For public - Contains no AIC /CIC data

NICE National Institute for Health and Care Excellence

Andexanet alfa for reversing anticoagulation

3rd Appraisal Committee meeting

Chair's presentation

Lead team: Rita Faria, Alice Turner, Pam Rees
ERG: BMJ-TAG
Chair: Jane Adam
Technical team: Emma Douch, Lorna Dunning, Janet Robertson
Company: Alexion Pharmaceuticals (previously Portola Pharmaceuticals)
February 2021

Key issues

Model driver

- **Is the committee content with the recommendation for GI bleeds?**
- **How robust is the evidence for 30 day mortality benefit for ICH compared with PCC?**
- **Should haematoma expansion be considered a relevant outcome for intracranial haemorrhage (ICH)?**
  - How does this impact the modelling and mortality results
- **Does andexanet alfa improve long-term morbidity in ICH?**
- **Should a utility benefit be modelled for andexanet alfa?**
  - Is the Delphi panel an adequate method for estimating utility benefit?
  - If yes, what quality of life increase is most plausible (+0.05, +0.075, +0.10 or +0.11 utility)?
  - How should this be modelled?
- **Will the ongoing ANNEXA-I randomised controlled trial resolve the uncertainty on long-term clinical outcomes in the ICH cohort?**
- **How does the presence of significant clinical uncertainty impact the cost effectiveness threshold used for this appraisal?**
- **Could the current access to andexanet alfa result in an equalities issue?**
  - For people whom blood products such as PCC are not acceptable?

Recap: Decision problem

Intervention	Andexanet alfa, one-off bolus for 15 to 30 minutes, followed by 2-hour infusion
Population	People taking a direct factor Xa (FXa) inhibitor who had an acute major bleed. Subgroups: 1. People with intracranial haemorrhage (ICH) + severe gastrointestinal (GI) bleeds 2. People with ICH alone 3. People with severe GI bleeds alone
Marketing authorisation	Indicated for adults who had a direct factor Xa inhibitor (apixaban or rivaroxaban) when reversal is needed due to life-threatening or uncontrolled bleeding
Comparators	Prothrombin complex concentrate (PCC), off label use
Clinical trial	ANNEXA-4 Single-arm, open-label, prospective, multicentre Phase IIIb/IV trial

Andexanet alfa

Post conditional marketing authorisation measures	To substantiate correlation of anti-FXa-activity with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the company should submit results of a global **RCT** of andexanet alfa vs standard of care in patients with **ICH** (ANNEXA-I, results expected 2025)
Dosage and administration	2 possible doses based on type and timing of last dose of FXa inhibitor: Low dose: 400 mg IV bolus then 4mg/min IV High dose: 800 mg IV bolus then 8mg/min
Mechanism of action	Specific reversal agent for FXa inhibitors – Predominant action is binding and sequestration of the FXa inhibitor
Average list price per course of treatment	£15,081 based on the proportion receiving each low and high dose with wastage
Patient access scheme	Confidential discount on list price

Recap: committee considerations at ACM1/2

Clinical need

- Direct anticoagulants are associated with a serious risk of major bleeding
- There is a clinical need for effective anticoagulation reversal agents

Intervention / population

- It is not appropriate to combine all bleed types for decision making

Clinical trial evidence

- Evidence available for andexanet alfa is limited
- No direct comparative evidence for andexanet alfa compared with PCC
- ANNEXA-4 – single arm clinical trial:
  - 2 haematological primary outcomes: change in 'anti-factor Xa activity' and haemostatic efficacy
    - Clinical experts explained that haemostatic efficacy as defined in the trial could not be predictive of clinical outcomes
  - Safety outcome: 30-day mortality
  - Disability measured by modified Rankin score (mRS):
    - collected at day 30 for survivors of an ICH
    - Scale of 0 - 6 where 0 = no disability, 6 = death

Recap clinical evidence: ANNEXA-4

Population (N=352)	Apixaban, rivaroxaban, edoxaban, or enoxaparin with acute major bleeding and baseline anti-fXa activity≥75ng/mL • most received apixaban or rivaroxaban (n=322)
Exclusion criteria (not exhaustive)	• **Expected survival > 30 days** • **People with ICH with any of the following: Glasgow coma score <7 or estimated intracerebral haematoma volume > 60cc as assessed on imaging**
Intervention	Low dose: 400 mg IV bolus then 4mg/min IV High dose: 800 mg IV bolus then 8mg/min
Endpoints	• Primary endpoints: • % change in anti-FXa activity • rate of excellent/good haemostatic efficacy 12 hours after andexanet alfa infusion • Secondary endpoint: Relationship between anti-FXa activity and haemostatic efficacy, (is anti-FXa activity predictor of haemostatic efficacy) • **Safety endpoint: 30-day all-cause mortality and overall safety**
Protocol amendment	Amendment 4: 1) Threshold time and dose criteria to determine a low vs high dose 2) Population enriched with ICH people. 139 people enrolled under Amendment 4 of the protocol

2 additional RCT vs placebo in healthy volunteers (ANNEXA-A and ANNEXA-R) supported application for marketing authorisation but not used in model

Recap: Definitions of haemostasis outcomes for ICH used in ANNEXA-4

ANNEXA-4 haemostasis outcomes for ICH. Source: adapted from company submission, table 4.

