in clinical practice. But high response rates were observed in placebo arm (MTX/csDMARDs) in FINCH trials. It is not appropriate to assume 0% clinical efficacy for the initial BSC, while assuming the full clinical efficacy for the filgotinib arm.	The company submitted updated base case which incorporates response rate from placebo/MTX arm of FINCH 1 data (moderate population) to model initial BSC; subsequent BSC assumed to have no efficacy. Cost of BSC assumed to equal the cost of MTX.	The technical team agrees with the revised approach to model efficacy of initial and subsequent BSC. **Further discussion (slide 24):** When using direct head-to-head trial, should direct EULAR or mapped (from ACR) responses be used to model efficacy of filgotinib and BSC?	Yes



*Cost of MTX also assumed for MTX-ineligible population, as a proxy for the cost of csDMARDs (limited impact on results expected)

Issue 8: Utility values

Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
EQ-5D scores were mapped from HAQ-DI and pain scores (Hernandez-Alava et al; TA375) The company used HAQ-DI scores to estimate VAS pain scores The ERG used baseline VAS pain scores from FINCH (constant) The technical team considered both approaches have limitations and both may be relevant to decision-making; it requested scenario analysis using empirical EQ-5D data from the trial	The company submitted cross-comparison of the total QALYs accrued with the mapping algorithm (company approach) and EQ-5D data from the trial The ERG was satisfied that QALY outputs are similar using empirical and mapped EQ-5D values and preferred to use the company approach in its base case (original ERG approach used in scenario analysis).	Agrees with the ERG opinion but this should be further discussed by the committee.	Yes (original and updated base case)

Further discussion (slide 25): Is company's approach to mapping utility values acceptable for decision-making?

Outstanding issues after technical engagement

- **Issue 2 Relevant comparators and treatment sequences:** Is selection of comparators and treatment sequences appropriate for decision-making (severe population)? S
- **Issue 3 Generalisability of FINCH trials:**
  - Are FINCH trials generalisable to the decision problem and NHS clinical practice? M S
  - Is it appropriate to use data from moderate-severe population to model efficacy in severe RA? S
  - Is it appropriate to assume monotherapy has similar efficacy to combination therapy? M S
- **Issue 4 Network meta-analysis:** Is company's network meta-analysis suitable for decision-making for severe RA population? S
- **Issue 5. Rate of progression from moderate to severe RA:** Is the company's revised approach to modelling progression appropriate? M
- **Issue 6 Treatment sequence upon progression from moderate to severe RA:** What is the most appropriate treatment sequence after progression? M
- **Issue 7 Modelling BSC:** When using direct head-to-head trial, should direct EULAR or mapped (from ACR) responses be used to model efficacy of filgotinib and BSC? M
- **Issue 8 Utility values:** Is company's approach to mapping utility values acceptable for decision-making? M S

Issue 2. Relevant comparators and treatment sequences

Background

- Company submission (base case) might have omitted relevant comparators and treatment sequences:

Population	Comparators for filgotinib	Subsequent treatment sequence
2a	ADA, ETN, BAR, TCZ CS	ABT SC→BSC
2b1	ADA*, ETN*, BAR*	RTX*→TCZ SC*→BSC
2b2	ADA*, ETN*, BAR*	TCZ SC*→BSC
2b3	ADA*, ETN*, BAR*	ABT SC*→BSC
3a	ABT SC, BAR, TOF	BSC
3b	ABT SC*, TCZ SC*, SAR*, BAR*	BSC
4	RTX*	TCZ SC*→BSC
5	TCZ SC*, SAR*	BSC

Responses – comparators missing:

ERG: **2b:** TOF (included in ERG scenario analyses)

Clinical expert: other JAK inhibitors (especially **5**)

Responses – treatment sequences

Clinical expert & BSR:
- Generally agree with modelled sequences
- Certolizumab used in women of child-bearing age (no placental-foetal transfer)

2a second-line advanced treatment:
- TCZ/SAR most relevant
- ABT second most relevant
- RTX used in some trusts** (but not standard care in the UK)

Company: provided scenario analyses using TCZ or SAR as second-line advanced treatment for population **2a**

2a, 3a, 3b third-line treatment: BSC, TCZ, SAR, ABT or other JAK inhibitors
NRAS: unlikely BSC used as 3rd line

Technical team: Modelling 3rd line BSC aligned with prior appraisals

Is selection of comparators and treatment sequences appropriate for decision-making?

