Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

For public – contains no confidential information

Technology appraisal committee D [04 April 2024]

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Company: Sobi

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- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on haemophilia A

Causes: inherited disorder causing mutations in genes encoding FVIII lead to deficiency / absence of FVIII

- Results: inadequate thrombin for stable clot formation → excessive bleeding

Epidemiology: ~9,000 UK patients; ~25% have severe haemophilia A*

Diagnosis and classification: determined by severity of condition. Company submission focuses on severe only:

	Severe
FVIII level	Less than 1 IU/dL (1%)
Bleeding	Bleeding into joints and muscles, may not be obvious cause or after dental / surgery or minor injuries
Diagnosis	Early infancy
Mortality	Increased risk vs. mild and moderate haemophilia A. Most deaths due to bleeds in brain*

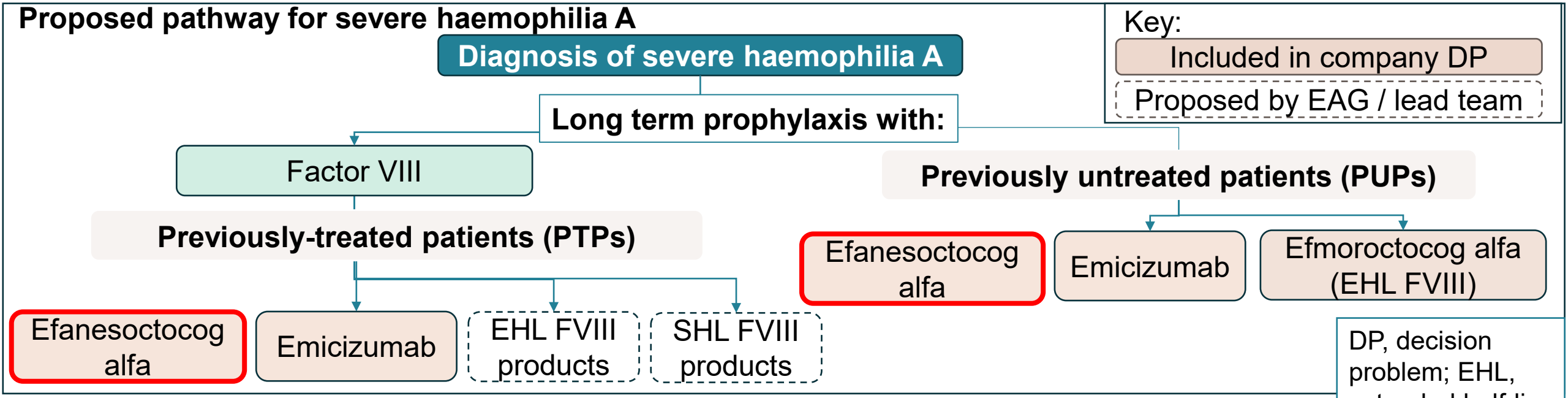
Current treatment for severe haemophilia A:

- Prophylaxis to replace missing clotting factor (FVIII replacement therapy) or restore function (emicizumab)
- On demand (O-D) FVIII used with prophylaxis for breakthrough bleeds / surgery
- Around 20% people with haemophilia A develop neutralising antibodies to FVIII replacement therapy ("inhibitors"): more frequent in severe disease → Inhibitors make FVIII treatment less effective

* Source: Registry data from UK Haemophilia Centres Doctors' Organisation (UKHCDO). FVIII, factor VIII, IU, international unit; dL, deciliter

Treatment pathway

Treatment options include FVIII replacement or non-factor-based therapy (emicizumab)



DP, decision problem; EHL, extended half-lie; FVIII, factor VIII; IV, intravenous; SC, subcutaneous; SHL, short half-life; QW, weekly, Q2W, 2 weekly

Treatment options for severe haemophilia A

Treatment class	Treatments	Administration
SHL FVIII	Octocog alfa, moroctocog alfa, simoctocog alfa	IV every 2 days
EHL FVIII (current)	Efmoroctocog alfa, rurioctocog alfa pegol, turoctocog alfa pegol	IV every 3 days
EHL FVIII (new)	Efanesoctocog alfa	IV QW
Non-factor based	Emicizumab	SC QW/Q2W

- What is standard NHS clinical practice for PUPs and PTPs with haemophilia A?
- Where would efanesoctocog alfa be used in NHS clinical practice?
- What determines the need for changing treatment in PTPs?
- Would emicizumab be used in all PTPs? If not, why and in how many people?

Link to supplementary appendix, company's comparators and company's pathway with O-D treatment

Patient organisation perspectives

Submission from the Haemophilia Society and patient experts

Lifelong, debilitating inherited disorder with major QoL impact:

- Risk of bleeding affects daily living: limits jobs, sports and activities
- Joint damage painful and may progress to affect mobility and require surgery
- High psychological burden: risk of bleed associated with anxiety and stress

Current treatment inefficient at controlling microbleeds and burdensome for patients:

- FVIII injections every 2 to 3 days require time off work/school and regular travel
- Injections can cause 'vein collapse': pain, bruising and irritation
- Emicizumab: weekly / biweekly treatment beneficial vs. FVIII injections but cannot use as O-D treatment and more complicated bleed management

Weekly dosing with efanesoctocog alfa offers maintained FVIII levels for longer:

- Improves independence and vein health. Convenience benefits entire family
- May protect from further joint damage and bleeds: better health in later life
- IV administration may be harder than subcutaneous emicizumab, especially if needle phobia / venous access issues / less experienced at self-administration

"regular accessing of veins leaves little time for the veins to fully heal between injections which causes extra discomfort, pain and bruising and a higher amount of 'vein collapse' …which causes feelings of anxiety and stress"

"[On efanesoctocog alfa], I am almost free of major bleeds now, and the worry of injury or spontaneous bleeds…is now not as completely occupying"

FVIII, factor VIII, IV, intravenous; O-D, on-demand; QoL, quality of life;

Clinical perspectives

Submission from UKHCDO and clinical experts

Primary prophylaxis should be offered to all children and is standard of care for severe haemophilia A; most people have emicizumab:

- SHL and EHL FVIII prophylaxis unlikely to stop breakthrough bleeds
- Emicizumab available for people with severe disease without inhibitors
- Aim of treatment: prevent joint damage and fatal bleeds

Clinically significant treatment response: no spontaneous bleeds, mild to moderate FVIII levels

Efanesoctocog alfa is a paradigm shift in haemophilia A treatment:

- Higher FVIII trough levels provide better bleed protection than comparator
- Particular benefits of weekly administration in children include reduced need for central venous access device (with infection risk and need for surgical placement)
- Improved quality of life for entire family: convenient, less psychological burden
- Available for self-treatment with extra doses for trauma or breakthrough bleeds

…[people with severe haemophilia] may also experience spontaneous and potentially fatal bleeds in any tissue.

Once-weekly dosing of factor VIII should allow far greater freedom and independence from a chronic condition or disease-focused lifestyle

EHL, extended half-lie; FVIII, factor VIII; SHL, short half-life; UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation

Equalities

Stakeholders raised the following concerns during the appraisal:

1. People who carry the haemophilia gene may have mild or, rarely, moderate to severe symptoms of bleeding and should not be excluded from accessing the technology. All carriers have XX chromosomes, so carrier status is impacted by biological sex

2. Some FVIII replacement treatments include blood products derived from humans, animals or animal cells
    - Some people are unable to have these products because of their religious faith or beliefs.

3. Some groups would benefit more from weekly dosing as are currently disadvantaged by frequency of FVIII injections. For example:
    - People with haemophilia related joint disease
    - Children in single-parent households

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Key issues

Issue	Resolved?	ICER impact
Company's population does not align with licenced population or pivotal clinical trial	No – for discussion	Unknown
Standard half-life (SHL) and extended half-life (EHL) FVIII replacement therapy not included as a comparator for PTPs	No – for discussion	Unknown
Disutility applied for people with less than 20% FVIII activity levels	No – for discussion	Large
Dose of efanesoctocog alfa used to treat bleeding episodes may not reflect expected clinical practice	No – for discussion	Large
ITC (methods, choice of arms) and modelling of comparators may not be appropriate	No – for discussion	Unknown
Generalisability to the UK population	No – see supplementary appendix for further info	Unknown
Issues with SLR	No – see EAG report	Unknown

FVIII, factor VIII; ITC, indirect treatment comparison; PTPs, previously treated patients; SLR, systematic literature report

Efanesoctocog alfa ([redacted], Sobi)

Details of the technology

Proposed marketing authorisation	[redacted]
Mechanism of action	Activated extended half-life (EHL) factor VIII therapy: promotes downstream activation of factors IX and X, which increases thrombin production and clot formation.
Administration	Administered by IV injection: • On demand: 50 IU/kg with additional doses dependant on severity of factor VIII deficiency, location / extent of bleeding and clinical condition • Prophylaxis: 50 IU/kg once weekly
Price	• List price: £2,400 per pack of 1,000 IU (£2.40 per IU) • Available as 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU, 4000 IU packs • List price for 12 months of treatment: £435,874 per patient • A patient access scheme has been agreed.