Bleed type	Definition criteria (compared to baseline)	Excellent (effective)	Good (effective)	Poor (not effective)
		≤ 20% increase:	> 20% but ≤ 35% increase:	> 35% increase:
Intracerebral haematoma	**Change in haematoma volume** on repeat CT or MRI scan	both 1- and 12-hours post infusion	+12-hours post infusion	+12-hours post infusion
Subarachnoid bleeding	**Change in maximum thickness** on follow-up	both 1- and 12-hours post infusion	+12-hours post infusion, using the most dense area	+12-hours post infusion, using the most dense area
Subdural haematoma	**Change in maximum thickness** on follow-up	both 1- and 12-hours post infusion	+12-hours post infusion	+12-hours post infusion

- Rate of haemostatic efficacy in ANNEXA-4:
  - ICH bleed cohort: 71% excellent, 9% good, 20% poor

Haemostasis results in the trial

Clinical experts' comments

- These criteria are not used routinely
- Large bleed at presentation prognostic of poor outcomes
- Not all bleeds enlarge: criteria used in the trial for haemostasis not in line with clinical practice.
- No haemostasis data from ORANGE study

***Committee**: Clinical evidence available for andexanet alfa was limited to only 30-day mortality*

- *What percentage of intracranial bleed enlarge after the initial scan in routine care?*
- *Would an expansion of up to 35% be regarded as a good clinical outcome?*

Recap Clinical Results: 30-day mortality rates in ANNEXA-4

30-day mortality results from ANNEXA-4. Source: adapted from company submission, table 33

Patients with apixaban or rivaroxaban in the ANNEXA-4 trial	
	Deaths within 30 days % (95%CI)
Whole cohort ([redacted])	[redacted]
ICH ([redacted])	[redacted]
GI bleed ([redacted])	[redacted]
Other major bleeds ([redacted])	[redacted]
Classed as pericardial, peritoneal, intraocular, intraspinal	[redacted]

Recap: Indirect treatment comparison

Propensity score matching analysis used to adjust estimates of treatment effect to account for differences in trial populations, but not matched for severity of bleeds.
Model informed by results of indirect treatment comparison

Andexanet alfa

ANNEXA – 4 (N=352)

- Single arm clinical trial
- Excluded people with expected lifespan <1 month, ICH with Glasgow coma score <7 or estimated intracerebral haematoma volume > 60cc
- Primary endpoints:
  - % change in anti-FXa activity
  - rate of excellent/good haemostatic efficacy 12 hours after andexanet alfa infusion

Vs

PCC

ORANGE (N=149 taking PCC)

- UK observational study
- People taking anticoagulants admitted to hospital with a major bleed
- Outcomes:
  - Clinical outcomes at 30 days, death or discharge
  - Comorbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days

Committee concerns with ITC from ACM1 and ACM2

- Different inclusion criteria in the two trials
- Comparability of 30-day mortality rate outcome across trials uncertain
- Key prognostic factors (e.g. volume and severity of bleed) not included in analysis

Recap: Gastrointestinal bleeds

Results from propensity matching analysis, andexanet alfa v PCC. Source: ERG report, table 45

Population	Number of matches	Matched 30-day mortality (%) (95% CI)	
		PCC	Andexanet alfa
GI subgroup	[redacted]	[redacted]	[redacted]

US multi-centre real-world study

Andexanet alfa use within licensed indication, did include people with <1 month expected survival (excluded in ANNEXA-4)

- US data reports **lower** in-hospital :
  - ANNEXA-4 [redacted]%, US RWE: [redacted]%

NB: In-hospital mortality different to 30-day mortality

- Supports generalisability of ANNEXA-4: limited impact of survival exclusion criteria
- Unclear who had treatment/ what other treatments used

Rockall Score

Validated predictor of mortality

30-day mortality in ANNEXA-4 ([redacted]%) **lower** than predicted by Rockall score ([redacted]%)

- Supports reduction of 30-day mortality with andexanet alfa

Committee: *Andexanet alfa likely to reduce 30-day mortality for people with GI bleeds BUT uncertainties: no direct evidence, thrombosis risk & other treatments available*

Recap: Intracranial haemorrhage

Results from propensity matching analysis, andexanet alfa v PCC. Source: ERG report, table 45

Population	Number of matches	Matched 30-day mortality (%) (95% CI)	
		PCC	Andexanet alfa
ICH subgroup	[redacted]	[redacted]	[redacted]

Mortality

Unclear if a survival benefit seen in andexanet alfa would translate in a whole unselected UK population

Marketing authorisation conditional on ANNEXA-I RCT results in 2025 (n=900 with ICH)

- Collects clinical outcome and thrombotic risk data ([redacted]% had thrombotic event in trial)

Morbidity

Modified Rankin scale (mRS) scores influence mortality risks, costs and utilities in economic model