*In combination with MTX; **as monotherapy or in combination with leflunomide; ABT=abatacept; ADA=adalimumab; BAR=baricitinib; BSC=best supportive care; ETN=etanercept; FIL=filgotinib; MTX=methotrexate; RTX=rituximab; SAR=sarilumab; TCZ=tocilizumab

Issue 3. Generalisability of FINCH trials

Background

- All patients enrolled in FINCH trials received filgotinib with methotrexate or other csDMARDs. The company assumed monotherapy would have similar efficacy
- The company used data from the moderate-severe population to model efficacy in the severe population (21% to 24% patients had moderate disease)
- 14 UK participants (0.8%) in FINCH 1 and 9 UK participants (2%) in FINCH 2

Responses from engagement

Company: provided subgroup data for patients with severe RA from both FINCH 1 & 2 trials

Clinical expert & BSR:

- Generally bDMARDs in combination are more effective than bDMARD monotherapy but this is less clear for IL-6 and JAK inhibitors; FINCH 3 data may suggest that monotherapy is not significantly different to combination therapy in csDMARD naïve individuals
- Treatment response linked to the initial burden of disease, so ACR 50 and 70 responses, and good EULAR responses harder to reach in severe disease

ERG: Baseline patient characteristics in FINCH indicate generalisability to NHS clinical practice

- Severe population: ACR responses similar to the full trial population; EULAR responses lower

Technical team: Similar efficacy of combination therapy and monotherapy accepted in prior appraisals (e.g. TA485); using data from moderate-severe population to model severe population is consistent with prior appraisals (e.g. GID-TA10389)

Are FINCH trials generalisable to the decision problem and NHS clinical practice? Is it appropriate to use data from moderate-severe population to model efficacy in severe RA? Is it appropriate to assume monotherapy has similar efficacy to combination therapy?

Issue 4. Network meta-analysis (NMA)

Background

- Direct evidence only against adalimumab and BSC (MTX/csDMARDs)
- Company did 2 NMAs, for csDMARD-IR and bDMARD-IR populations
- Outcomes: ACR response at 12 and 24 weeks, and EULAR response at 24 weeks
- Studies for monotherapies and studies prior to 1999 were excluded

Responses from engagement

Company provided a rationale for excluding studies identified by the ERG as potentially relevant, and a cross-comparison of their NMA and NMA published by Fakhouri et al. 2020

Comparison: cDMARD-IR population; 24 weeks data	Fakhouri et al. 2020			Filgotinib NMA			Absolute difference		
	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70
FIL 200mg +MTX	n/a	n/a	n/a	[redacted]	[redacted]	[redacted]	n/a	n/a	n/a
BARI 4mg + MTX	65.9%	41.0%	21.8%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40mg + MTX	58.2%	38.3%	17.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200mg + MTX	70.2%	46.1%	27.2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN + MTX	71.8%	49.2%	23.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 3mg + MTX	55.5%	33.4%	14.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT IV 10mg + MTX	57.8%	33.8%	13.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT SC + MTX	59.1%	38.5%	16.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MTX	56.1%	32.2%	11.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SARI 200mg +MTX	60.8%	38.7%	16.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ 8mg IV + MTX	57.3%	40.4%	25.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO/MTX	27.3%	12.3%	4.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG still believes that potentially relevant studies were excluded from the NMA

Is company's NMA suitable for decision-making for severe RA population?

Issue 5. Rate of progression from moderate to severe RA

Background

- Model assumes a proportion of patients with moderate disease (DAS28 3.2 to 5.1) can progress to severe disease (DAS28 > 5.1) each year, and start treatment for severe RA.
- Company used linear mixed model, gamma, and a midpoint DAS28 score of 4.15 as a mean baseline value; the ERG used the mean DAS28 score from the FINCH trials ([redacted]).
- Company's approach seems to underestimate and the ERG's overestimate progression

Responses from engagement

Company: provided analysis using mean DAS28 score from FINCH1 ([redacted]). When BSC placebo response is incorporated (issue 7), rate of progression is lower than in the ERG analysis

Time	Company initial base case: midpoint DAS28 at baseline*	ERG base case: FINCH 1 DAS28 mean at baseline*	Company updated base case: FINCH1 DAS28 mean*; placebo effect incorporated
Year 2	5%	26%	11%
Year 3	12%	44%	24%
Year 4	14%	49%	29%
Year 5	24%	59%	39%
		* linear mixed model, gamma, used in all analyses	