IU, international unit; IV, intravenous; kg, kilogram

Key issue: FVIII therapy as a comparator

Unclear if EHL and SHL FVIII replacement therapies relevant comparators in PTPs

Background: Comparators in NICE scope: *FVIII replacement therapy (prophylaxis and O-D) and emicizumab*

- Company excludes prophylaxis SHL FVIII as comparator and only includes EHLs (efmoroctocog alfa) for PUPs

Company:

- SHL FVIII: Increased emicizumab and decreased SHL FVIII market share over time:
  - ❖ SHL FVIII also used O-D for breakthrough bleeds on emicizumab prophylaxis
  - ❖ Clinical experts expect SHL FVIII prophylaxis will be rarely used within 5 years
- EHL FVIII: Efanesoctocog alfa positioned after EHLs in PTPs, so emicizumab only relevant comparator
  - ❖ PUPs: Parental choice of emicizumab vs. EHL FVIII (may start for emergency treatment of severe bleed)
  - ❖ Severe disease presents in children: efmoroctocog alfa only EHL licenced for under 12-year-olds

EAG comments: SHL FVIII has a significant proportion of market share so is relevant comparator

Technical team: EHLs may be used in PTPs, so may be relevant comparator: supported by UK market share data in people 12 years and over with severe haemophilia A (see supplementary appendix – FVIII comparator data).

Clinical experts: Efanesoctocog alfa can be used where FVIII currently used.

- SHL FVIII used in clinical practice but expect decrease over time as people move to EHLs / emicizumab

- Would efanesoctocog alfa be used at the same point in pathway as SHLs and other EHL FVIIIs?
- Should EHL FVIIIs be included as comparators for PTPs? If so, which EHL(s) are used in PUPs and PTPs?

EHL, extended half-life; FVIII, factor VIII; MA, marketing authorisation; O-D, on-demand; PUPs, previously untreated patients; PTPs, previously treated patients; SHL, short half-life. see supplementary appendix – FVIII comparator data 1 and 2

Key clinical trial

Pivotal trial is XTEND-1: open-label trial using different regimens of efanesoctocog alfa

	XTEND-1 (NCT04161495)
Design	Phase 3, open-label, multinational, multicentre, non-randomised
Number	159
Population	PTPs ≥12 years old with severe haemophilia A (<1 IU/dL [<1%] FVIII or documented genotype) with no FVIII inhibitors having: • Arm A: Prior prophylaxis (FVIII / emicizumab ≥6 months in last year. If treated with emicizumab cannot have received within 20 weeks of screening) • Arm B: Prior on-demand (1 or more bleed per month over last 6 / 12 months)

Intervention	• Arm A (prophylaxis): 50 IU/kg IV QW for 52 weeks
	• Arm B: 2 phases
	  • Phase 1 (on-demand): 50 IU/kg IV QW PRN for 26 weeks
	  • Phase 2 (prophylaxis): QW to week 52

1° outcome	ABR to week 52
Key 2° outcomes	Intra-patient ABR comparison for efanesoctocog alfa Arm A vs. historical control (minimum 6 months prophylaxis treatment (EHL / SHL FVIII) in observational pre-study 242HA201/OBS16221), further FVIII injections, change in FVIII activity levels, joint complications, PK, AEs, mortality, HRQoL
Locations	Global including 3 UK sites
In model?	**Yes**

EAG: Generalisability of XTEND-1 baseline characteristics to UK population uncertain

Link to supplementary appendix, XTEND-Kids and XTEND-1 clinical trial design and XTEND-1 generalisability

ABR, annualised bleeding rate; AE, adverse event; dL, decilitre; EHL, extended half-life; FVIII, factor VIII; HRQoL, health rated quality-of-life; IU, international unit; IV, intravenous; N, number; PK, pharmacokinetic; PTPs, previously treated patients; PRN, as required; QW, every week; SHL, short half-life

Key issue: Population

Company's population narrower than scope [redacted] includes only people with severe haemophilia A

Background Population in NICE scope: *People with haemophilia A*

- Company's DP narrower than scope but wider than pivotal trial

Company: Severe disease aligns with data source (XTEND-1)

- Company's clinical experts: Efanesoctocog alfa unlikely routinely used in mild / moderate disease; PTP data generalisable to PUPs considering no direct data
- XTEND-Kids data not used in model but similar bleeding outcomes and PK to XTEND-1: data generalisable to under 12-year-olds
  - Disease mechanism same for adults and children

EAG: Company defined population according to trial not scope:

- Relevant population unclear
- Uncertain if XTEND-1 data generalisable to groups excluded from trial

Clinical experts: Benefits in moderate / mild (less hospitalisation, inhibitor risk, joint disease)

- PUPs and young children likely to benefit more from treatment: weekly administration reduces need for venous access device

- Would clinicians use efanesoctocog alfa in mild/moderate disease or in people with FVIII inhibitors (if available)?
- Should the decision problem be limited to people with severe haemophilia A?
- Is the data and population characteristics (e.g. absolute bleeding risk) from XTEND-1 generalisable to: a) [redacted] b) [redacted] c) [redacted]

Differences in the company's DP, scope, MA and trial populations

Population	[redacted] and scope	Company DP?	XTEND-1 trial?
Severe haemophilia A	[redacted]	Y	Y
Mild/moderate haemophilia A	[redacted]	N	N
PTPs	[redacted]	Y	Y
PUPs	[redacted]	Y	N
<12 years	[redacted]	Y	XTEND-Kids
FVIII inhibitors	[redacted]	Y	N

DP, decision problem; FVIII, factor VIII; MA, marketing authorisation, PK, pharmacokinetic; PUPs, previously untreated patients; PTPs, previously treated patients; QW, weekly

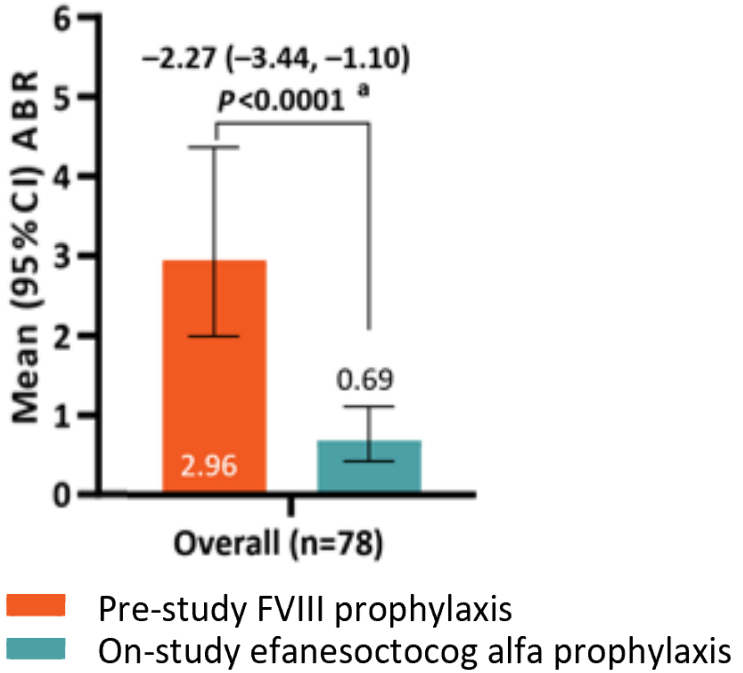
XTEND-1: key results

Lower ABRs with efanesoctocog alfa prophylaxis than on-demand efanesoctocog alfa and historical SHL / EHL FVIII replacement therapies

XTEND-1 key bleeding outcomes, FAS

Week 52 results	Arm A Prophylaxis N=133	Arm B O-D N=26	Arm B Prophylaxis N=26
Baseline characteristics, mean (SD)			
Bleeds in past 12 months	3.2 (5.4)	35.7 (22.2)	35.7 (22.2)
Mean ABRs			
Treated bleeds (SD)	**0.71** ([redacted])	21.42 (7.41)	0.69 (1.35)
All bleeds (95% CI) (negative binomial model)	**1.11** (0.83, 1.48)	22.21 (19.41, 25.42)	0.88 (0.42, 1.84)
Number of bleeds per year			
0 (%)	86 (65)	0	20 (77)
5 or less (%)	131 (99)	[redacted]	[redacted]

ABR between Arm A and pre-study prophylaxis, FAS



- Day 7 FVIII activity:
  - similar at week 1 and 26 in Arm A: suggests durable response to treatment
  - similar for Arms A and B after Day 1 injection: suggests consistent PK at baseline for O-D and prophylaxis
- Improvement from baseline in Haem-A-QoL Physical Health score and EQ-5D

ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; FVIII, factor VIII; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; N, number; O-D, on-demand; SD, standard deviation. **Bold** = used in company model

Clinical effectiveness of efanesoctocog alfa vs. emicizumab

MAIC methodology associated with uncertainty: small ESS as only adjust XTEND-1 data

Background: No direct trials and no common comparator to form network

- Separate ITCs for each comparator using trials in PTPs aged 12+ with severe disease and no FVIII inhibitors.