Company assumed andexanet alfa reduced severity of long-term disability in ICH vs PCC:

- Based on naïve comparison of ANNEXA-4 (andexanet alfa) with a retrospective study by Øie *et al* 2108 (standard of care with PCC)
- Øie *et al* included only intracerebral haemorrhage (more severe bleeds) so may overestimate disability for people who had PCC
- Benefit on long term disability is a key model driver

***Committee**: The extent that andexanet alfa reduces mortality in ICH is unclear*
Benefit on long-term disability after an ICH not supported by evidence

Recap: Other major bleeds

Results from propensity matching analysis, andexanet alfa v PCC. Source: ERG report, table 45

Population	Number of matches	Matched 30-day mortality (%) (95% CI)	
		PCC	Andexanet alfa
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

- Other major bleeds = pericardial, retroperitoneal, intraspinal and intraocular
- 30-day mortality worse with andexanet alfa than PCC in propensity matching analysis
- Small sample and evidence lacking to justify company's assumptions of:
  - 25% reduction in blindness and paralysis after intraspinal and intraocular bleeds
  - 25% relative reduction in mortality for pericardial and retroperitoneal bleeds

***Committee**: The evidence in 'other major bleeds' is too unreliable for decision making*

History of appraisal

Committee meeting 1 March 2020

- **No direct evidence** with comparator
- **Long-term evidence uncertain** for:
  - Disability reduction following intracranial haemorrhage
  - Paralysis following intraspinal bleed
  - Molecular blindness after intraocular bleed
- **Cost-effectiveness estimates uncertain**

Not recommended

Consultation

Committee meeting 2 June 2020

GI bleeds

Rockall score and US multicentre real-world in-hospital mortality data supports ANNEXA-4 GI mortality benefit

Recommended

ICH

Size of mortality benefit and impact on long-term quality of life unclear

Recommended only in research

Other bleeds

Evidence insufficient for decision making

Not recommended

Consultation

Committee meeting 3 February 2021 (today)

GI bleeds

No further evidence submitted

Other bleeds

No further evidence submitted

ICH

Delphi panel survey of clinical experts to support improved long-term quality-of-life after taking andexanet alfa

Committee to consider

Recap ACM conclusions: summary of cost effectiveness

Bleed type	Committee's conclusion
GI ***Recommended***	**Likely to be cost effective compared with PCC**
ICH ***Recommended in research***	ICERs within cost effectiveness range but uncertain • *Heterogeneity in cohort* • *Benefit uncertain: ICER uncertain* • *Concerns about methods and assumptions used in model* • *Long-term disability uncertain* **Company ICERs within range normally considered cost-effective but evidence too uncertain**
Other major bleeds ***Not recommended***	ICERs very uncertain • *Mortality worse than PCC in indirect comparison* • *Assumptions not supported by evidence* **Not shown to be cost effective**

ACD2: recommendation

1.1 Andexanet alfa is **recommended as an option** for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:

- the bleed is in the gastrointestinal tract and
- the company provides andexanet alfa according to the commercial arrangement.

1.2 Andexanet alfa is **recommended only in research** for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage)

Consultation comments on ACD2

ACD consultation responses

Professional organisations	• Royal College of Pathologists and British Society for Haematology (RCPath and BSH)
Patient organisations	• Anticoagulation UK (ACUK)
Company	• Portola
Public (web) comments	• NHS clinician #1 • NHS clinician #2 • Public commentator

Theme 1: GI bleeds: Andexanet alfa should only be used in research

ACD: "Andexanet alfa is **recommended as an option** for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if: the bleed is in the gastrointestinal tract…" [1.1]

Further evidence required

- Recommendation means no future clinical trials will compare efficacy and safety of andexanet alfa with PCC for major or life threating GI bleeds
  - If trials in ICH fail to show better safety and efficacy compared to PCC andexanet alfa still approved for GI bleeding in the absence of proper RCTs (RCPath and BSH)
- Committee notes that most GI data poor quality but advocates for GI bleeding because cost effective (NHS clinician #1).
- More data for andexanet alfa and PCC in ICH than GI: evidence on GI retrospective propensity matching analysis unlikely to be adequate (NHS clinician #2)
  - Recommendation based on unpublished US real world data and 1 study of direct oral anticoagulants and PCC: RCT also needed in non-ICH cohort (including GI bleeding)
- Most later deaths with GI bleed relate to comorbid disease: relevance of 30-day mortality outcome questionable (NHS clinician #2)

Preference for using PCC

- PCC more logical to manage GI bleed than andexanet alfa (NHS clinician #1):
  - PCC reverses the effects of the factor Xa inhibitors and also repletes clotting factors (which andexanet alfa does not).

