NICE National Institute for Health and Care Excellence

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Slides for the public

Fedratinib for splenomegaly and symptoms in myelofibrosis [ID1501]

Chair's presentation – Stephen O'Brien

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ERG: ScHARR

Technical team: Stephen O'Brien, Catie Parker, Charlie Hewitt, Ross Dent

Company: Celgene, a BMS Company

ACM 2: 11 August 2021

Fedratinib (Inrebic, Celgene)

Company's positioning is narrower than full marketing authorisation

Marketing authorisation (granted 08/02/2021)	'For the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor-naïve or who have been treated with ruxolitinib.' Fedratinib has not been studied in patients with platelets <50 x 10^9 /L at baseline and may not be appropriate for use in this population
Mechanism of action	Kinase inhibitor with activity against wild-type and mutationally activated JAK2
Administration	Single oral dose of 400 mg daily (4 x 100 mg capsules) taken with or without food
Price	• The list price is £6,120 per pack (120 x 100 mg capsules) • [redacted] 52-week cost (about 1 year) • Simple PAS discount approved – **updated after first committee meeting**

JAK, Janus kinase; PAS, patient access scheme

Background

Comparator	Best available therapy (BAT, 88.5% ruxolitinib)
Clinical trial	JAKARTA-2, single-arm phase 2 study (N=97, intermediate-2/high-risk group n=81)
Key results (CHMP response definition*)	Proportion of patients with spleen response after 6 cycles: ITT population, 22.7% and **intermediate-2/high-risk population,** [redacted]
ITC for response with BAT	No direct evidence vs. BAT, so company did a matching-adjusted indirect comparison (MAIC)
ITC result vs. BAT	Spleen/symptom response at 24 weeks: OR [redacted] (95% confidence interval [redacted])
BAT overall survival	Schain et al. 2019 (post-ruxolitinib discontinuation)
Model	Discrete event simulation. 5 health states: BAT, fedratinib, BAT (post-fedratinib), supportive care, death. 2 event types: treatment discontinuation and death
Updated ICERs after ACD consultation (fedratinib PAS, ruxolitinib list price)**	
Company ICER	£18,294/QALY
ERG-preferred ICERs	£43,729/QALY (no ruxolitinib wastage) £23,186/QALY (including ruxolitinib wastage)

* Counting people responding after up-titration as non-responders

** Accounting for confidential discounts for other treatments increases ICERs

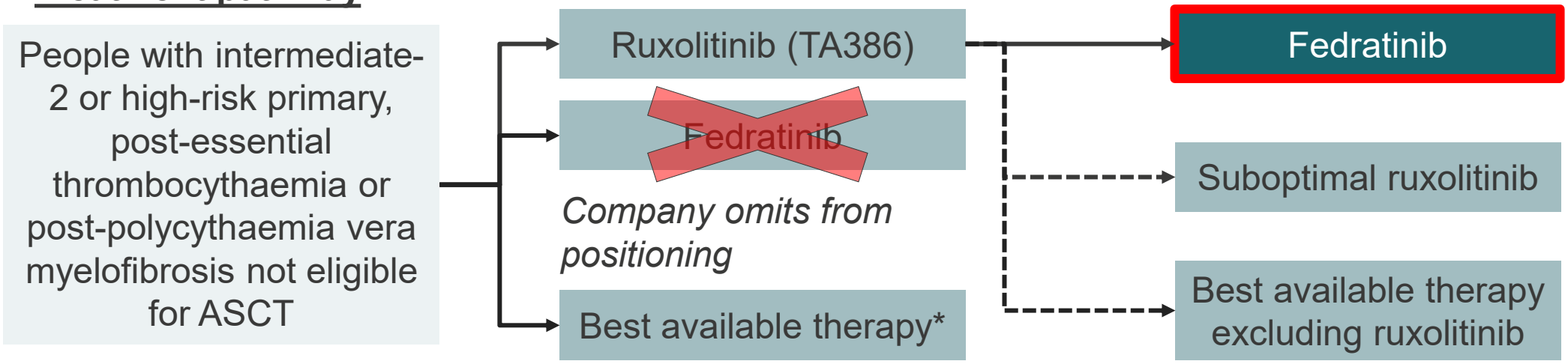
CHMP, Committee for Medicinal Products for Human Use; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intent to treat; OR, odds ratio; QALY, quality-adjusted life year

Myelofibrosis background and treatment pathway

Company positions fedratinib in people who have had ruxolitinib

- Bone marrow cancer in which the marrow is replaced by scar (fibrous) tissue
- ~2-3 per 100,000 diagnosed annually
- Presents as primary or secondary to polycythaemia vera or essential thrombocythaemia
- Symptoms include spleen enlargement (splenomegaly), dyspnoea (shortness of breath), early satiety (feeling full), faecal incontinence, fatigue and severe itching

Treatment pathway



Committee's conclusion (ACD 3.3)

Fedratinib positioning appropriate: intermediate-2/high-risk after ruxolitinib

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* Best available therapy includes: hydroxycarbamide, other chemotherapies, androgens, radiation therapy, red blood cell transfusion ASCT, allogenic stem cell transplant