Issue 5. Rate of progression from moderate to severe RA

Clinical expert & BSR:

- Expected mean/median DAS28 score among people with moderate RA in the UK:
  - Pan et al. 2019: mean, 4.34 (SD, 0.5);
  - Hyrich et al. 2009: median, 4.33 (IQR, 3.84 to 4.68)
- Expected progression among people with moderate RA in the UK
  - ERAN database (Kiely et al. 2009): 19% at 2 years
  - Accurate long-term data lacking

NRAS:

- Submitted unpublished analysis of ERAN database: 1,465 patients with early RA (<2 years disease duration, no prior csDMARD) recruited between 1986 and 1999 from nine hospitals in England, followed yearly for up to 25 years (median follow-up, 10 years)
- Average annual HAQ progression was 0.012 among all patients
- 868 patients had a mean DAS28 in the moderate range:
  - 36.8% had high HAQ progression, defined as a progression rate ≥0.06 per year
  - Only 119 (13%) patients had a DAS28 that was never in the severe range

ERG is satisfied that the company's new approach uses trial data from FINCH 1: it results in a progression rate that is closer to that observed in the ERAN database

Is the company's revised approach to modelling progression appropriate?

SD=standard deviation; IQR: interquartile range.

Moderate RA

Issue 6. Treatment sequence upon progression from moderate to severe RA

Background

- Technical team: treatment upon progression could depend on initial treatment for moderate RA

	Initial treatment	Treatment upon progression from moderate to severe RA			
		Company base case	Scenario 1a*	Scenario 2a*	Scenario 3a*
1a	Filgotinib	ADA→ABT→BSC	ADA→TCZ→BSC	ADA→ABT→BSC	ADA→TCZ→BSC
	BSC	ADA→ABT→BSC	ADA→TCZ→BSC	ADA→TCZ→BSC	ADA→FIL→BSC
1b	Filgotinib	ADA→RTX→TCZ→BSC	as base case	ADA→RTX→ABT→BSC	ADA→RTX→TCZ→BSC
	BSC	ADA→RTX→TCZ→BSC	as base case	ADA→RTX→TCZ→BSC	ADA→RTX→FIL→BSC

*Scenarios 1b/2b/3b used sarilumab instead of tocilizumab (similar ICERs)

Responses from engagement

Company submitted scenario analyses with alternative treatment sequences but noted that Scenario 2&3 do not assess cost-effectiveness of filgotinib, but rather of 2 different sequences

Clinical expert & BSR:
- Would follow standard treatment sequence for severe disease: no data to support alternative sequence if filgotinib received for moderate disease (could impact on considering another JAK inhibitor)
- Filgotinib could be used if not used for moderate disease (at any line)

Technical team: Scenario 2 was considered plausible by clinical experts in GID-TA10759

ERG: All but scenario 1 in population 1b increased the ICERs (scenarios 3 the most)
- Alternative sequences appropriate if they follow rules that could be plausible in clinical practice (for example, use of one treatment precludes the use of another treatment later on)
- Run a scenario using etanercept as first line advanced treatment – no impact on ICERs

What is the most appropriate treatment sequence after progression?

Issue 7. Using direct versus mapped EULAR data

- Company's NMA mapped ACR to EULAR reposes because the latter were rarely reported in studies included in the NMA
- FINCH 1 study reported EULAR responses, which could be directly used for analyses based on head-to-head trial data (moderate RA)

In company's revised base case for moderate RA population, based on direct head-to-head data, EULAR responses were mapped from ACR

The ERG noted company's approach is consistent with their approach for severe population, but using EULAR data collected in the trial could provide more accurate estimates

In response to ERG request, **the company** provided analyses using direct EULAR data. This slightly increases ICERs compared to their base case approach.

The ERG prefers using EULAR data collected in the trial in their base case (small in crease in ICER compared to company base case)

Technical team: using direct EULAR data is aligned with GID-TA10759

When using direct head-to-head trial, should direct EULAR or mapped (from ACR) responses be used to model efficacy of filgotinib and BSC?