GI bleeds: Summary of clinical evidence

Results from propensity matching analysis, andexanet alfa v PCC. Source: ERG report, table 45

Population	Number of matches	Matched 30-day mortality (%) (95% CI)	
		PCC	Andexanet alfa
GI subgroup	[redacted]	[redacted]	[redacted]

US real-world analysis

- US data reports **lower** in-hospital mortality:
  - ANNEXA-4 [redacted]%, US RWE: [redacted]%

NB: Different outcome to 30-day mortality

Rockall Score

30-day mortality in ANNEXA-4 ([redacted]%) **lower** than predicted by Rockall score ([redacted]%)

No new evidence submitted at consultation

- *Given consultation comments, is the committee still confident that andexanet alfa reduces 30-day mortality for people with GI bleeds?*
- *Is there a research study ongoing?*

Theme 2: Long-term outcomes for andexanet alfa in ICH unknown, further research required

Future data collection

- Quality of life after treatment unclear for people with an ICH, recovery differs per patient (ACUK)
  - access to andexanet alfa should consider patient's broader health profile
- ICH bleed can lead to mortality and long term disability but risk of thrombosis with andexanet alfa: stopping a ICH bleed may cause distress and morbid disability (ACUK)
- Cohort studies of real-world PCC show higher haemostatic efficacy than ORANGE (NHS clinician #2).
- Current clinical trial data includes only a small cohort (n=90 with non-ICH bleeds) reduced further by propensity matching (NHS clinician #2).

Recommendation

- NICE should review recommendations once results of ongoing RCT in ICH published. (ACUK)
- Agree for use in research setting for ICH (NHS clinician #2):
  - Significant thrombosis rates (20%) and poor efficacy (<50%) reported in observational case series in extracranial bleeds – rates also high in phase 2 andexanet study

Theme 3: Access. High clinical need and variations in service provision

Service provision

- Local approval to use andexanet alfa in ICH: geographical variation in access (RCPath and BSH)
- Implementation of 'in research' recommendation unclear. There are variations in access to research. Clinicians compromised if unable to access treatment for a patient who could benefit: suggest exceptional circumstances protocols for use outside of research
  - what settings will be eligible to participate in ICH research?
  - who will decide patient eligibility and will all patients with ICH will have access? (ACUK)

Clinical need

- GI bleeds may be managed using endoscopy, embolization or surgery but limited options in 'other bleeds': inability to access andexanet alfa may impact long term health outcomes (ACUK)
- Clinical need for effective anticoagulation reversal agents (public commentator):
  - Critical for people with lifelong bleed problem on long term aspirin (e.g. people with atrial fibrillation) who bleed when prescribed rivaroxaban.
  - May have less than therapeutic dose of an alternative, e.g. apixaban, but still observe occasional small bleed.

Company’s additional information

Company's additional information - summary

Additional information was submitted post ACM2 **only in ICH cohort**:

- **Delphi panel** survey of clinical experts to further support a quality-of-life improvement following andexanet alfa compared with PCC in patients with an ICH
  - Iterative rounds of structured conversation
  - Used to fill literature gaps and draw consensus on a specific problem
  - Evidence generated by Delphi panel could be inputted into model to produce probable ICER range
- Scenario's modelling different long-term **utility benefits for andexanet alfa**

No new evidence in GI or other bleeds.

Company's base cases unchanged from ACM2.

Delphi panel: Methodology

[redacted]

[redacted]

[redacted]

[redacted]

Source: Company additional information ACD2, figure 1

Delphi panel initial questions

Focus	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Delphi panel results, Question 1b: Population

Round 1, question 1b:

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Consensus statement for question 1b: [redacted]

Delphi panel results, Question 2: Morbidity

Round 1, question 2: [redacted]

Round 1 individual expert answers: [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Delphi panel results, Question 2: Morbidity (continued)

Round 1 individual expert answers to question 2 (continued): [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Round 2: [redacted]

Consensus statement for question 2: [redacted]

Response to consultation: haematoma expansion

Company comment: haematoma expansion is a key prognostic factor for mortality and morbidity. ANNEXA-4 study demonstrated a clinically meaningful effect on limiting haematoma expansion.

Supported by literature
Davies *et al* meta-analyses:
- 10% increase in haemorrhage growth = 5% more likely to die and 16% more likely to increase 1 mRS point.

Company comment: committee concerned about severity of people with ICH bleed enrolled in ANNEXA-4, but people entered the trial within 3-4 hours of symptom onset and baseline haematoma volume included a spectrum of bleed volumes up to 60 ml so people were at high risk of haematoma expansion.

Company comment: Results were clinically meaningful in people with spontaneous ICH:
- 79% achieved <35% limitation in haematoma expansion at 12 hours, of which 91% rated 'excellent' (defined as <20% expansion 1 hour from baseline sustained 12 hours after andexanet alfa).