Patient, carer & clinical perspectives

- **Unmet need** for new treatment options after ruxolitinib. Often disease does not adequately respond to ruxolitinib (or loses response)
- Treatment aims to **improve symptoms**, **reduce spleen size**, and **improve life expectancy**

People with myelofibrosis experience:

- **Fatigue** or debilitating exhaustion that reduces quality of life
- **Enlarged spleen** associated with pain, discomfort and early satiety
- **Severe itching** described as 'being rolled naked in nettles'
- **Night sweats**
- **Bone pain** not alleviated by painkillers
- **Mental health** challenges such as worrying about limited treatment options

> My fatigue and anaemia had a lot of impact on my high intensity job as a doctor, I had to reduce hours"

> My work efficiency fell to 50-60%. I recognised that any further deterioration to my health would result in my giving up work"

> I participate[d] in the JAKARTA trial. My symptoms lessened – spleen reduced, appetite improved, fatigue lessened and I started to lead a normal life, working full-time"

ACD consultation responses

- Consultee comments from:
  - Celgene, a BMS company (company)
  - Leukaemia Care
  - MPN Voice
  - Claire Harrison (clinical expert)

Consultation comments summary

Expert and patient organisation responses to ACD

Unmet need in a population with a short life expectancy

People whose disease does not respond to ruxolitinib have no other effective treatment options. These people have a poor prognosis

Rarity of myelofibrosis impacts the appraisal

- Myelofibrosis is a relatively rare disease. This makes it more difficult to collect data but does not affect the effectiveness of fedratinib or the unique benefit it provides
- Myelofibrosis is not so rare that fedratinib could qualify as a highly specialised technology
- People with myelofibrosis for whom ruxolitinib is no longer appropriate are being treated unfairly, and are being disadvantaged by the single technology appraisal process

Fedratinib improves quality of life

Fedratinib can improve quality of life for a group of people with a high symptom burden

The Cancer Drugs Fund could resolve uncertainty

Given the unmet need and the ongoing FREEDOM-2 trial, fedratinib should be considered for the Cancer Drugs Fund

Summary of company's ACD response (1/2)

Key uncertainty	Committee's conclusion	Company response
Comparator *(ACD 3.4)*	Mixed comparator of people having ruxolitinib and BAT appropriate, but evidence in model should reflect it	No response
Model *(ACD 3.9)*	A simpler model may have been more robust, given available data	Provided justification for model structure
BAT evidence *(ACD 3.10)*	Using multiple sources of evidence for BAT increases uncertainty	No response
Fedratinib survival *(ACD 3.11)*	Fedratinib likely to extend survival, but extent of survival benefit highly uncertain	Evidence from 4 studies quantifying spleen response and survival relationship
Next treatment *(ACD 3.13)*	Most people would likely continue fedratinib after disease loses response, but the proportion is uncertain	Updated assumption: 65% of initial responders continue fedratinib after relapse

ACD, appraisal consultation document; BAT, best available therapy; ITC, indirect treatment comparison

Summary of company's ACD response (2/2)

Key uncertainty	Committee's conclusion	Company's response
Ruxolitinib costs *(ACD 3.15)*	Ruxolitinib costs are uncertain but not a key driver of results (at ACM1)	Provided rationale for including 5% ruxolitinib wastage
End of life *(ACD 3.16)*	Fedratinib does not meet end of life criteria	Justification for meeting end of life (including chart review baseline characteristics)
Cost-effectiveness *(ACD 3.17)*	Cost-effectiveness estimates above range considered an acceptable use of NHS resources	• Updated PAS • Updated base case assumptions
Cancer Drugs Fund *(ACD 3.21)*	Not recommended for use in the Cancer Drugs Fund	• Reiterated CDF and FREEDOM-2 could resolve uncertainty • Stated that crossover in trial should not prevent a CDF recommendation → it has been a feature of other successful appraisals (TA386, ruxolitinib)

ACD, appraisal consultation document; CDF, Cancer Drugs Fund; PAS, patient access scheme

Key unresolved issues after first meeting

Issue	Impact on ICER	Resolved?
Complexity of cost-effectiveness model (*ACD 3.9*) Is the model robust for decision making?		
Survival modelling and fedratinib survival benefit (*ACD 3.11*) Should fedratinib be assumed to have a survival benefit in the model?		
Proportion of people continuing fedratinib after relapse (*ACD 3.13*) • What % of people would continue fedratinib after relapse? • Would this % only apply to people initially responding to fedratinib?		
Ruxolitinib wastage (*ACD 3.15*) • Should 5% ruxolitinib wastage be included? • Does committee agree with basing ruxolitinib dosing on platelet count from global chart review (updated ERG assumption post-ACD)		
End of Life (*ACD 3.16*) Does the information presented change the committee's view on EoL?	N/A	

Partially resolved/for brief discussion Unresolved issue for committee discussion

 **Model driver**  **Unknown impact**  **Small impact**

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ACD, appraisal consultation document; EoL, end of life