Issue 8. Utility values

Background

- EQ-5D scores were mapped from HAQ-DI and pain scores (Hernandez-Alava et al; TA375)
- The company used HAQ-DI scores to estimate VAS pain scores
- The ERG used baseline VAS pain scores from FINCH (constant)
- The technical team considered both approaches have limitations and both may be relevant to decision-making; it requested scenario analysis using empirical EQ-5D data from the trial
- This has limited impact on the cost-effectiveness results (net health benefits) in the severe RA subgroup, but may have more impact on cost-effectiveness analyses in the moderate subgroup

Responses from engagement

Company submitted cross-comparison of the total QALYs accrued with the mapping algorithm (company approach) compared with the empirical values

Moderate population	Filgotinib 200mg	BSC (placebo/MTX)	Incremental
Total QALYs using mapping algorithm	[redacted]	[redacted]	[redacted]
Total QALYs using empirical trial data	[redacted]	[redacted]	[redacted]

ERG:

- Was satisfied that QALY outputs are similar using empirical and mapped EQ-5D values
- Agreed with the company's approach to map utilities and used this approach in its base case; used original ERG approach in scenario analyses for moderate population (ICERs increase)

Is company's approach to mapping utility values acceptable for decision-making?

Confidential discount for filgotinib

The company agreed 2 PAS discounts with NHS England:

- one applicable to moderate-severe population (higher discount),
- one applicable if filgotinib is recommended in severe RA population only (lower discount)

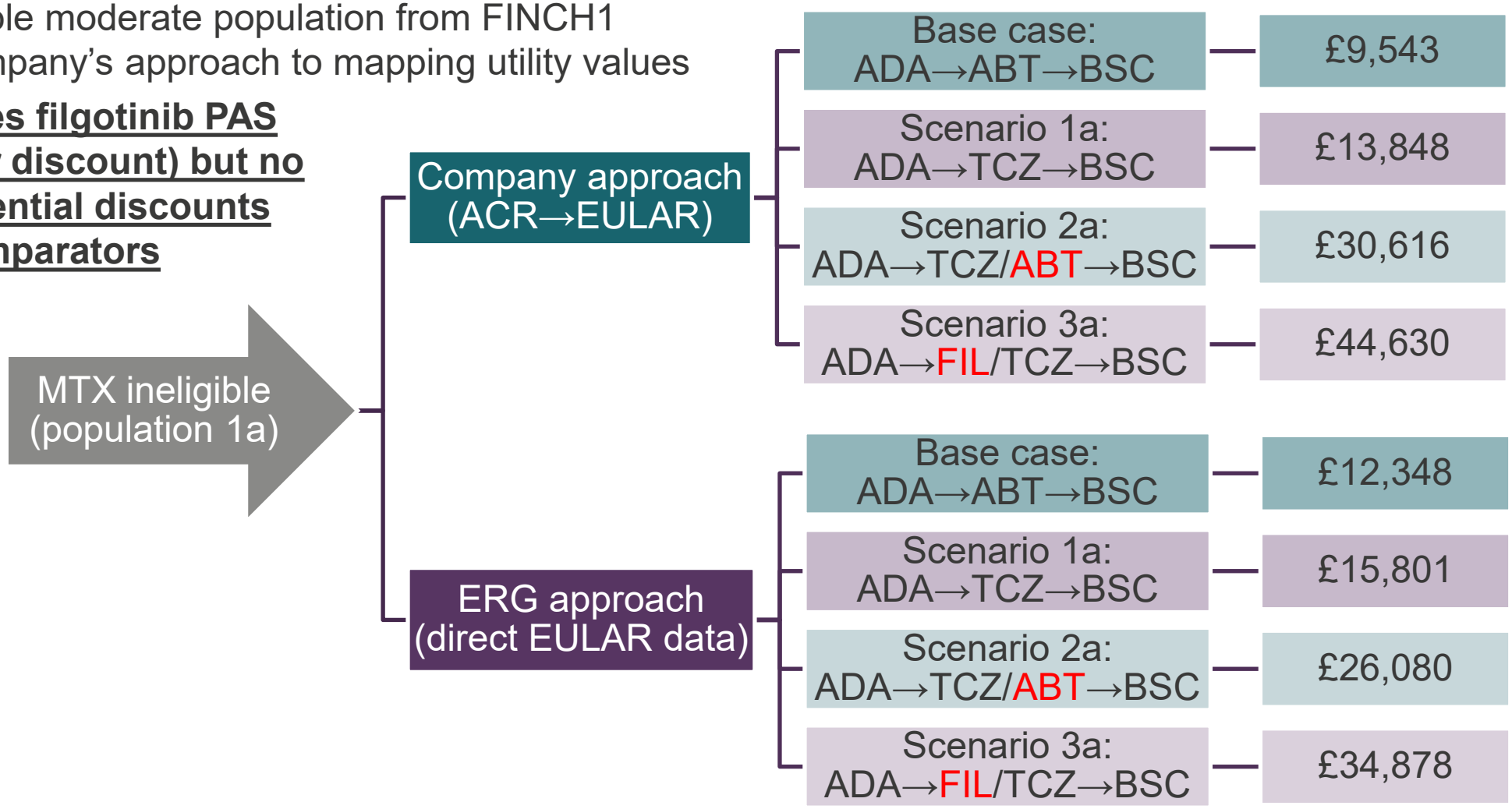
During technical engagement, the company submitted improved PAS discount for the moderate-severe population