ERG comments: Haematoma expansion as a prognostic factor for mortality and morbidity

In ANNEXA-4:

- Only [redacted] of people with ICH had haematoma expansion (defined as >35% increase in size from baseline to 1 and 12 hours)
- No mortality and morbidity data specifically relating to volume of haematoma expansion

- Delphi panel **statements plausible but require confirmation** through further research

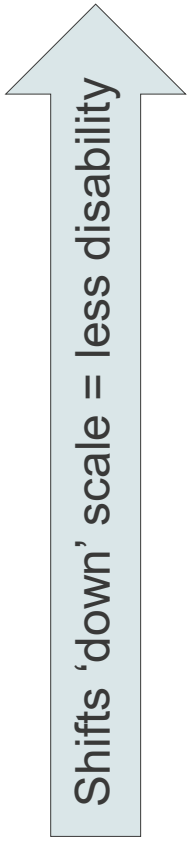
- Meta-analysis by Davis *et al*:
  - Only included people with intracerebral haemorrhage, a subtype of ICH
  - Not limited to people taking oral anticoagulants such as apixaban and rivaroxaban
  - ***Extrapolating findings to andexanet alfa population purely speculative***

- *What is the committee's opinion on haematoma expansion as relevant outcome?*
- *How would this outcome impact the modelling and mortality benefit for andexanet alfa if included?*

Recap: Modified Rankin Scores

Modified Rankin Score (mRS) Scale. Source: company response to ACD2, table 12

mRS score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderate to severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead



Delphi panel results, Question 3: mortality and associated disability

Round 1, question 3: [redacted]

Question 3, round 1: individual experts answering yes ([redacted])

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Individual experts answering no ([redacted])

- [redacted]
- [redacted]
- [redacted]

Round 2: [redacted]

Consensus statement: [redacted]

Delphi panel results, Question 4: mRS scores post treatment

Round 1, question 4: [redacted]

Question 4, round 1: individual experts answering yes ([redacted])

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Individual experts answering no ([redacted])

- [redacted]
- [redacted]

Round 2: [redacted]

Consensus statement: [redacted]

Response to consultation: morbidity and associated quality of life in ICH patients

ACD: "The benefit of andexanet alfa on long-term disability after an ICH is not supported by evidence." [3.10]

Company comments:

- Andexanet alfa will improve morbidity and associated quality of life in ICH patients
- Improvement in morbidity would be expected across the spectrum of disability

Additional support for morbidity improvement:

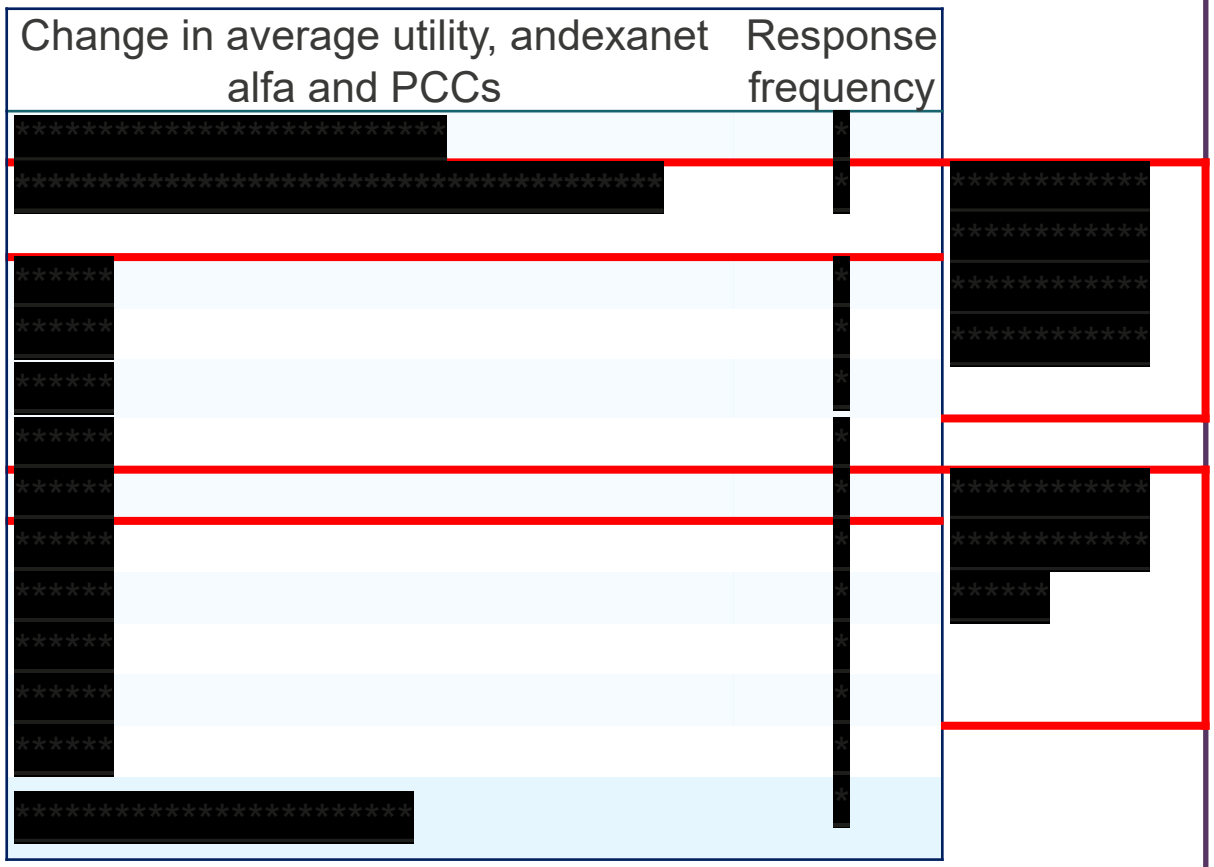
- Naïve comparison: mRS scores higher in Øie *et al.* than ANNEXA-4
- Observational data (Ganesh *et al*.) suggests mRS improves by at least 1 point between 30 and 90 days post ischemic stroke