Company model complexity

Issue background (ACD 3.9)

- **Company:** used discrete event simulation model similar to TA386 (ruxolitinib)
- **ERG:** model is complicated, models treatment arms differently and mixes evidence for BAT
- **Committee:** a simpler model structure may have been more robust, given available data

Company's ACD response

- Model structure challenges relate to weaknesses in data. Only overcome with more data
- Treatment arm modelling differences due to: data availability; different treatment pathways
- Some complexity arises from responder/non-responder split. A pooled approach (possible in existing model) yields similar ICERs, within 2% → supports modelling assumptions
- Oversimplifying a challenging decision problem may create separate issues
- Updated base case uses same AML transformation rate for both arms (committee preference). Otherwise company has not changed structure of model or evidence sources

ERG critique of company's ACD response

- Assessment of model is based on available data, not data that could become available
- View unchanged: model overly complex given data available (single-arm trial, clinical hold)

Is the company's model robust for decision making?

ACD, appraisal consultation document; AML, acute myeloid leukaemia; BAT, best available therapy; ICER, incremental cost-effectiveness ratio

Fedratinib survival benefit (1/2)

Issue background (ACD 3.11)

- **Company:** did naïve OS comparison of JAKARTA-2 and Schain et al. 2019 (company considered Schain represented people expected to have fedratinib)
  - Survival benefit for fedratinib vs BAT from model: 6.2 months
  - Association between spleen response and improved survival
- **ERG:** Schain not appropriate: reflects different population than model. JAKARTA-2 comparison with SIMPLIFY-2 (used for spleen response ITC) suggests no survival benefit
  - Acknowledges spleen response/survival link, but size of survival benefit uncertain
  - Assumed no survival benefit for fedratinib in base case
- **Committee:** fedratinib likely to extend survival, but extent of benefit is highly uncertain

Company's ACD response

- Spleen response rate in JAKARTA-2 was [redacted]%
  - Significantly higher than spleen response rate for BAT in SIMPLIFY-2 and PERSIST-2
- Noted 4 studies quantifying spleen response and survival
- Expect fedratinib would extend survival by more than 3 months

Stakeholder ACD comments

- Clinical expert opinion on fedratinib survival benefit not understood or accounted for
- Reduction in spleen size likely reflected in extended survival. Discussed internationally and accepted by other bodies including the FDA
- Although the fedratinib trial data does not prove a survival benefit, expert opinion is clear

ACD, appraisal consultation document; BAT, best available therapy; FDA, Food and Drug Administration; ITC, indirect treatment comparison

Fedratinib survival benefit (2/2)

ERG critique of company's ACD response

- JAKARTA-2 versus SIMPLIFY-2 showed no survival benefit at week 24 (crossover time in SIMPLIFY-2), table and figure right
- Survival benefit cannot be ruled out as short follow-up, but very uncertain
- Large survival difference in company's model at week 24 ([redacted]% fedratinib vs [redacted]% BAT) does not align with SIMPLIFY-2
- Company base case does not use spleen response as survival surrogate

MAIC results: Fedratinib vs BAT (SIMPLIFY-2), depending on prognostic factors matched

Prognostic factors	HR (95% CI)
None (naïve)	[redacted]
Risk category*	[redacted]
Risk category*, age and haemoglobin	[redacted]
Risk category*, age, haemoglobin, transfusion dependence, platelet counts	[redacted]

% of patients having ruxolitinib:

Schain:	0%
SIMPLIFY-2	88.5%
BAT arm in model	88.5%

Company survival comparison: fedratinib vs BAT (Schain)

[redacted]

[redacted]

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Is the company's modelled fedratinib survival benefit plausible?

ACD, appraisal consultation document; BAT, best available therapy; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison

Treatment after disease relapse (1/2)

Issue background (ACD 3.13)

- **Company:** Base case assumed people on BAT continue ruxolitinib after relapse, but people on fedratinib discontinue to BAT without ruxolitinib or supportive care after relapse
- **ERG:** Inconsistent assumptions. Likely most people would continue fedratinib or have ruxolitinib
- **Clinical experts:** expect people would continue fedratinib after relapse
- **Committee:** Most people likely to continue fedratinib, but the proportion is uncertain

Company's ACD response

- Updated base case assumes 65% of **initial responders** continue fedratinib after relapse
- JAKARTA-2 had 35% discontinuation (before clinical hold), US data [redacted]% discontinuation, suggesting discontinuation of less than 35% is not appropriate
- Scenario with [redacted]% RDI for continued fedratinib (vs [redacted]% for fedratinib before relapse)

ERG critique of company's ACD response

- Still inconsistent assumption between fedratinib and BAT: people on BAT (88.5% ruxolitinib – fixed proportion for model duration) do not stop ruxolitinib until supportive care, but some people having fedratinib stop fedratinib before supportive care
- Proportion continuing fedratinib has large impact on cost-effectiveness results
- [redacted]% is an arbitrary value. Dosing for ruxolitinib solely based on platelet count in model