Cost-effectiveness results: population 1a (MTX-ineligible)

All analyses based on direct head-to-head trial data for both filgotinib and BSC (placebo/csDMARDs):

- Whole moderate population from FINCH1
- Company's approach to mapping utility values

Includes filgotinib PAS (higher discount) but no confidential discounts for comparators



Note: Differential treatment (depending if filgotinib was used for moderate RA or not) highlighted in red.

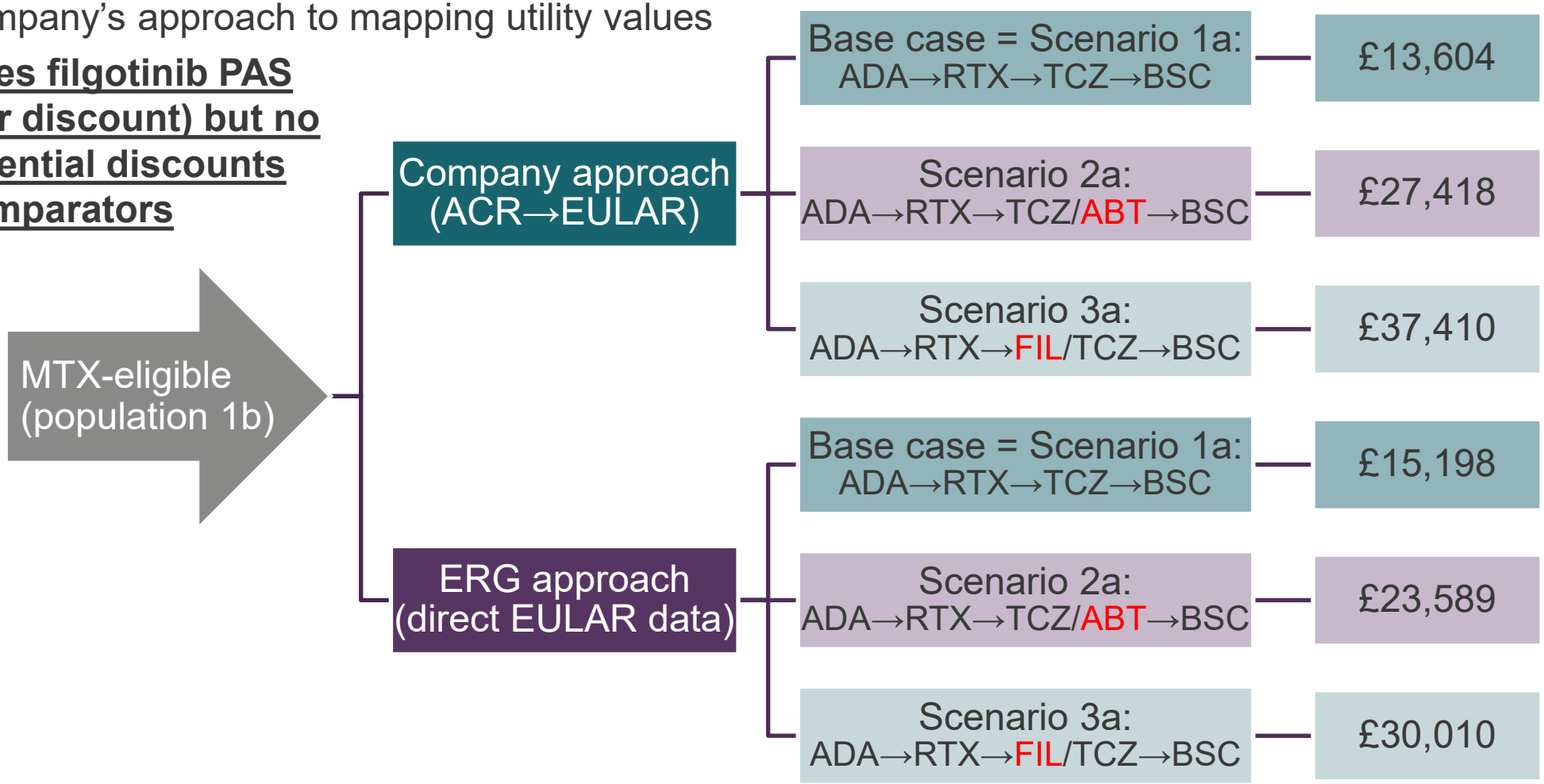
Note: Scenarios **b** include sarilumab instead of tocilizumab and produce very similar ICERs to scenarios **a.**

