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

For public – CON information redacted

Technology appraisal committee D 7th August 2024

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Company: Sobi

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- ✓ **Recap to background and key issues**
- ❑ Summary of consultation comments
- ❑ Company's new evidence

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Background on haemophilia A

Chronic condition causing excessive bleeding; company focuses on severe form only

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: Company submission focuses on severe only:

- FVIII level of less than 1 IU/dL (1%). Characterised by:
  - ❖ Bleeding into joints and muscles, without obvious cause or after surgery or minor injuries
  - ❖ Subclinical bleeds cause chronic pain and joint damage - may affect mobility / need surgery
  - ❖ Diagnosed in early infancy
  - ❖ Increased risk of death vs. people with FVIII levels over 1% (defined as mild and moderate haemophilia). Most deaths due to brain bleeds*
  - ❖ Mainly affects men and boys. Women and girls may carry haemophilia gene - usually mild symptoms.

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

Efanesoctocog alfa (Altuvoct, Sobi)

Details of the technology

Proposed marketing authorisation	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Efanesoctocog alfa can be used for all age groups.
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

Equalities

Considerations raised by stakeholders include age and haemophilia A severity

The following equalities issues were raised at ACM1:

1. Some people cannot have FVIII replacement treatments that include blood products derived from humans, animals or animal cells because of religious faith or beliefs.
2. Some groups would benefit more from weekly dosing as currently disadvantaged by frequency of FVIII injections (e.g. people with haemophilia related joint disease)

Stakeholders raised the following potential equality issues during consultation:

1. **Clinical expert:** Children are typically most active subgroup of haemophilia A population: most at risk of trauma-induced bleeding

- weekly treatment has enormous consequences for emotional, mental and physical health of young children with haemophilia A

2. **UKHCDO:** People with FVIII levels over 1% (defined as mild or moderate haemophilia A)

- Some may have similar bleeding phenotype to severe haemophilia A and have prophylactic treatment as standard
- Most unable to self-treat: impacted more by frequency of treatment as must travel to centre for FVIII injections.

ACM, appraisal committee meeting; FVIII, factor VIII, UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation

Summary of appraisal to date (clinical effectiveness)

Recommendation after ACM 1: Efanesoctocog alfa is not recommended, within its anticipated marketing authorisation, for treating and preventing bleeding episodes in people with haemophilia A (congenital factor VIII deficiency).

Table: Committee considerations from ACM1

Issue	Resolved	Committee conclusion / request	Company updated?	ICER impact
Comparator	Partially	Requested analyses in PTPs and PUPs including: emicizumab, SHLs and EHLs	Base case + scenarios	Large
ITC	Partially	Separate ITCs for each comparator: • MAIC vs. emicizumab (EMI): not reliable → unanchored, differences in ABRs + outcomes • PSM vs. efmoroctocog alfa (EFMOR): informative, uncertain over adjusted variables Results favoured efanesoctocog alfa (EFA) vs. comparators but approaches not comparable: • Lack face validity vs. HAVEN-3 pre-study • MAIC + PSM adjust to different populations ***Explore alternative approaches to ITC.***	Base case + scenarios	Large

ABR, annualised bleeding rate; ACM, Appraisal committee meeting; EHL, extended half-life; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PSM, propensity score matching; PUPs, previously untreated patients; PTPs, previously treated patients; SHL, short half-life

Summary of appraisal to date (cost effectiveness)

Committee considerations from ACM1

Issue	Resolved?	Committee conclusion / request	Company updated?	ICER impact
Utilities for bleeds	Partially	Company approach (TOBIT model utilities for all comparators) inappropriate as does not capture QoL differences between treatments and impact of chronic pain	Base case + scenarios	Large
Disutility for low FVIII activity levels	Partially	Disutility for FVIII activity levels under 20% inappropriate, especially for emicizumab (does not increase FVIII activity levels)	Base case + scenarios	Large
Resolved issues: not discussed in ACM2 – see supplementary appendix				
Wastage costs	Yes	Model wastage costs for all treatments, including 'rounding up' of IV doses	Base case	-
Bleed management	Yes	Consider including costs for resolving bleeds via phone by specialist nurses	Base case	-
On-demand dose	Yes	Prefer 50 IU/kg efanesoctocog alfa for treating bleeds whilst on prophylaxis	Base case	-

ACM, appraisal committee meeting; FVIII, factor VIII; ICER, incremental cost-effectiveness ratio; IV, intravenous; IU, international unit; kg, kilogram; QoL, quality of life

Additional analyses requested at postponed ACM2

Committee request at postponed ACM2

Issue	Company provided?
Priority issues: company to provide written response	
Justify preferred SHL usage data	Yes
Further detail on alternative ITC approaches and rationale for variation in results	Yes
ABR spread (histogram) for different treatments	Yes
Additional info on TOBIT model inputs and results	Yes
Potential concerns that may warrant further discussion during the ACM: no written response requested	
Trial reporting criteria for bleeds	Yes
Evidence that [redacted]% people will switch from emicizumab to efanesoctocog alfa if recommended	Yes
Registry data on bleed rates for modelled treatments	No: full data not available
Results of outstanding ITC (O-D arms to anchor ITC) or justification for not conducting	Justification only
Application of TOBIT model parameters to economic model	Yes
Effect on PSA of correlation of coefficients according to variance-covariance matrix	No: to be available for discussion at ACM
Evidence supporting disutility for low FVIII and suggested threshold	Justification only