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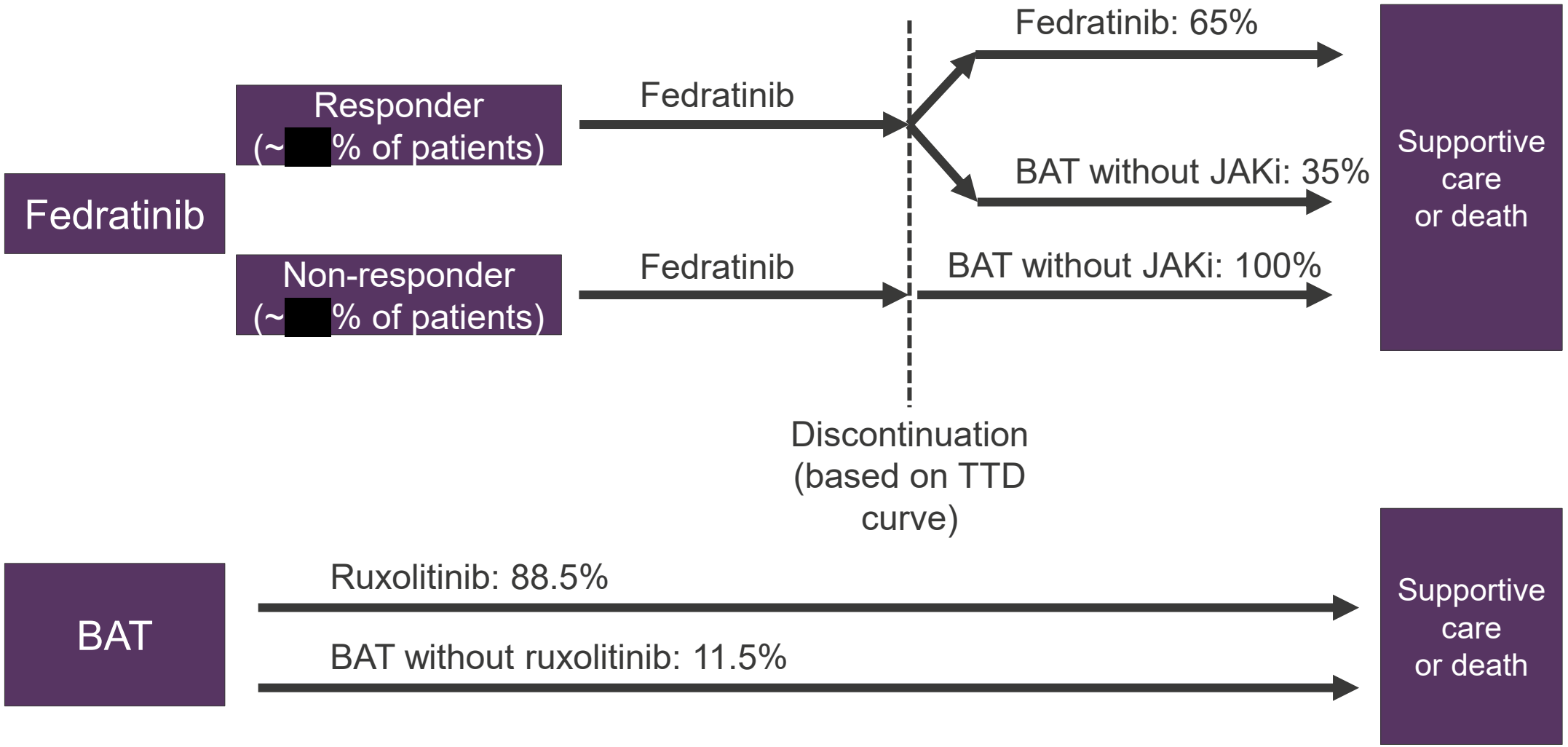
What proportion of people would continue fedratinib after relapse?

ACD, appraisal consultation document; BAT, best available therapy; RDI, relative dose intensity

Treatment after disease relapse (2/2)

Updated company base case: assumptions for fedratinib and BAT arms



BAT, best available therapy; JAKi, janus kinase inhibitor; TTD, time-to-treatment discontinuation

Ruxolitinib costs

Issue background (ACD 3.15)

- **Company:** Used platelet count distribution from JAKARTA-2 to estimate ruxolitinib costs and included 5% ruxolitinib wastage based on ERG analyses from TA386
- **ERG:** Mismatch between platelet count distribution from JAKARTA-2 and SIMPLIFY-2 (BAT response rate is taken from SIMPLIFY-2). Ruxolitinib costs likely overestimated
  - Inclusion of drug wastage not appropriate in line with committee decision from TA386
- **Committee:** Noted the uncertainty of ruxolitinib costs, but not key model driver (at ACM1)

Company's ACD response

- Informal discussions with clinicians suggest drug wastage for ruxolitinib may occur in practice
- Base case remains 5% ruxolitinib wastage

Platelet count	Ruxolitinib dose
<100 x 10^9/L	5 mg (lower price)
≥100 x 10^9/L	10/15 mg (higher price)

ERG critique of company's ACD response

- Inclusion of drug wastage not appropriate in line with committee decision from TA386
- Updated analyses use platelet count data from global chart review (unavailable before first meeting) as it likely better resembles SIMPLIFY-2, which is used for response ITC
  - [redacted]% (after removing people with unknown values) had platelet count < 100 x 10^9/L and therefore would have lower ruxolitinib dose, vs. [redacted]% from JAKARTA-2

Should ruxolitinib wastage be included? Does committee agree with basing ruxolitinib dosing on platelet count from global chart review?