Cost-effectiveness results: population 1b (MTX-eligible)

All analyses based on direct head-to-head trial data for both filgotinib and BSC (placebo/csDMARDs):

- Whole moderate population from FINCH1
- Company's approach to mapping utility values

Includes filgotinib PAS (higher discount) but no confidential discounts for comparators



Note: Differential treatment (depending if filgotinib was used for moderate RA or not) highlighted in red.

Note: Scenarios **b** include sarilumab instead of tocilizumab and produce very similar ICERs to scenarios **a.**

Cost-effectiveness results: additional scenarios

All analyses based on direct head-to-head trial data for both filgotinib and BSC (placebo/MTX)

Includes filgotinib PAS (higher discount) but no confidential discounts for comparators

	ICER for population 1a (MTX-ineligible)	ICER for population 1b (MTX-eligible)
Company base case	**£9,543**	**£13,604**
Scenario: using efficacy data for FINCH 1 moderate subgroup with ≥2 csDMARD exposures	£9,794	£14,000
Scenario: using efficacy data for FINCH 1 moderate subgroup with ≥2 csDMARD failures*	£5,448	£10,109
ERG base case	**£12,348**	**£15,198**
Scenario: progression based on DAS28 midpoint score (lower progression rate)	£14,584	£16,924
Scenario: utilities based on baseline pain	£15,996	£19,616
Scenario: etanercept as first-line advanced treatment after progression to severe RA	£11,966	£14,759

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*defined as prior csDMARD discontinuation due to inadequate response, loss of response or intolerance which included allergic response.
Note: company scenarios for alternative populations were not verified by the ERG.

Introduction to net health benefit analysis

- Directly addresses the question on how to maximise health from a defined budget
- Net health benefit (NHB) is a difference between the total expected QALYs gained (or lost) by the individual having treatment and the QALYs lost (or gained) elsewhere in the system as a result of the money expended (or saved) by adopting the new intervention compared with another (opportunity cost)
- Converts costs to units of health effect using maximum acceptable ICER as an "exchange factor":

$$NHB = QALYs - (costs / maximum\ acceptable\ ICER)$$

- **The highest NHB indicates the most cost-effective intervention**

Summary of cost-effectiveness results: severe RA

Using confidential commercial arrangements for FIL, ABA, BAR, SAR, TOF, and biosimilars: ADA (Humira), ETN, RTX (cheapest biosimilars available); NHBs at £20,000 and £30,000/QALY gained

Population	Company base-case (higher FIL discount; company utilities)	ERG new base-case (lower FIL discount; company utilities)	ERG scenario (lower FIL discount, alternative utilities)	2a: 2nd line SAR/TCZ[a] 2b: TOF as comparator[b]
2a	• Highest NHB	• Similar NHB to ADA and ETN • Positive NHB vs BAR and TCZ	• Similar NHB to ADA and ETN • Positive NHB vs BAR and TCZ	• Similar NHB to ADA and ETN • Positive NHB vs BAR and TCZ
2b1	• Highest NHB	• Similar NHB to ADA and ETN • Positive NHB vs BAR	• Similar NHB to ADA and ETN • Positive NHB vs BAR	• FIL similar NHB to ADA and ETN; • Positive NHB vs BAR and TOF
2b2	• Highest NHB	• Similar NHB to ADA and ETN • Positive NHB vs BAR	• Similar NHB to ADA and ETN • Positive NHB vs BAR	• Highest NHB (ADA not included in comparison)
2b3	• Highest NHB	• Similar NHB to ADA and ETN • Positive NHB vs BAR	• Similar NHB to ADA and ETN • Positive NHB vs BAR	• Highest NHB (ADA not included in comparison)
3a	• Highest NHB	• Highest NHB	• Highest NHB	n/a
3b	• Highest NHB	• Highest NHB	• Highest NHB	n/a
4	• Negative NHB vs RTX[c]	• Negative NHB vs RTX[c]	• Negative NHB vs RTX[c]	n/a
5	• Highest NHB	• Highest NHB	• Highest NHB	n/a