Matching adjusted indirect comparison (MAIC) vs emicizumab

XTEND-1 and HAVEN-3 arms

Intervention	Efanesoctocog alfa (50 IU/kg IV)	Emicizumab (given SC)
Trial	XTEND-1 (n=159)	HAVEN-3 (n=152)
Prior prophylaxis	A: QW (n=133)	D: 1.5 mg/kg QW (n=63)
Prior O-D	B: O-D for 26 weeks, then QW to 52 weeks (n=26)	A: 1.5 mg/kg QW (n=36); B: 3.0 mg/kg Q2W (n=35); C: no prophylaxis (n=18)

- No IPD data for HAVEN-3 so company adjusted only XTEND-1 baseline characteristics (see MAIC methodology).
  - ❖ High uncertainty inherent in MAIC, especially if covariate overlap poor so small effective sample size (ESS) / not all prognostic factors included
- Company did several MAICs varying HAVEN-3 and XTEND-1 arms and pooling data
- ABR for emicizumab in model calculated using MAIC IRRs applied to XTEND-1 ABRs

Company: No common comparator for anchored MAIC: O-D treatment and inclusion criteria differ between trials.

- Base case arms (HAVEN-3 Arm B and XTEND-1 Arm B) based on Q2W emicizumab dosing: clinical experts state most plausible frequency
- Company's preferred arms favour efanesoctocog alfa for all outcomes except ABR for spontaneous treated bleeds

ABR, annualised bleeding rate; IU, international unit; ITC, indirect treatment comparison; IPD, individual patient data; IRR, Incidence rate ratios
kg, kilogram; MAIC, matching-adjusted indirect comparison; O-D, on demand; PTPs, previously untreated patients; RCT, randomised controlled trial; Q2W, biweekly; QW, weekly; SC, subcutaneous. Link to supplementary appendix, company's ITC methodology, full ITC results

Key issue: Methodology and arms of the ITC

EAG: HAVEN-3 and XTEND-1 arms in company base case unjustified and considerably reduce sample size

EAG: Concerns over MAIC methodology and lack of justification for:

- HAVEN-3 arms chosen for base case (prior O-D vs. prophylaxis)
- Outcomes assessed and population trimmed from XTEND-1 differed by arms chosen
- Matched different covariates in all analyses

Prefer: IRR from HAVEN-3 Arm D vs. XTEND-1 Arm A for emicizumab: both prior prophylaxis; result in much larger sample size

MAIC ABR IRRs using company and EAG preferred arms

	Company	EAG
Effective sample size after matching		
HAVEN-3 arm	B (prior O-D): N=35	D (prior prophylaxis): N=63
XTEND 1 arm	B (prior O-D): N=19	A (prior prophylaxis): N=76
ABR IRR (95% interval). Less than 1 favours efanesoctocog alfa, 1 = no difference, over 1 favours comparator.		
Any bleed	0.28 (0.10; 0.81)	0.32 (0.19; 0.56)
Any treated bleed	0.47 (0.15; 1.44)	0.50 (0.29; 0.86)

Technical team: O-D and prophylaxis arm patient populations may differ in baseline characteristics:

- Differences in baseline characteristics for O-D and prophylaxis populations (see generalisability of XTEND-1 trial)
- In Arm B (O-D) of XTEND-1, people switched to prophylaxis after 26 weeks
- Different pre-trial regimens and inclusion criteria: emicizumab as pre-study prophylaxis in XTEND-1, different bleeding criteria for O-D arms (see summary of ITC arms and pre-study regimens)

Is the ITC suitable for decision-making? If yes, which base case assumptions are most appropriate for the comparison with emicizumab?

ABR, annualised bleeding rate; IPD, individual patient data; IRR, incidence rate ratios; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; n, number; O-D, on demand; PSM, propensity score matching; Q2W, biweekly.

Link to supplementary appendix, full ITC results

Clinical effectiveness of efanesoctocog alfa vs. efmoroctocog alfa

PSM uses patient data for both trials. Results favour efanesoctocog alfa.

Propensity score matching (PSM) vs efmoroctocog alfa

XTEND-1 and A-LONG arms

Intervention	Efanesoctocog alfa (50 IU/kg IV)	Efmoroctocog alfa (IV)
Trial	XTEND-1 (n=159)	A-LONG (n =165)
Prior prophylaxis	A: QW (n=133)	1: 2x weekly Day 1, 25 IU/kg, Day 4, 50 IU/kg, 25-65 IU/kg every 3-5 days (n=118)
Prior O-D	B: O-D for 26 weeks, then QW to 52 weeks (n=26)	Could enter Arm 1 or be Rx to: 2: QW at 65 IU/kg (n=24); 3: O-D (10 to 50 IU/kg) (n=23)

PSM ABR IRRs

Outcome	Company and EAG preferred
Effective sample size after matching	
A-LONG arm	Pooled arms: 30
XTEND 1 arm	Pooled arms: 87
ABR IRR (95% interval). <1 favours efanesoctocog alfa, 1 = no difference, >1 favours comparator	
Any bleeds	Not recorded in A-LONG
Any treated bleeds	0.29 (0.17; 0.51)

- IPD data for both trials: weight baseline data from both (PSM methodology slide)

Results vs efmoroctocog alfa: Analyses using pooled arms favours efanesoctocog alfa for all outcomes. FVIII consumption, Haem-A-QoL total and Physical score not statistically significant.

Technical team:

- Pooled arms included different on-trial and pre-trial regimens
- XTEND-1 supports benefit in treatment effect for efanesoctocog alfa prophylaxis (Arm A) with historical pre-study EHL and SHL (ABR IRR any treated bleed = 0.23)

Is the PSM suitable for decision-making?

ABR, annualised bleeding rate; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults ITC, indirect treatment comparison; IPD, individual patient data; IRR, Incidence rate ratios; O-D, on demand; PSM, propensity score matching; Rx, randomised. Link to supplementary appendix, full ITC results; summary of ITC arms and pre-study regimens

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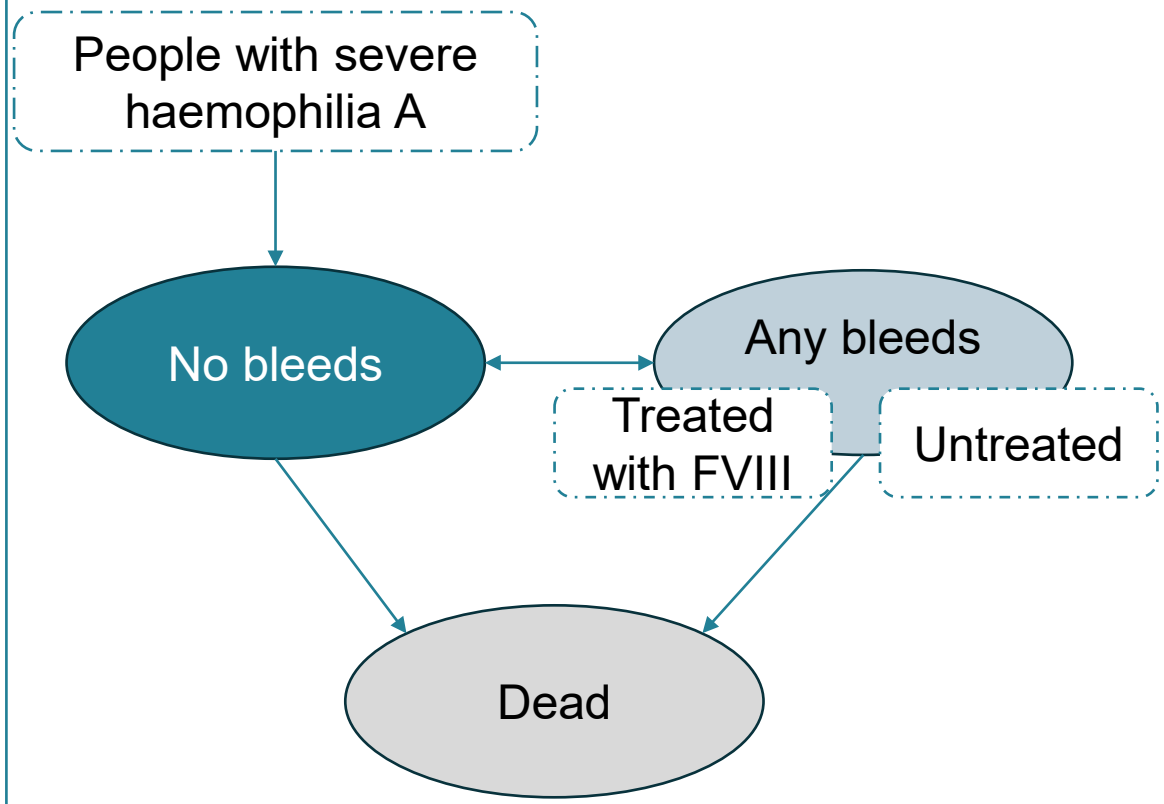
Company's model overview

Markov model with some people modelled to have bleeds each cycle

Company's model structure



- All people start in "No bleeds" state
- Some have a bleeding event each cycle:
  - Severity of bleed: treated (1x extra FVIII treatment) or untreated (mild bleed so no treatment)
- Lower utility (disutility) applied to people with lower FVIII level: Base-case differentiates between FVIII above or below 20%. Scenarios consider 5% threshold
- 6-month cycle, half cycle correction, lifetime time horizon