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ACD, appraisal consultation document; ACM1, first appraisal committee meeting BAT, best available therapy; ITC, indirect treatment comparison

End of life, short life expectancy

Issue background (ACD 3.16)

- **Company:** Survival in patients who have had ruxolitinib are poor, around 13 to 16 months
- **Clinical experts:** Survival for disease relapsed/refractory to ruxolitinib is 18-24 months
- **ERG:** Studies cited by company done in people who stopped ruxolitinib. Does not match comparator in economic model (88.5% continue ruxolitinib)
  - Company's base case mean life expectancy for people on BAT is more than 2 years
- **Committee:** Uncertain, but evidence is not sufficiently robust to conclude that fedratinib met the criteria for end of life treatments

Life expectancy from model (months)

Life expectancy	Intervention	Company base case (Weibull for BAT)	ERG base case	Exponential curve for BAT*
Mean life expectancy (months)	Fedratinib	34.9	34.9	34.9
	BAT	28.7	34.9	23.3
	Incremental	6.2	0.0	11.6
Median life expectancy (months)	Fedratinib	[redacted]	[redacted]	[redacted]
	BAT	[redacted]	[redacted]	[redacted]
	Incremental	[redacted]	0.0	[redacted]

* See slide 19

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Does the information presented change the committee's view on EoL?

ACD, appraisal consultation document; BAT, best available therapy

End of life, short life expectancy

Company's ACD comments

- TA386: high-risk disease met end of life criteria. Therefore, it should hold for 42% of this modelled population (high-risk)
- Committee used mean life expectancy from company base case model to reject the criterion, but median is more appropriate because of immature Kaplan-Meier data
- Median modelled life expectancy is [redacted] months (BAT arm)
- Exponential curve is clinically plausible and yields mean life expectancy of 1.94 years
- Global chart review supports short life expectancy (below). To demonstrate similarities with JAKARTA-2, provided baseline characteristics for chart review at ACD consultation

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ACD, appraisal consultation document; BAT, best available therapy

End of life, short life expectancy

ERG critique of company's ACD response

- Values discussed at ACM1 and in company's response are from people who stop ruxolitinib → but model assumes 88.5% of people continue ruxolitinib based on proportion in SIMPLIFY-2, where survival appears better than Schain up to week 24
- Limited information on chart review; remains unclear how similar it is to JAKARTA-2 in terms of: high-risk disease status, relapsed/refractory and intolerant, and transfusion dependence

- Platelet count distribution appears very different between JAKARTA-2 and chart review
- Unclear what difference is between people classed as r/r/i and those with progressed disease in chart review
- Company did not use formal methods with clinicians to elicit estimates
- However, Weibull extrapolation aligns better with clinician consensus values

	BAT mean survival
Weibull	28.7 months
Exponential	23.3 months

ACD, appraisal consultation document; BAT, best available therapy; r/r/i relapsed, refractory, intolerant

Summary of key differences in revised base cases

Assumption	Company	ERG
Fedratinib survival benefit	Yes	No
% people continuing fedratinib after relapse	65% of responders (~[redacted]% of all people having fedratinib*)	88.5% of all people having fedratinib
Ruxolitinib wastage	Included	Included / excluded

ERG	Analyses also exclude gender from utility regressions, use [redacted]% 'suboptimal' fedratinib dose intensity and use platelet count distribution from chart review (provide scenarios with JAKARTA-2)

* 65% x [redacted]% of people responding to fedratinib

Company's cost-effectiveness results (FED PAS, RUX list price)

Technologies	Total			Incremental			
	Costs (£)	Life years	QALYs	Costs (£)	Life years	QALYs	ICER (£/QALY)
Deterministic							
BAT	[redacted]	2.394	1.359	-	-	-	-
Fedratinib	[redacted]	2.912	1.833	8,667	0.518	0.474	**18,294**
Probabilistic							
BAT	[redacted]	3.113	1.458	-	-	-	-
Fedratinib	[redacted]	3.986	2.138	17,783	0.873	0.681	**26,130**

Cost effectiveness results with confidential commercial arrangement for ruxolitinib will be considered in part 2. Accounting for this increases the cost-effectiveness estimates