Green = cost-effective vs comparator(s) | Yellow = similar cost-effectiveness | Red = not cost effective

[a] ERG scenario analysis using SAR/TCZ as a second-line treatment option for population 2a; [b] ERG scenario including TOF as a comparator for population 2b (ERG utilities); [c] RTX dominates FIL (RTX is cheaper and more effective than FIL); ABA=abatacept; ADA=adalimumab; BAR=baricitinib; ETN=etanercept; FIL=filgotinib; NHB=net health benefit; RTX=rituximab; SAR=sarilumab; TCZ=tocilizumab; TOF=tofacitinib.

Innovation

- Oral treatment rather than SC or IV
- Additional JAK inhibitor option
- The technical team considers that all benefits of the treatment are captured in the model

Equality and diversity

- People with RA may be protected under Equality Act 2010 (disability)
- BAME populations underrepresented - education also needed to ensure adherence to treatment
- Filgotinib and some other bDMARDS may be contraindicated for pregnant women

Outstanding issues after technical engagement

- **Issue 2 Relevant comparators and treatment sequences:** Is selection of comparators and treatment sequences appropriate for decision-making (severe population)? — S
- **Issue 3 Generalisability of FINCH trials:**
  - Are FINCH trials generalisable to the decision problem and NHS clinical practice? — M S
  - Is it appropriate to use data from moderate-severe population to model efficacy in severe RA? — S
  - Is it appropriate to assume monotherapy has similar efficacy to combination therapy? — M S
- **Issue 4 Network meta-analysis:** Is company's network meta-analysis suitable for decision-making for severe RA population? — S
- **Issue 5. Rate of progression from moderate to severe RA:** Is the company's revised approach to modelling progression appropriate? — M
- **Issue 6 Treatment sequence upon progression from moderate to severe RA:** What is the most appropriate treatment sequence after progression? — M
- **Issue 7 Modelling BSC:** When using direct head-to-head trial, should direct EULAR or mapped (from ACR) responses be used to model efficacy of filgotinib and BSC? — M
- **Issue 8 Utility values:** Is company's approach to mapping utility values acceptable for decision-making? — M S

Issue 1 Comparison of ACR and EULAR responses at 24 weeks across moderate RA populations

ACR responses at 24 weeks

	Filgotinib 200mg			Placebo		
	Overall moderate population (n=104)	≥2 prior DMARDs (N=53)	1 prior DMARD (N=51)	Overall moderate population (n=128)	≥2 prior DMARDs (N=66)	1 prior DMARD (N=62)
ACR20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company submission pages 80 to 81 and Figure 14; company responses to TE, Tables 53, 56, 59.
Note: Tables 53, 56, 59 incorrectly labelled number of patients as 35 and 37 – correctly by NICE technical team.

EULAR responses at 24 weeks

	Filgotinib 200mg			Placebo		
	Overall moderate population (n=[redacted]*)	≥2 prior DMARDs (N=[redacted]*)	1 prior DMARD (N=[redacted]*)	Overall moderate population (n=[redacted]*)	≥2 prior DMARDs (N=[redacted]*)	1 prior DMARD (N=[redacted]*)
Good	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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*with outcome assessment at 24 weeks.
Source: Company submission Table 14, company responses to TE, Tables 67 and 68.

Issue 2. Scenario analyses for population 2a

Analyses include filgotinib PAS (higher discount) but not confidential discounts for comparators