- *Would a morbidity improvement be expected after treatment with andexanet alfa?*
- *Is a larger mRS improvement expected for people treated with andexanet alfa than people treated with PCC?*

Delphi panel results, Question 5: Translating mRS benefit into utility

Question 5, round 1: Individual expert statements:

[redacted]



Source: company additional info ACD2, Table 16

Company comments:

- Uncertainty relates to extent of quality of life improvement with andexanet alfa

Round 2, experts asked

[redacted]

Consensus statement for question 5:

[redacted]

- *Does the Delphi panel consensus statement correctly capture the expert's expected utility benefit with andexanet alfa?*
- *Should a utility benefit be modelled for andexanet alfa? If yes, which quality of life increase is most plausible?*

Response to consultation: Morbidity benefit

ERG comments on Delphi panel statements:

- Results subjective
- Doesn't address **lack of clinical evidence** for morbidity benefit in ICH: further research needed
- Remains unknown if long-term utility of 0.72 (company base case) plausible for an ICH survivor. No information provided by Delphi panel.
- Consensus statement that [redacted] not consistent with company full report:
  - Several comments suggest mRS benefit of [redacted], particularly for intracerebral types of ICH
  - Improvement of [redacted] mRS = utility benefit of [redacted]. Contradicts Delphi panel consensus (Q5, round 1), which suggests likely benefit is [redacted]
- ERG unable to verify the Delphi panel consensuses with own clinical experts

Explanatory analysis:

Company scenarios: utility benefit of +0.05, +0.075 and +0.10 compared with PCC. Using various baseline utility values.

ERG comments:

- Explanatory analyses useful but **company's approach inappropriate**:
  - Benefit should be added to utility for andexanet alfa, not subtracted from standard care (utility deemed too low by company previously)
- Morbidity benefit has large impact on analysis so should be verified by other stakeholders
- Only outcomes with comparative data are 30-day mortality and length of hospital stay

⊙ *How does the company's new evidence reduce uncertainty about morbidity improvement after andexanet alfa in people with ICH?*

Response to consultation: ANNEXA-I addressing long-term morbidity uncertainty

ACD: "The committee noted an ongoing randomised controlled trial of the effectiveness of andexanet alfa compared with prothrombin complex concentrate in people with ICH." [5.1]

ANNEXA-I study (required as part of the conditional marketing)

- Randomised controlled trial in people with an ICH taking apixaban, rivaroxaban, or edoxaban
  - andexanet alfa versus standard care (*N.B not specifically PCC)*
  - Timeframe: within 6 hours of symptom onset and 15 hours of oral factor Xa inhibitor

Company comment: ANNEXA-I not designed to address uncertainties regarding long-term disability

  - No outcomes > 30 days being collected

ERG Comments

ANNEXA-I limitations:

- Not expected to complete recruitment until 2023
- Generalisability to UK unknown:
  - Open label comparator arm (standard care) may differ by geographical location

Main outcomes assessed max 24 hours after treatment: **will not resolve uncertainty on:**

  - Long-term morbidity
  - Long-term mortality
  - 30-day mortality

RCT will provide **stronger evidence** on:

  - haemostatic efficacy at 12 hours
  - neurological deficit at 24 hours

⊙ *Will ANNEXA-I resolve uncertainty on long-term clinical outcomes in the ICH cohort?*

Response to consultation: The recommendations in their current form raise concerns over equality.

Company comment on inequalities:

- People with rivaroxaban or apixaban related major gastrointestinal bleeding will be able to access andexanet alfa, whereas those with intracranial bleeding will not
  - ~[redacted] deaths per year in the UK are related to an ICH
- People who refuse blood products or derivatives due to religious reasons (e.g. Jehovah's witnesses) have no other treatment option as cannot take PCCs

⊙ *What are the committee's views on issues raised around equality of access to treatment?*

Company response to consultation: Summary

	Company comment on andexanet alfa:	Included in
2	Novel mechanism of action has benefits over PCC	PMB
3	Haematoma expansion is key prognostic factor for mortality and morbidity	ACM
4	Improves morbidity and associated quality of life in ICH for anticipated UK use	ACM
5	Limits further neurological deterioration in persons likely to survive. Patients and relatives should be engaged in joint clinical decision making	PMB
6	Uncertainty relates to how much quality of life improves in ICH patients versus PCC	ACM
7	Base case and scenarios for ICH show cost-effective use of NHS resources	ACM
8	Should only be used in licensed indication, where potential for benefit	PMB
9	ANNEXA-I will not address uncertainties about long term morbidity in ICH	ACM
10	Accept decision on 'other bleeds' but expect benefit in this group despite limited evidence	PMB
11	Current recommendations raise concerns over equality	ACM