- Treatment affects QALYs by:
  - Decreased number of bleedings
  - Increased time spent with higher FVIII activity levels
- Treatment affects costs by:
  - Changing costs of treatments and treating bleeds
- Assumptions with greatest effect on ICER:
  - Source used for baseline ABR rates
  - Choice of treatment arms in ITC
  - Assumption that less than 20% FVIII activity level = decreased QoL

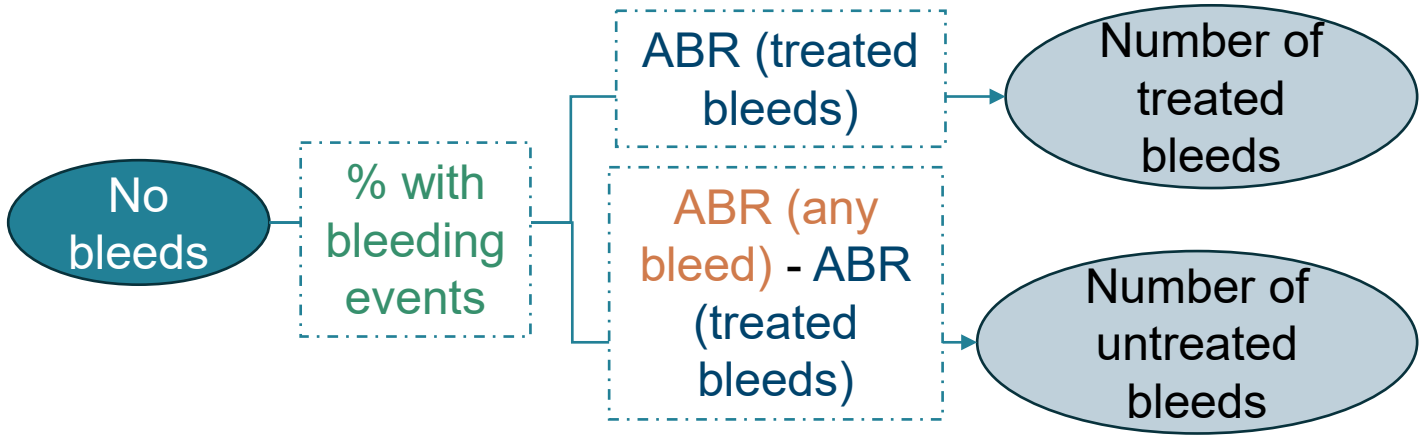
EAG comments: No transition probabilities between bleeds and no bleeds need to be estimated.
- May miss granularity in bleeding levels and locations

ABR, annualised bleeding rate; FVIII, factor VIII; ICER, incremental cost effectiveness ratio; ITC, indirect treatment comparison; QALYs, quality adjusted life years; QoL, quality of life

Treatment effectiveness in model

Treatment effectiveness based on % with bleed and ABRs for any bleed and treated bleeds

Sources of clinical effectiveness evidence in company model



Costs: use number treated bleeds / cycle
QALYs: use % with bleeding event and number bleeds / cycle

- **No bleeds:** Age-adjusted population utility
- **Any bleeds:** XTEND-1 EQ-5D-5L mapped to ED-5D-3L, fitted to TOBIT models to get disutilities for long- (6 month) and short- (7 day) term bleeds (model results here)
- Extra disutility for FVIII activity levels less than 20%

Clinical effectiveness inputs in the company model

Efficacy measure	Efanesoctocog alfa		Emicizumab				Efmoroctocog alfa	
	Source	Value	Company source	Company value	EAG source	EAG value	Source	Value
% bleeds treated	XTEND-1: Arm A	64%	HAVEN-3 Arm D	38%	MAIC IRR applied to XTEND-1 ABR: HAVEN-3 Arm D, XTEND-1 Arm A	41%	PSM IRR applied to XTEND-1 ABR: pooled arms	64%
ABR, any bleed		1.11	MAIC IRR applied to XTEND-1 ABR: HAVEN-3 Arm B, XTEND-1 Arm B	3.96		[redacted]		3.83
ABR, treated bleed		0.71		1.51		1.42		2.45

ABR, annualised bleeding rate; FVIII, factor VIII; MAIC, matching-adjusted indirect comparison; O-D, on demand; PSM, propensity score matching

How company incorporated evidence into model

Baseline characteristics based on PTPs in XTEND-1; wastage costs only for octocog alfa

Input	Assumption and evidence source
Baseline characteristics	- PTPs: XTEND-1 (severe haemophilia A only) - PUPs: Assumed enter the model aged 1. Weight from growth charts <18 years old, then = PTPs
Time in FVIII activity levels	Efanesoctocog alfa and efmoroctocog alfa: pharmacokinetic data from XTEND 1 and A-LONG Emicizumab: Retout et al, 2020 with conversion factor of 0.3 Shima et al. (2016).
Costs	- Treatment acquisition costs and medical costs of treating bleeds: NHS reference prices and BNF - No treatment administration costs. - Wastage costs for octocog alfa only (octocog alfa assumed to be used for O-D therapy in people with breakthrough bleed on emicizumab) - Cost for bleed management equal for all severities
Resource use	Health care professional contacts from US data verified by clinical experts
AEs	Not included
Mortality	Based on general population mortality

EAG comments: Base case preferences on above inputs aligned with company but raise concerns with treatment administration and wastage costs, inclusion of specialist visits and costs for bleeding events

AE, adverse event; BNF, British National Formulary; FVIII, factor VIII; O-D, on-demand; PTPs, previously treated patients; PUP, previously untreated patients; US, United States

Key issue: Disutility related to low FVIII levels

EAG: FVIII monitoring frequency in NHS makes disutility for activity levels <20% implausible?

Background: Company assumes disutility of –0.0277 for people with FVIII levels 20% or less, regardless of whether they have bleeding event. Calculated using TOBIT models based on XTEND-1 EQ-5D trial data.

Company: clinical expert advice: people with lower FVIII levels have higher risk of bleeding so limit activities
Scenario: a) Disutility for people with 5% or less FVIII activity level; b) No disutility for low FVIII activity levels

EAG comments: Unclear how often people monitored outside trials. If unaware of FVIII levels, unlikely to amend activities or have bleed-related anxiety so QoL only decreased by bleed → captured in model

- Monitoring frequency (and impact of FVIII activity levels on QoL) may differ by treatment
- XTEND-1: TOBIT models found disutility for mild, moderate and severe disease, independent from bleeding events but FVIII levels regularly monitored in trial
- Company assumes FVIII levels decrease between administrations: variation in patient responses uncaptured
- TOBIT models assume impact of age on utility equal for general public and XTEND-1 population: feasible?

Patient experts: FVIII monitored 4-6 monthly: when aware FVIII levels low limit certain activities with high risk of bleed (e.g. crowds). FVIII of 5% or under would impact life substantially but restrict activities well before this.
Clinical experts: bleed risk may make some patients unduly cautious and avoid physical activity

- No exact FVIII level impacting QoL but would not expect spontaneous bleeds at 10 IU/dL (10%) or more

- How often are people monitored for FVIII levels in clinical practice?
- If people are aware of low FVIII levels, does this impact activities and mental health?
- Should a disutility be applied for low FVIII levels? If yes, less than 20% or less than 5%?
- Is the company's disutility of -0.0277 appropriate for people with FVIII levels 20% or less?

Link to supplementary appendix, Utilities. dL, decilitre; FVIII, factor VIII; QoL, quality of life; IU, international units

Key issue: Dose of efanesoctocog alfa for bleeding events

Company uses 25 IU/kg efmoroctocog alfa to treat bleeding events; EAG prefers 50 IU/kg in line with trial data

Background: In 'any bleeds' health state, proportion assumed have bleeding event needing O-D treatment

- O-D doses based on clinical opinion to company (restoring FVIII to normal levels with extra doses stops most bleeds)
- Emicizumab: O-D treatment uses most recent FVIII therapy (company assumes octocog alfa)

Doses used to treat bleeds in company model

Treatment	Dose, IU/kg
Efanesoctocog alfa	25
Efmoroctocog alfa	50
Octocog alfa (emicizumab arm)	50

Company: Clinical advice suggests sustained PK profile of efanesoctocog alfa will resolve bleeds with 25 IU/kg dose that would need 50 IU/kg with octocog alfa or efmoroctocog alfa

- XTEND-1 Arm B (O-D): 97% of bleeds controlled by 1 dose (30 to 50 IU/kg)

EAG comments: In XTEND-1 Arm A (prophylaxis) most people (77%) had ~50 IU/kg for bleeds.

- 50 IU/kg aligns with SmPC for octocog alfa and company assumption that need ~4000 IU rFVIII to treat bleeds

EAG base case: 50 IU/kg efanesoctocog alfa for bleeds

Technical team: SHLs other than octocog alfa may be used for bleeds on emicizumab but little impact on ICER

Clinical experts: dosing of bleed highly individualised based on size (small child needs more FVIII per kg than adult), bleed severity, timing of most recent FVIII, availability of subsequent dosing.