	Incr costs (£)	Incr QALYs	ICER vs FIL (£/QALY)	Incr ICER (£/QALY)	NHB @ £20,000	Incr NHB vs FIL	NHB @ £30,000	Incr NHB vs FIL
Second-line abatacept (company original base case)								
FIL	-	-	-	-	1.924		3.946	-
ADA	18,514	-0.013	Dominated	Dominated	0.985	-0.939	3.316	-0.630
ETN	3,251	0.076	342,679 SW	42,543	0.898	-1.025	3.284	-0.662
BAR	8,015	-0.039	1,231,213 SW	Dominated	0.459	-1.465	2.978	-0.969
TCZ SC	5,001	-0.048	Dominated	Dominated	0.161	-1.763	2.763	-1.183
Second-line sarilumab								
FIL	-	-	-	-	2.77	-	4.491	-
ADA	18,316	-0.013	Dominated	Dominated	1.841	-0.929	3.868	-0.624
ETN	4,173	0.079	341,862 SW	52,901	1.712	-1.058	3.807	-0.684
BAR	7,546	-0.041	1,208,118 SW	Dominated	1.293	-1.477	3.515	-0.976
TCZ SC	4,390	-0.050	Dominated	Dominated	1.024	-1.746	3.319	-1.173
Second-line tocilizumab								
FIL	-	-	-	-	2.908	-	4.552	-
ADA	18,278	-0.014	Dominated	Dominated	1.981	-0.928	3.928	-0.623
ETN	4,510	0.086	317,669 SW	52,727	1.841	-1.067	3.864	-0.688
BAR	7,355	-0.045	1,109,973 SW	Dominated	1.428	-1.480	3.574	-0.978

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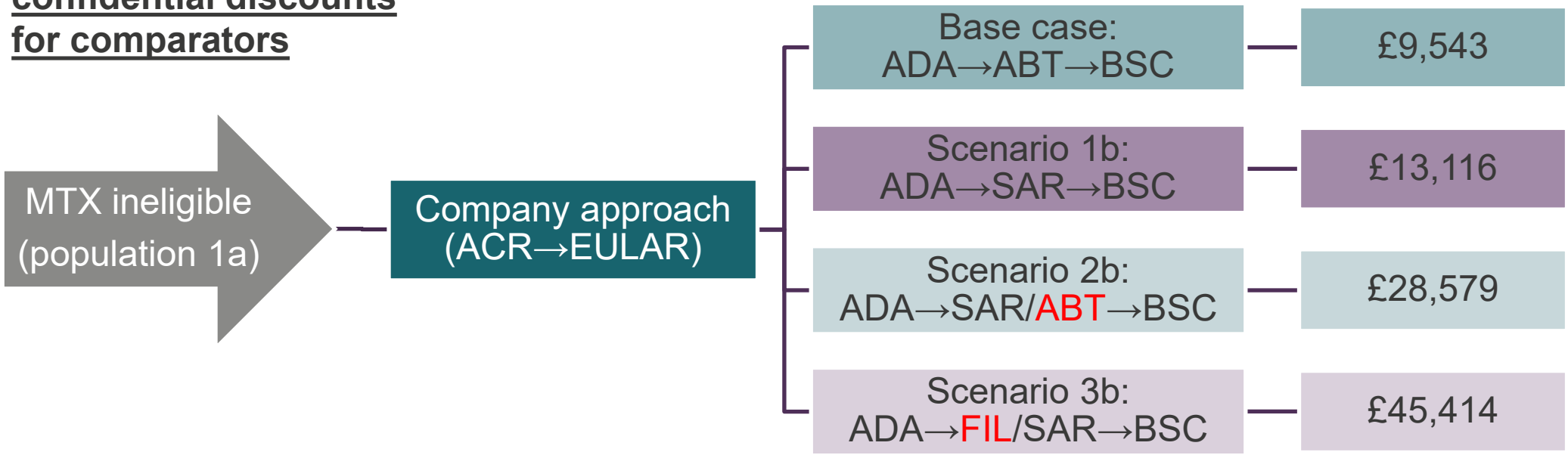
ADA=adalimumab; BAR=baricitinib; ETN=etanercept; FIL=filgotinib; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SC=subcutaneous; TCZ=tocilizumab.
Note: NHBs calculated by NICE (small discrepancies possible due to rounding).

Cost-effectiveness results: population 1a (MTX-ineligible) Scenarios B (with sarilumab instead of tocilizumab)

All analyses based on direct head-to-head trial data for both filgotinib and BSC (placebo/MTX):

- Whole moderate population from FINCH1
- EULAR mapped from ACR

Includes filgotinib PAS (higher discount) but no confidential discounts for comparators



Cost-effectiveness results: population 1b (MTX-eligible) Scenarios B (with sarilumab instead of tocilizumab)

All analyses based on direct head-to-head trial data for both filgotinib and BSC (placebo/MTX):

- Whole moderate population from FINCH1
- EULAR mapped from ACR

Includes filgotinib PAS (higher discount) but no confidential discounts for comparators