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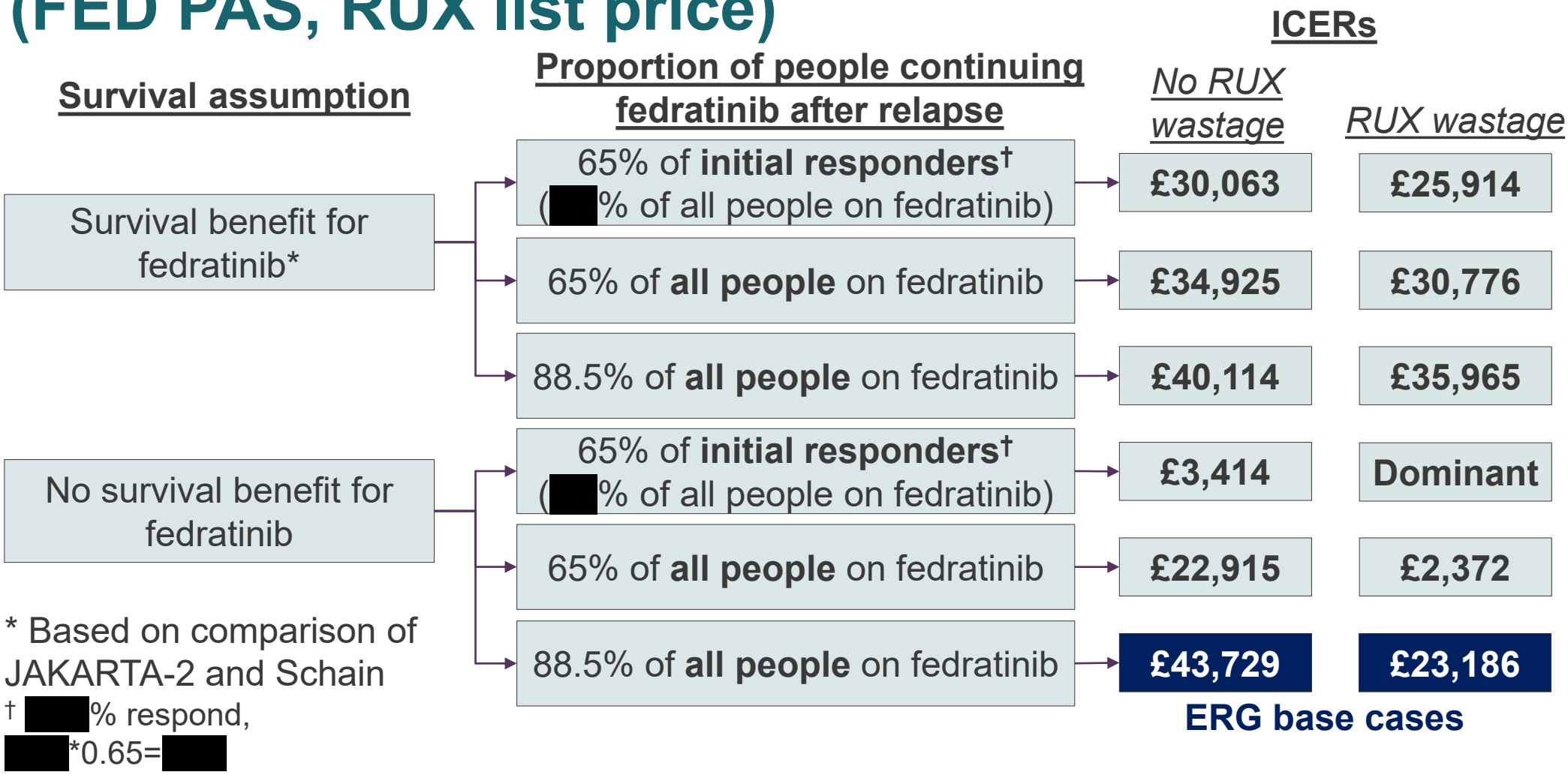
BAT, best available therapy; FED, fedratinib; PAS, patient access scheme; RUX, ruxolitinib; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

ERG scenarios, platelet count from chart review (FED PAS, RUX list price)



* Based on comparison of JAKARTA-2 and Schain

† [redacted]% respond, [redacted]*0.65=[redacted]

All people = people on fedratinib whose disease does/does not respond to fedratinib.
All ICERs include ERG-preferred assumptions (see slide 20), including platelet count distribution from chart review