- Most bleeds on emicizumab need extra 50 IU/kg FVIII therapy

Is there reason to assume the dose of efanesoctocog alfa used for bleeding episodes would be lower than that for efmoroctocog alfa and octocog alfa?

rFVIII; Recombinant clotting factor VIII; IU, international unit; ITC, indirect treatment comparison; O-D, on-demand; kg, kilogram; SHL, short half-life; SmPC, summary of product characteristics

Summary of company and EAG base case assumptions

Main differences: ABR source, frequency of emicizumab, dose efanesoctocog alfa for bleeds

Assumptions in company and EAG base case

Assumption	Company base case		EAG base case	
	Assumption	Rationale	Assumption	Rationale
Fixing errors	-		Corrected errors in company model	
ABRs	HAVEN 3 Arm B vs. XTEND-1 Arm B (prior O-D)	Q2W dosing for emicizumab	HAVEN 3 Arm D and XTEND-1 Arm A (prior prophylaxis)	• Bigger ESS • QW and Q2W dosing showed similar effects • Aligns with arms used for % with bleeding event
Frequency of emicizumab dosing	Q2W	Clinical opinion, National Haemophilia Database data.	QW	• No appropriate dosing regimen data • Younger patients likely higher / more frequent dosing schedules • National haemophilia data does not support Q2W emicizumab
Dose efanesoctocog alfa to treat bleeds (model driver)	25 IU/kg	Sustained PK profile of efanesoctocog alfa vs. comparators	50 IU/kg	Aligns with dosing used in XTEND-1 to treat bleeds

ABR, annualised bleeding rate; ESS, effective sample size; IU, international unit; kg, kilogram; O-D, on-demand; PK, pharmacokinetic; Q2W, every 2 weeks; QW, weekly

Other considerations

Other issues highlighted by the EAG

Description	EAG comment
Wastage costs	Company models no wastage for prophylactic FVIII therapies and emicizumab
	Method for calculating wastage costs for octocog alfa uncertain and lack face validity
Specialist visits for bleeding events	Resource use does not account for bleeds resolved by phone contact by specialist nurses
Costs for bleeding events	Set to £610.45 irrespective of severity. Likely that mild and moderate bleeds will be resolved by phone: costs overestimated.
	2020/2021 costs for Haemophilia Nursing Service lower than 2021/2022: model not reflective of UK costs

Uncaptured benefits: some potential benefits of efanesoctocog alfa (especially in children) not included in company model. Clinical and patient expert statements highlighted:

- Impact on family: convenience of weekly dosing and reduced fear of bleed
- Educational attainment as less school absences for treatment and bleeding episodes
- Improved relationship with healthcare providers from a young age
- Improved treatment adherence
- Less fear and resentment of condition
- Improved vein health from less frequent administration

Severity: no case made for applying a severity weighting

FVIII, factor VIII; UK, United Kingdom

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential commercial arrangements for the intervention and comparators

- Company base case – dominant against emicizumab (PUPs and PTPs), within the threshold usually considered an acceptable use of NHS resources against efmoroctocog alfa (PUPs)
- EAG base case – dominant against emicizumab (PUPs and PTPs), above the threshold usually considered an acceptable use of NHS resources against efmoroctocog alfa (PUPs)

Scenarios in which each of the company's preferred assumptions (where different from EAG's preferred assumptions) are applied individually to EAG base case will also be considered

PAS, patient access scheme; PTPs, previously treated patients; PUP, previously untreated patients;

NICE National Institute for Health and Care Excellence

Thank you.

Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

Population, intervention, comparators and outcomes from the scope

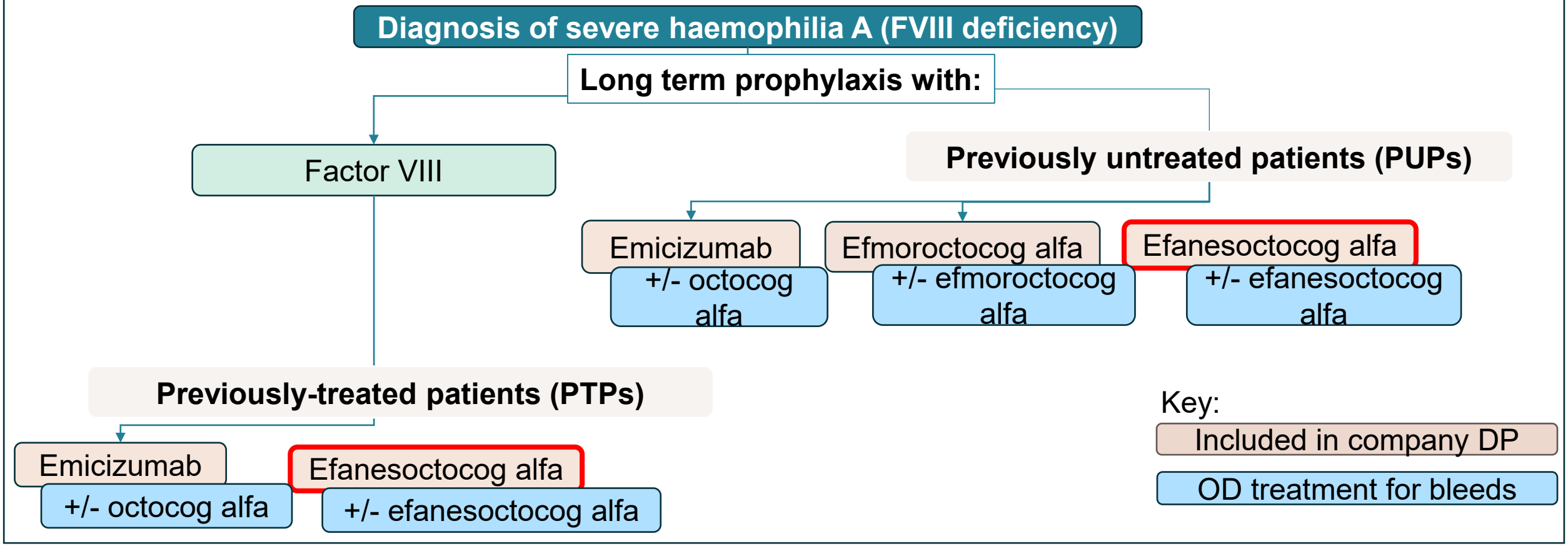
	Final scope	Company	EAG comments
Population	People with haemophilia A	Patients with severe haemophilia A to align with XTEND-1 study which recruited previously treated patients (PTPs) with severe haemophilia A.	• See key issue: populaiton • XTEND-1 only included 12 years and over but [redacted] • Clinical data supports extrapolation of data from PTPs to PUPs
Intervention	Efanesoctocog alfa	As per final scope	-
Comparators	Established clinical management, including: • Prophylaxis and on-demand treatment with FVIII replacement therapy • Emicizumab	• PTPs: Emicizumab • PUPs: Emicizumab and efmoroctocog alfa	• Asked company to justify exclusion of FVIII replacement therapy, see key issue: comparators • Company should use current SoC rather than future trends • Emicizumab and efmoroctocog alfa not used together in PUPs

FVIII; factor VIII; MA, marketing authorisation; PUP, previously untreated patients; PTPs, previously treated patients; SHL, short half-life; SoC, standard of care

Company's treatment pathway with O-D treatment

Company excludes EHL and SHL FVIII products for PTPs; efmoroctocog alfa only EHL for PUPs

Company's proposed pathway for severe haemophilia A



DP, decision problem; EHL, extended half-life; FVIII, factor VIII; HRQoL, health related quality-of-life; SHL, short half-life.

Link to main slides: treatment pathway

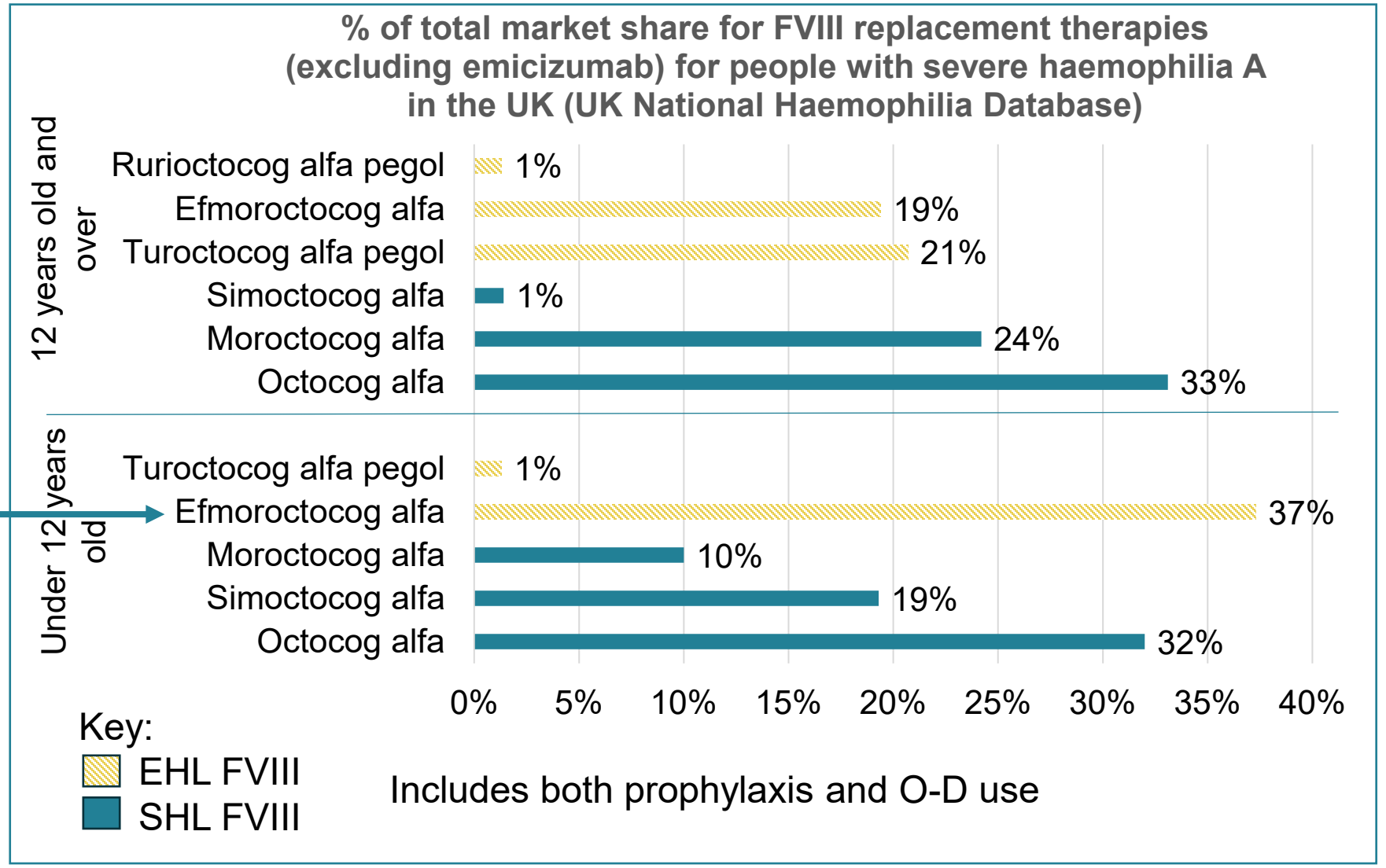
Key issue: EHL FVIII therapy as a comparator (1)