- *Does the committee have concerns about any of the company's additional comments or Delphi panel results?*

Cost effectiveness

Company's and ERG's base cases: Unchanged from ACM2

Assumptions relating to base case in ICH cohort	Included?	
	Company's base case	ERG's base case
Utility values based on NICE TA341 (post-acute intracranial bleed)	Y	N
mRS scores based on Øie 2018 for PCC (utility benefit of 0.11)	Y	N
ICH rehabilitation 12 months	Y	Y
30-day mortality benefit for andexanet alfa	Y	Y
Weighted utility values by mRS (Issue 6)	N	Y
Utility values based on ANNEXA-4	N	Y
mRS distributions from ANNEXA-4 applied to both treatment arms	N	Y

Company and ERG base case results, PAS for andexanet alfa, list price for PCC

Source: adapted from company response to ACD1, ERG review of company response to ACD1, tables 12-14.

Population	Company deterministic	Company probabilistic	ERG deterministic
ICH cohort	[redacted]	[redacted]	[redacted]
GI cohort	[redacted]	[redacted]	[redacted]

- *How does the presence of significant clinical uncertainty impact the cost effectiveness threshold used for this appraisal?*

Company's ICH scenario analyses – utility benefit

Scenario analyses varying the utility benefit for andexanet alfa in the ICH cohort, PAS for andexanet alfa, list price for PCC. Source: adapted from company response to ACD2

Baseline utility value for both andexanet alfa and PCC	Utility benefit with andexanet alfa	ICER	
0.61 (utility value for post-acute intracranial bleed from TA341) Company preferred assumption	+0.05	[redacted]	
	+0.075	[redacted]	
	+0.10	[redacted]	**Company base case**
	+0.11	[redacted]	
0.53 (utility value mapped from ANNEXA-4) ERG preferred assumption	No benefit	[redacted]	**ERG base case**
	+0.05	[redacted]	
	+0.075	[redacted]	
	+0.10	[redacted]	

Company comments:

- Most likely clinical scenario (baseline utility of ~[redacted] with some form of clinical benefit on quality of life for andexanet alfa). ICER = <[redacted]
- Uncertainty in quality of life **does not translate into large differences** in cost-effectiveness
  - **all estimates provided by the Delphi panel** fall within range considered cost-effective use of NHS resources.

ERG's ICH scenario analyses

Alternative methods to model utility benefits

- **Company method:** Utility benefit subtracted from standard care, utility for andexanet alfa remains at 0.53
- **ERG method:** Utility benefit added to andexanet alfa, utility for standard care remains at 0.53

Exploratory scenarios changing the long-term utility among ICH survivors using the ERG and company methods, PAS for andexanet alfa, list price for PCC.

Source: ERG review of company response to ACD2, table 1

Baseline utility value, both andexanet alfa and PCC	Utility benefit with andexanet alfa	ICER using company method	ICER using ERG method	
0.53 (utility value mapped from ANNEXA-4)	No utility benefit	[redacted]	[redacted]	ERG base case
	+0.05	[redacted]	[redacted]	
	+0.075	[redacted]	[redacted]	
	+0.10	[redacted]	[redacted]	

Assuming no 30-day mortality benefit for andexanet alfa

ERG and company scenarios assuming no 30-day mortality benefit for andexanet alfa in the ICH cohort, PAS for andexanet alfa, list price for PCC. Source: ERG review of company response to ACD, table 15

Assumptions	ICER £/QALY
Company base case, no mortality benefit	[redacted]
ERG base case, no mortality benefit	[redacted]

- *What are the committee's view on modelling utility benefit for andexanet alfa?*
- *Should a 30-day mortality benefit be accepted for andexanet alfa?*