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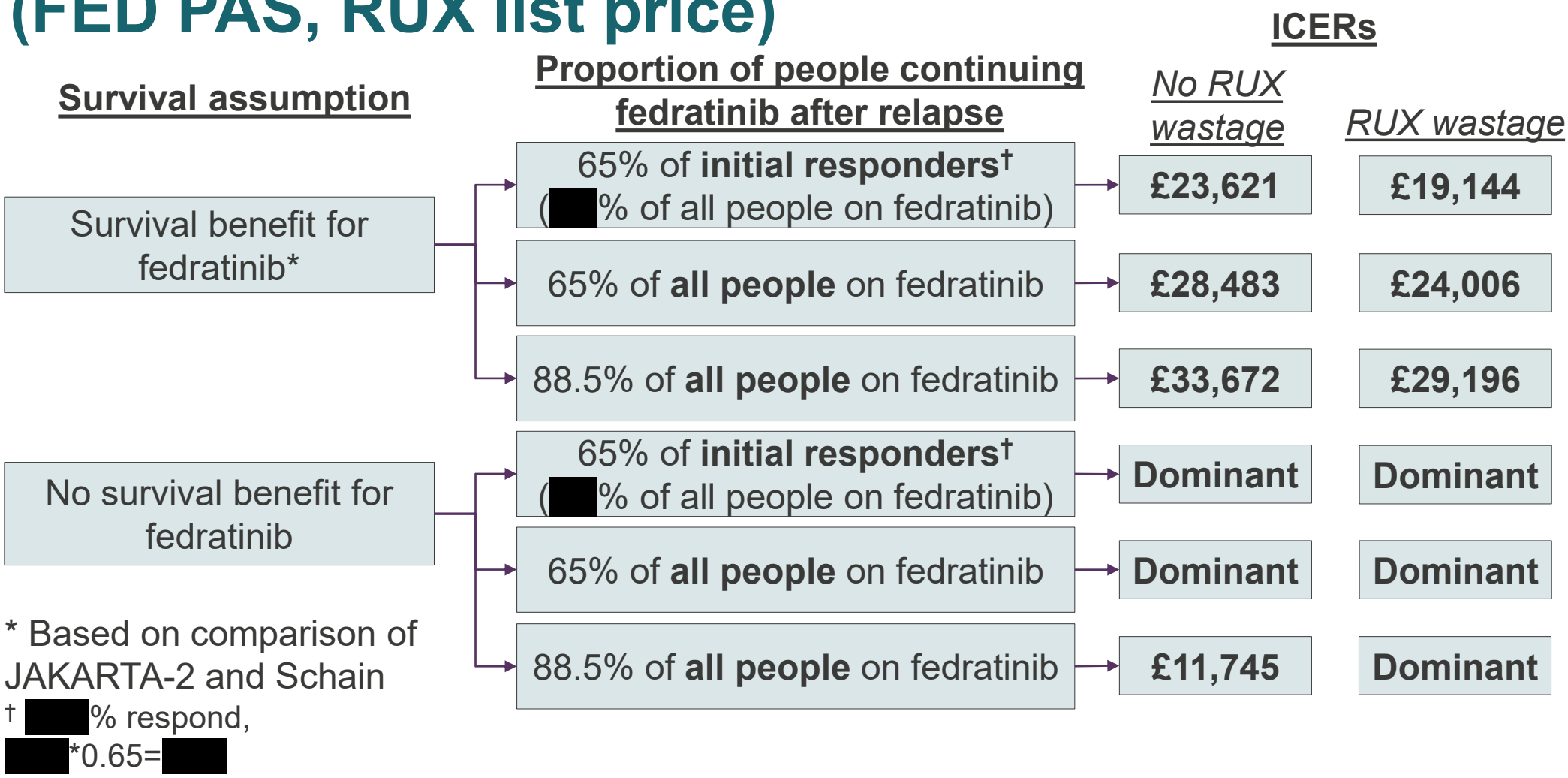
FED, fedratinib; PAS, patient access scheme; RUX, ruxolitinib; ICER, incremental cost-effectiveness ratio; ITT, intent to treat

ERG scenarios, platelet count from JAKARTA-2 (FED PAS, RUX list price)