EHL FVIII replacement therapies may be relevant comparators in PTPs

Treatments for people with severe haemophilia A without inhibitors in the UK (UKHCDO 2022-3)

Treatment	Number
SHL FVIII	483
EHL FVIII	347
Emicizumab	1,261

Efmoroctocog alfa in PUPs is only FVIII replacement therapy included as comparator (prophylaxis) in company's model



EHL, extended half-life; FVIII, factor VIII; O-D, on demand; PUPs previously untreated patients; UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation; SHL, short half-life

Link to main slides: key issue: comparators

Link to main slides, treatment pathway

Potential comparators

Company included emicizumab and efmoroctocog alfa as comparators

Comparator	Recommended population	Company position in pathway
Emicizumab	NHS clinical commissioning policy for: • people of all ages with congenital haemophilia A without FVIII inhibitors	**Prophylaxis:** PUPs and PTPs **O-D:** Not licensed for on-demand therapy
Efmoroctocog alfa (EHL factor VIII)	Licenced for: • treatment and prophylaxis of bleeding in patients with haemophilia A • all ages	**Prophylaxis:** PUPs only: • severe haemophilia A presents in children • EHL often continued after a severe bleed at diagnosis requiring emergency FVIII therapy **O-D:** PUPs who have bleed on efmoroctocog alfa
Rurioctocog alfa pegol, turoctocog alfa pegol (EHL factor VIII)	Licenced for: • Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A	Not used: not licenced for people under 12 when company states EHLs would be used
Octocog alfa, moroctocog alfa, simoctocog alfa (SHL factor VIII)	Licenced for: • treatment and prophylaxis of bleeding in patients with haemophilia A • all ages	**Prophylaxis:** Not included in pathway due to declining market share **O-D:** PUPs and PTPs who have a bleed on emicizumab have octocog alfa (as octocog alfa has largest market share of SHLs)

EHL, extended half-life; FVIII; factor VIII; O-D, on demand; PUP, previously untreated patients; PTPs, previously treated patients; SHL, short half-life

Other key clinical trial: XTEND-Kids

XTEND-Kids in under 12 years olds: results suggest low bleed rate with efanesoctocog alfa

	XTEND-Kids (NCT04759131)
Design	Phase 3, open-label, non-randomised
n	74
Population	PTPs less than 12 years old with severe haemophilia A (less than 1 IU/dL [<1%] endogenous FVIII or documented genotype)
Efanesoctocog alfa	50 IU/kg IV QW for 52 weeks
1° outcome	Inhibitor development to 52 weeks
Key 2° outcomes	ABR, change in FVIII activity levels, joint complications, PK, HRQoL
Locations	Global including 2 UK sites
In model?	No

Company: XTEND-kids not used in submission as data unavailable at time of modelling and no comparator data in people under 12 years for ITC

Key XTEND-1 results:

1° endpoint: No FVIII inhibitor development during mean efficacy period

Key 2 ° endpoints at 52 weeks:

- Estimated mean ABR: 0.89 (95% CI: 0.56–1.42) (no baseline ABR provided)
- 64% had no bleeds, 88% had no spontaneous bleeds and 81% had no joint bleeds after 52 weeks.
- Most bleeds resolved with 50 IU/kg dose
- Overall half-life after 50 IU/kg injection: 40 hours

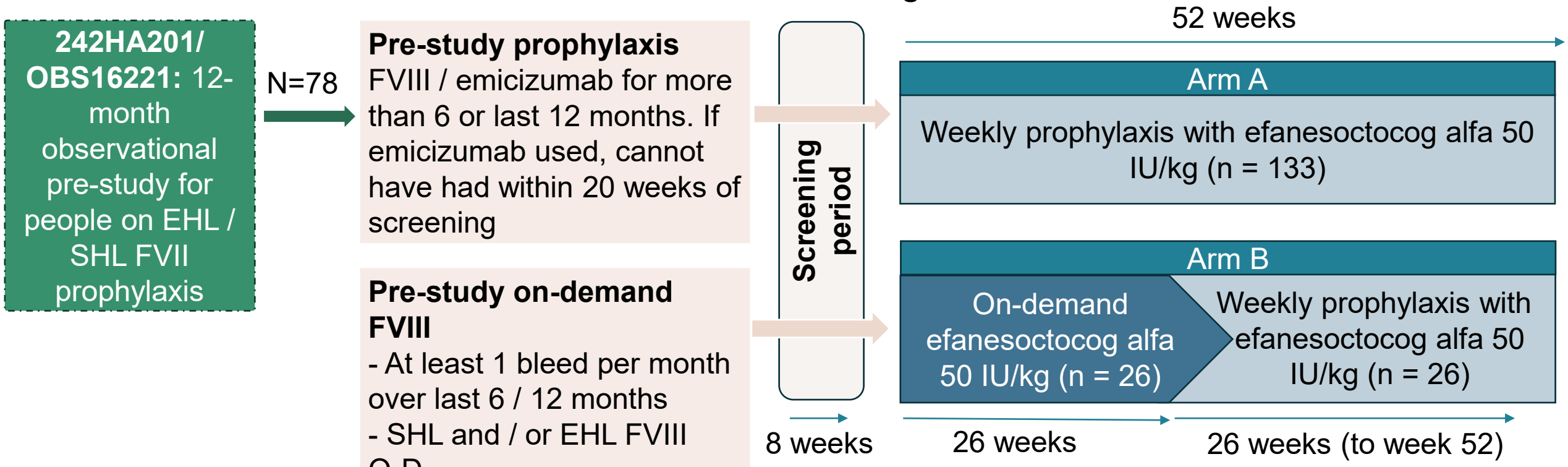
Link to main slides, key clinical trials

ABR, annualised bleeding rate; FVIII, factor VIII; HRQoL, health rated quality-of-life; IU, international unit; IV, intravenous; ITC, indirect treatment comparison; N, number; previously treated patients; PK, pharmacokinetic; QW, every week

XTEND-1 clinical trial design

52-week trial with different regimens for people on prior prophylaxis or on-demand FVIII therapy

XTEND-1 trial design



Key outcomes:

- 1° outcome: estimation approach to analyse mean ABR in Arm A
- Key 2 outcome: Intra-patient comparison of ABR between efanesoctocog alfa Arm A and those with at least 6 months of historical data on prophylaxis treatment from 242HA201/OBS16221.

Link to main slides, key clinical trial

ABR, annualised bleeding rate; EHL, extended half-life; FVIII, factor VIII; IU, international unit; kg, kilogram; N, number; PK, pharmacokinetic; SHL, standard half-life

Key issue: Generalisability of XTEND-1 baseline characteristics

EAG: UK specific baseline characteristics not provided so generalisability to UK population uncertain

Key baseline characteristics from XTEND-1

	Arm A, N=133	Arm B N=26	Overall N=159
Mean age, years (SD)	34 (15)	43 (12)	35 (15)
Female, n (%)	1 (1)	0	1 (1)
Europe, n (%)	67 (50)	14 (54)	81 (51)
Mean weight, kg (SD)	78 (19)	81 (18)	79 (19)
Age at 1st prophylaxis, years (%)	[redacted]	[redacted]	[redacted]
Mean bleeds in last year, n (SD)	3 (5)	36 (22)	8 (16)
Joint bleeds in last year, n	2 (5)	27 (19)	6 (12)
Family history of inhibitors			
Yes, %	4	0	3
No, %	75	96	79
Unknown, %	21	4	18

FAS, full analysis set; FVIII, clotting Factor VIII; n, number; O-D, on demand; SD, standard deviation; UK, United Kingdom.