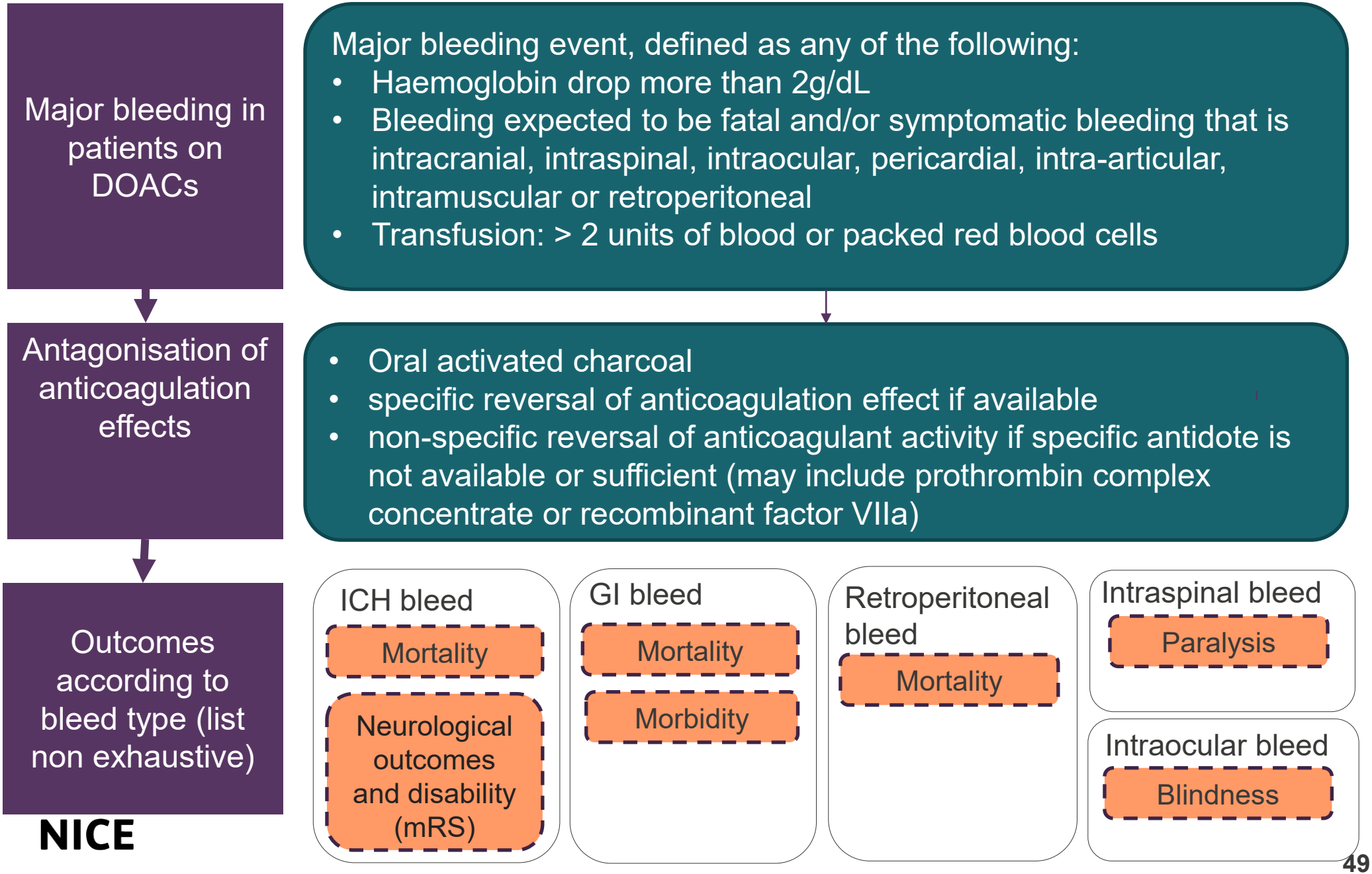
Key issues

Model driver

- **Is the committee content with the recommendation for GI bleeds?**
- **How robust is the evidence for 30 day mortality benefit for ICH compared with PCC?**
- **Should haematoma expansion be considered a relevant outcome for intracranial haemorrhage (ICH)?**
  - How does this impact the modelling and mortality results
- **Does andexanet alfa improve long-term morbidity in ICH?**
- **Should a utility benefit be modelled for andexanet alfa?**
  - Is the Delphi panel an adequate method for estimating utility benefit?
  - If yes, what quality of life increase is most plausible (+0.05, +0.075, +0.10 or +0.11 utility)?
  - How should this be modelled?
- **Will the ongoing ANNEXA-I randomised controlled trial resolve the uncertainty on long-term clinical outcomes in the ICH cohort?**
- **How does the presence of significant clinical uncertainty impact the cost effectiveness threshold used for this appraisal?**
- **Could the current access to andexanet alfa result in an equalities issue?**
  - For people whom blood products such as PCC are not acceptable?

Back up slides

Treatment pathway



NICE

ERG's ICH scenario analyses – mRS benefit

Delphi panel consensus statement: long-term mRS would [redacted] after andexanet alfa

- ERG modelled 'maximum' plausible mRS benefit by increasing utility for andexanet alfa from [redacted] to [redacted] at cycle 4.

ERG scenario assuming a mRS improvement of 1 for andexanet alfa in the ICH cohort, PAS for andexanet alfa, list price for PCC. Source: ERG review of company response to ACD2, table 2

	Total costs	Total QALYS	ICER
Andexanet alfa	[redacted]	[redacted]	
Standard care	[redacted]	[redacted]	[redacted]
Incremental value	[redacted]	[redacted]	

ERG considers the **scenario implausible** and **assumes no morbidity benefit in base case.**

- mRS benefit of [redacted] not supported by individual Delphi panel statements from questions 4 and 5
- When mRS benefit for andexanet alfa modelled, people with mRS =6 (death) excluded.

mRS distributions for andexanet alfa and standard care Source: adapted from ERG review of company response to ACD2, table 3

Average mRS score	Andexanet alfa, 30 days: intracranial haemorrhage	Andexanet alfa, 30 days: intracerebral haemorrhage	Øie et al. 2018, 90 days: intracerebral haemorrhage
Including death	3.16	3.24	4.41
Excluding death	2.16	2.53	2.07

Higher morbidity on standard care: scenarios that exclude death previously deemed clinically implausible