* Based on comparison of JAKARTA-2 and Schain

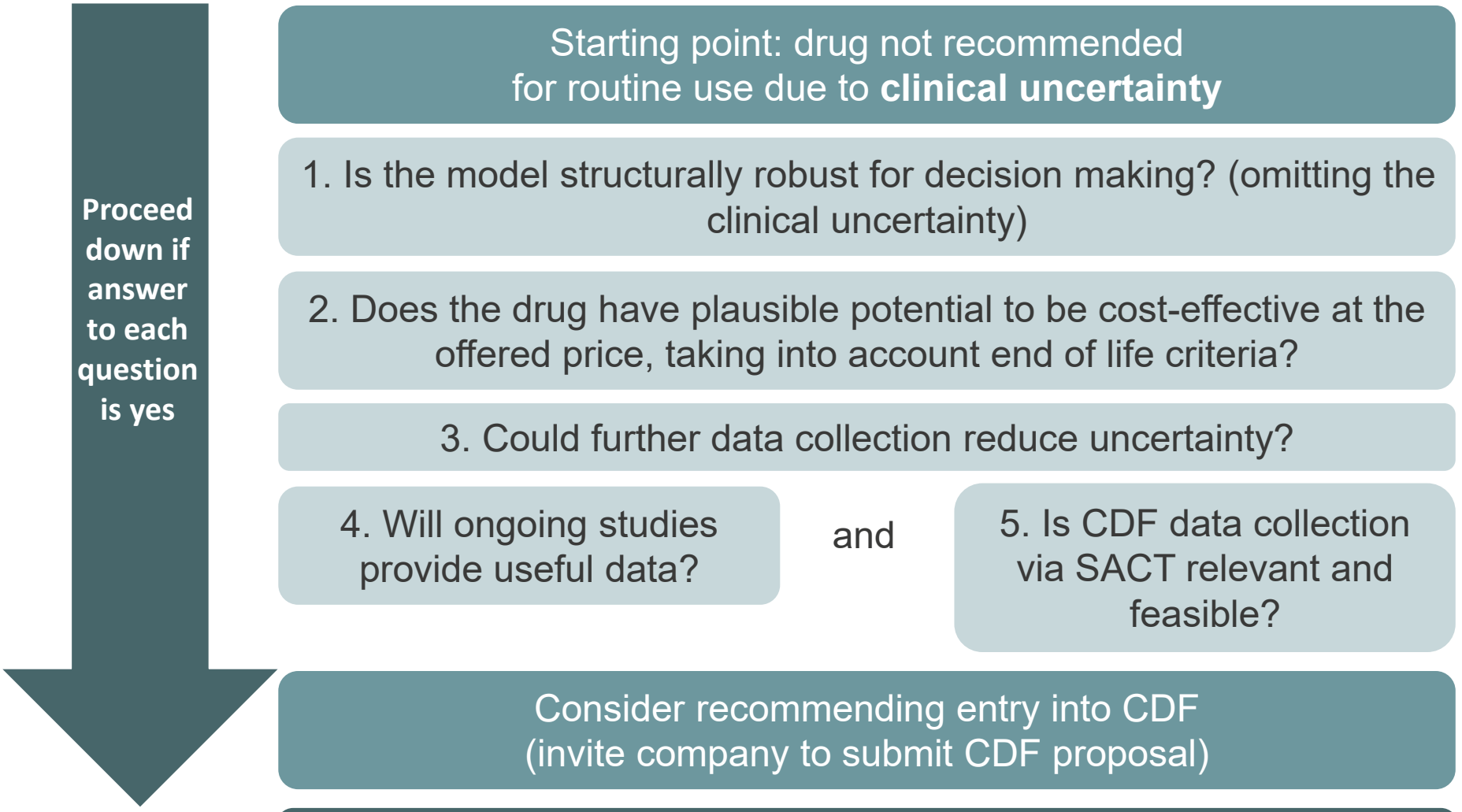
† [redacted]% respond, [redacted]*0.65=[redacted]

All people = people on fedratinib whose disease does/does not respond to fedratinib.
All ICERs include ERG-preferred assumptions (see slide 20), but platelet count from JAKARTA-2

FED, fedratinib; PAS, patient access scheme; RUX, ruxolitinib; ICER, incremental cost-effectiveness ratio; ITT, intent to treat

Cancer Drugs Fund

Committee decision making: CDF recommendation criteria



Cancer Drugs Fund

Issue background (ACD 3.21)

- **Company:** FREEDOM-2 and the CDF could resolve most of the issues raised by the ERG
- **ERG:** FREEDOM-2 may not fully resolve long-term survival uncertainty as people randomised to BAT can crossover to fedratinib after cycle 6 (or before with progression)
- **Committee:** FREEDOM-2 may not robustly resolve uncertainty of fedratinib survival benefit and there are additional uncertainties with model structure. Based on presented estimates, fedratinib is not plausibly cost-effective

Company's ACD response

- Previous NICE appraisals have considered evidence from trials with crossover (TA386)
- CDF could resolve uncertainties in the modelling inputs of prior treatment, response outcomes, discontinuation rate and composition of BAT for those who discontinue fedratinib

Stakeholder ACD comments

FREEDOM-2 should not be dismissed because of crossover, as this can be accounted for

ERG critique of company's ACD response

- Crossover is a feature of trials and appraisals, but it is hard to assess the robustness of any crossover adjustment prior to data being available
- In TA386, crossover allowed at 12 months in COMFORT-2 (ruxolitinib trial against BAT), later than in FREEDOM-2 (fedratinib trial). Crossover allowed at 6 months in COMFORT-1
- FREEDOM-2 is likely to address some but not all of the uncertainties in the model

ACD, appraisal consultation document; BAT, best available therapy; CDF, Cancer Drugs Fund

FREEDOM-2: phase 3, randomised study

Population (n=192)	Adults with primary, post-PV or post-ET myelofibrosis with splenomegaly • ECOG PS 0, 1 or 2 • DIPSS risk score of intermediate-2 or high • Previously treated with ruxolitinib
Locations	112 including 7 UK sites
Intervention	Fedratinib (400 mg/day)
Comparator	Best available therapy (BAT)
Follow up	For primary outcome 6 cycles (about 6 months), for overall survival about [redacted] months
Primary outcome	Proportion of subjects with ≥35% spleen volume reduction
Secondary outcomes	• Proportion of subjects with ≥50% reduction in total symptom score • Proportion of subjects with ≥25% reduction in spleen volume • Duration of ≥50% reduction in spleen size by palpation • Duration of ≥50% reduction in total symptom score • Time from randomisation to death (any cause) or disease progression • Health-related quality of life • Overall survival
Expected completion	• Primary completion [redacted] 2022

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Post-PV, post-polycythaemia vera; Post-ET, post-essential thrombocythemia; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status