EAG: Uncertain how generalisable full trial cohort is to UK population:

- UK specific baseline characteristics for comparison with full population not provided
- National Haemophilia Database data suggests mean weight may be higher in UK population than trial

Company: Full trial cohort comparable to UK population

- 67% from Europe or America (similar characteristics to UK): subgroup analyses likely to show similar results

Clinical experts: expect PTP data generalise to PUPs.

- Expect less subclinical bleeds and better trough levels in PUPs

Are the patient populations from Arms A and B comparable?

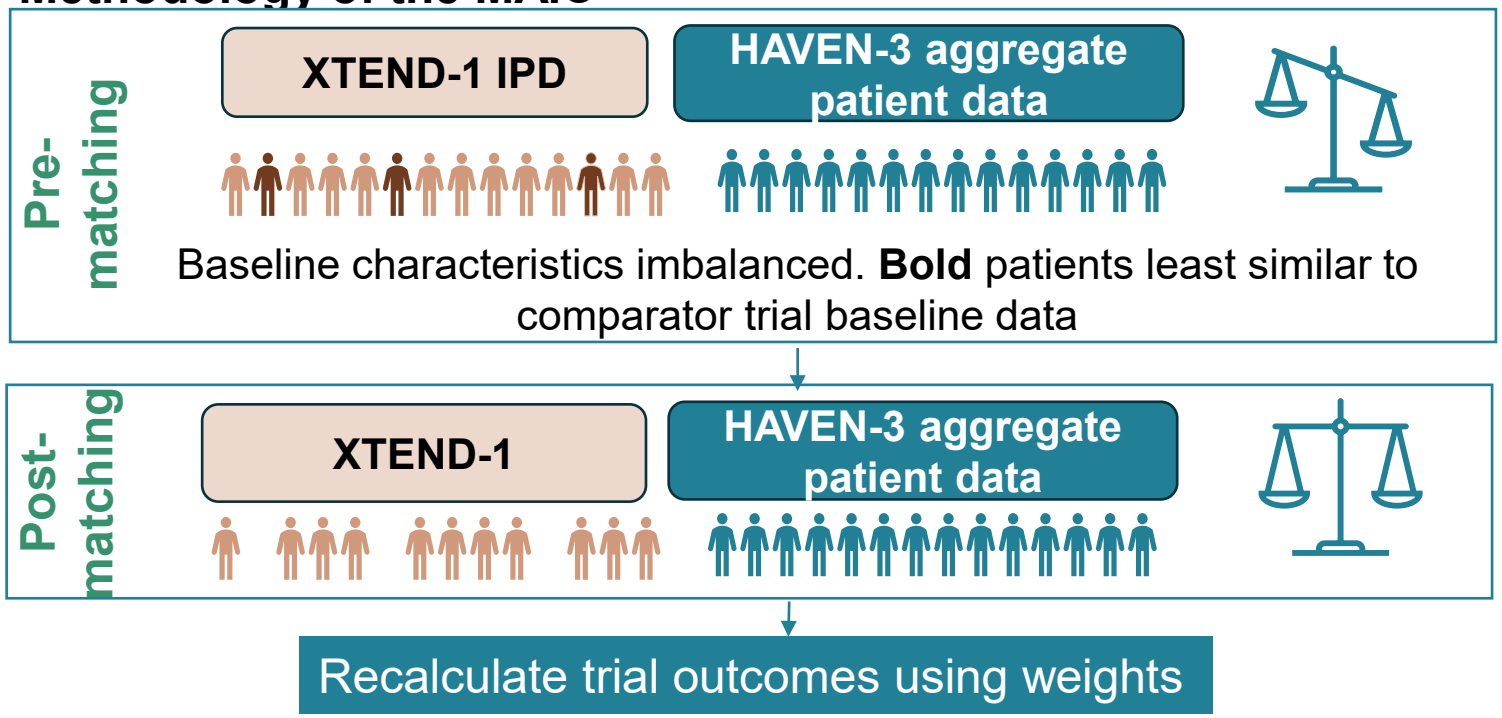
Link to main slides, key clinical trials

Company's IPD methodology

MAIC associated with uncertainty because only uses IPD data from intervention study

MAIC vs emicizumab

Methodology of the MAIC



- No IPD data for comparator trial. Can only weight XTEND-1 baseline characteristics
- XTEND-1 patients with baseline characteristics outside HAVEN-3 reported range trimmed
- Remaining patients weighted to balance covariates across trials (age, body weight/BMI, proportion with 1 or more target joint - exact covariates differed by arms)
- **High uncertainty,** especially if covariate overlap poor (small ESS) and not all prognostic factors included

ESS in the company and EAG's preferred ITCs

ESS	Company preferred (vs. HAVEN- Arm B N=35)	EAG preferred (vs. HAVEN-3 Arm D N= 63)
Before matching	XTEND-1 Arm B: 24	XTEND-1 Arm A: 119
After matching	XTEND-1 Arm B: 19	XTEND-1 Arm A: 76

Link to supplementary appendix, key issues #5 and #6, full ITC results

BMI, body mass index; ESS, effective sample size; IPD, individual patient data; MAIC, matching-adjusted indirect comparison

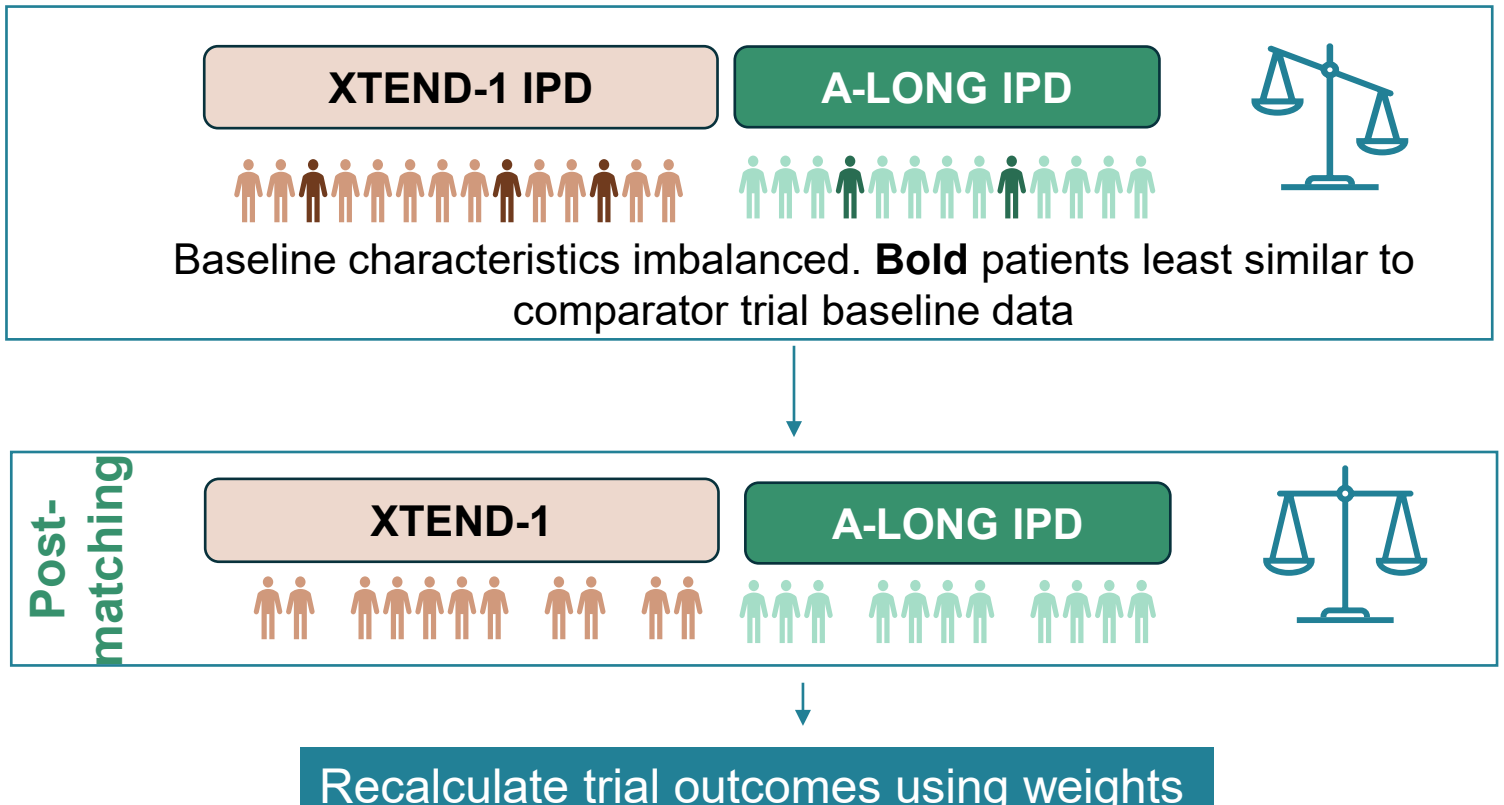
Company's IPD methodology: PSM

Propensity score matching (PSM) uses patient data for both trials

PSM vs efmoroctocog alfa

IPD data for both trials: weight baseline data from both

Methodology of the PSM



- Propensity score capturing all patient characteristics generated for each person for both trials
- Patients individually matched with most similar patient in comparator group

ESS in the company and EAG's preferred ITCs

ESS	Company and EAG preferred arms
Before matching	XTEND-1 pooled A and B: 145 A-LONG pooled 1,2 and 3: 116
After matching	XTEND-1 pooled A and B: 87 A-LONG pooled 1,2 and 3: 30

Link to supplementary appendix, key issues #5 and #6, full ITC results

ESS, effective sample size; IPD, individualised patient data; ITC, indirect treatment comparison; PSM, propensity score matching

Summary of ITC arms and pre-study regimens

Entry criteria, prior and trial regimens differ across treatment arms for trials in company's ITC

Trial arms, inclusion criteria and prior regimen for RCTs used in the company's ITC

Intervention	Efanesoctocog alfa		Emicizumab		Efmoroctocog alfa	
Trial	XTEND-1 (n=159)		HAVEN-3 (n=152)		A-LONG (n =165)	
Regimen	Prior regimen	Trial regimen	Prior regimen	Trial regimen	Prior regimen	Trial regimen
Prior prophylaxis	FVIII / emicizumab ≥6 months in last year. Cannot have had emicizumab in last 20 weeks.	A: 50 IU/kg IV QW (n=133)	- SHL or EHL FVIII prophylaxis for over 24 weeks prior to study	D: 1.5 mg/kg SC QW (n=63)	Prophylaxis at least 2 times per week with an FVIII product OR O-D with at least 12 bleeding episodes in the 12 months	1: 2x weekly Day 1, 25 IU/kg, Day 4, 50 IU/kg, 25-65 IU/kg every 3-5 days (n=118)
Prior O-D	- At least 1 bleed per month over last 6 / 12 months - SHL and / or EHL FVIII O-D	B: 50 IU/kg IV O-D for 26 wks, then QW to 52 wks (n=26)	- At least 5 bleeds in the last 24 weeks (5.5 months) - SHL and / or EHL FVIII O-D	A: 1.5 mg/kg SC QW (n=36); B: 3.0 mg/kg SC Q2W (n=35); C: no prophylaxis (n=18)	- At least 12 bleeding episodes in the 12 months - Any O-D FVIII	2: QW at 65 IU/kg (n=24); 3: O-D (10 to 50 IU/kg based on severity) (n=23)

FVIII, factor VIII; IU, international unit; ITC, indirect treatment comparison; kg, kilogram; O-D, on demand; Q2W, biweekly; QW, weekly; RCT, randomised controlled trial; SC, subcutaneous. SHL, short half-life. Link to main slides, ITC methodology

Results of the ITC

ITC favours efanesoctocog alfa for almost all outcomes

Endpoint	Efanesoctocog alfa *vs.* emicizumab (HAVEN 3)			Vs. efmoroctocog alfa (A-LONG)
XTEND-1 Arm	A (prophylaxis)	B (O-D)		
Comparator arm	D (prophylaxis)	A (O-D)	B (O-D)	Pooled arms
ABRs (IRR, [95% CI])				
Any bleeding	**0.32 [0.19; 0.56]**	**0.34 [0.12; 0.95]**	**0.28 [0.10; 0.81]**	N/A
Any treated bleeding	**0.50 [0.29; 0.86]**	0.46 [0.16; 1.37]	0.47 [0.15; 1.44]	**0.29 [0.17; 0.51]**
Spontaneous treated bleeding	0.62 [0.25; 1.50]	0.45 [0.11; 1.89]	1.35 [0.30; 6.18]	**0.21 [0.09; 0.49]**
Joint treated bleeding	**0.48 [0.24; 0.95]**	0.59 [0.18; 1.49]	0.63 [0.17; 2.29]	**0.37 [0.20; 0.71]**
XTEND-1 and HAVEN-3 pooled arms				
HJHS Total score (MD)			**–2.37 [–4.36; –0.39]**	N/A
HJHS Joint score (MD)			**–2.06 [–3.97; –0.14]**	N/A

	Favours Efanesoctocog alfa (IRR less than 1), significant
	Favours Efanesoctocog alfa (IRR less than 1), not significant
	Favours comparator (IRR over 1), not significant
N/A	*No data/analysis not feasible*
bold	***Statistically significant difference***

Other outcomes vs. efmoroctocog alfa (A-LONG)	
% without any treated bleeding (OR)	**1.99 [1.20; 3.30]**
% without spontaneous treated bleeding (OR)	**2.06 [1.21; 3.52]**
% without joint treated bleeding (OR)	**1.73 [1.12; 2.67]**
FVIII consumption, IU/kg/y (MD)	–1,032 [–2,621; 557]
Haem-A-QoL Total score (MD)	–2.43 [–8.48; 3.62]
Haem-A-QoL Physical score (MD)	–7.01 [–14.69; 0.67]

ABR, annualised bleeding rate; FVIII, factor VIII; HJHS, Haemophilia Joint Health Score; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; ITC, indirect treatment comparison; IRR, Incidence rate ratios; MD, mean difference; OR, Odds ratio; O-D, on demand. Red: used in company model. Link to supplementary appendix, MAIC metholodology

MAIC assumptions used in the base case and scenarios

ITC favours efanesoctocog alfa for almost all outcomes

MAIC assumptions used in base case and scenarios

HAVEN-3 arm	XTEND-1 arm
Company base case	
B (prior O-D)	B (prior O-D)
EAG base case	
D (prior prophylaxis)	A (prior prophylaxis)
Company scenarios	
B (prior O-D)	ABRs for comparators calculated relative to HAVEN-3 arm IRRs
D (prior prophylaxis)	
B (prior O-D)	B with ABRs from prophylaxis period only

ABR, annualised bleeding rate; IRR, Incidence rate ratios; O-D, on-demand. Link to main slide, MAIC methodology

Treatment effectiveness in model

Lower ABRs and less people accruing FVIII disutility = higher QALYs for efanesoctocog alfa

QALY accrual by treatment in the company's model

	QALYs accrued:	Efanesoctocog alfa	Emicizumab	Efmoroctocog alfa
PUPs	Cycles with no bleeds	[redacted]	[redacted]	[redacted]
	Cycles with bleeds	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
PTPs	Cycles with no bleeds	[redacted]	[redacted]	N/A
	Cycles with bleeds	[redacted]	[redacted]	N/A
	Total	[redacted]	[redacted]	**N/A**

EAG's model accrues similar QALYs (slightly lower total QALYs for emicizumab)

Efanesoctocog alfa accrues most QALYs versus comparators as it has:
- Much lower ABR (any bleed) and ABR (treated bleeds) -> less bleeds in cycles with bleeds = less QALY loss for bleeds
- Fewer people with FVIII levels 20% and under (main driver for disutility in emicizumab arm: 100% have FVIII levels between 5 and 20% (so accrue disutility) in model)

[redacted]

Link to main slide, modelling treatment effectiveness

ABR, annualised bleeding rate; FVIII, factor VII; PUPs, previously untreat patients; PTPs: previously treated patients; QALY quality adjusted life year;

Utilities in the company model

Company uses age adjusted general population utility with disutility for bleeds (acute and long term) and FVIII activity levels <20%

Utility values in the company's model

Health state	Utility	Justification
Baseline utility	Age-adjusted general population utility	Higher FVIII level with no bleeds in last 6 months comparable with general population
Disutility for FVIII <20%	–0.0277	Patients with lower FVIII less able to undertake usual activities -> higher risk of bleed
Long-term disutility due to bleeds	–0.0435	Patients with recent bleeds may have ongoing anxiety about repeated events and limit daily activities
Short-term disutility due to bleeds	–0.0663	Bleeds can be painful for patients and limit their ability to conduct usual activities

EAG: issues with company preferred model 1: coefficient for age and covariate for days since treatment initiation excluded. Suggest updating all regression models.

Disutility due to bleeds: company fitted 4 alternative TOBIT models to XTEND-1 patient level data with differing combinations of independent variables

Utility regression models based on trial data

Variable	Model 1	Model 2	Model 3	Model 4
Intercept	**0.4868**	**0.4864**	**0.4675**	**0.4491**
Baseline utility	**0.7692**	**0.7642**	**0.7747**	**0.7762**
7-day bleed disutility	**–0.0663**	**–0.0649**	**–0.0760**	**–0.0738**
6-month bleed disutility	**–0.0435**	**–0.0432**	**–0.0447**	**–0.0441**
Days since study initiation	**–0.00007**	**–0.00007**	Not used	Not used
Age	**–0.0053**	**–0.0052**	**–0.0053**	**–0.0052**
% of time in <5% FVIII level	Not used	–0.0782	Not used	**–0.1231**
% of time in <20% FVIII level	–0.0277	Not used	–0.0728	Not used

Bold = statistically significant. Red: used in model. Model 1 and 2 had lowest AIC/BIC data: considered better fit.

AIC, Akaike Information Criterion:, BIC Bayesian Information Criterion; FVIII, factor VIII. Link to main slides, key issue #7