ABR, annualised bleeding rate; ACM, Appraisal committee meeting; FVIII, factor VIII; ITC, indirect treatment comparison; O-D, on-demand; PSA, Probabilistic sensitivity analysis; SHL, short half-life

Key clinical trial and results

RECAP

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

XTEND-1, n = 159: Phase 3 open-label non-randomised trial in PTPs 12 years and over with severe haemophilia A and no FVIII inhibitors. Link to supplementary slides: XTEND-1 results

XTEND-1 trial design and results

	Arm A, n = 133	Arm B, n = 26
Prior regimen	Prophylaxis (emicizumab (if not used in last 20 weeks) or FVIII for over 6 months in last year)	O-D (1 or more bleed per month over last 6 / 12 months)
Trial regimen	50 IU/kg IV QW for 52 weeks	50 IU/kg IV: 26 weeks of O-D, then 26 weeks QW prophylaxis
Key results	• Mean ABR for treated and untreated bleeds reduced from baseline to week 52 with QW prophylaxis. Mean ABR reduced when Arm B switched from O-D to QW. • QW prophylaxis reduced ABR vs. pre-study prophylaxis with SHL or EHL FVIII	

XTEND-Kids: reported similar results for efanesoctocog alfa in PTPs under 12 years

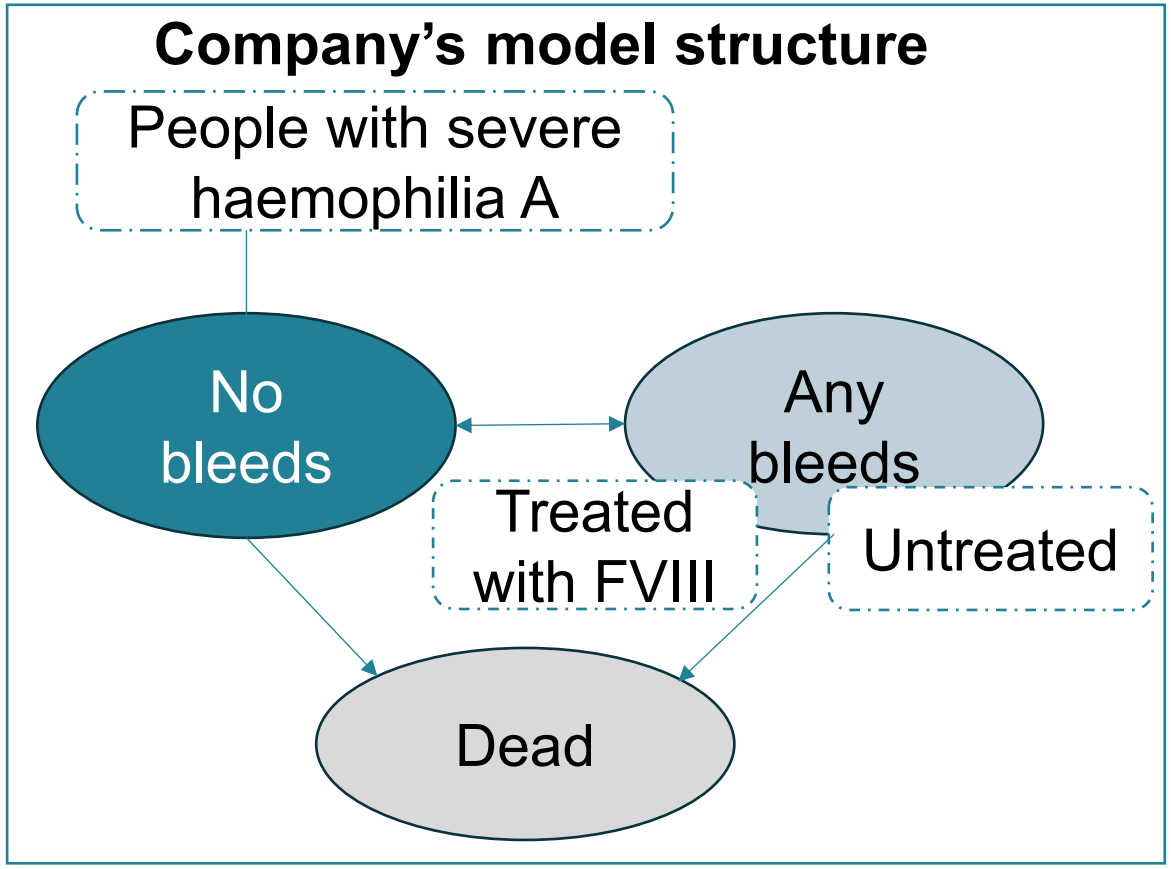
Committee conclusions, population and generalisability:

- No clinical or cost effectiveness data in FVIII over 1% (defined as mild to moderate)
- XTEND trials generalisable to PUPs
- Efanesoctocog alfa unlikely used in people with inhibitors.

ABR, annualised bleeding rate; EHL, extended half-life; FVIII, factor VIII; IU, international unit; IV, intravenous; N, number; kg, kilogram; O-D, on demand; PUPs, previously untreated patients; PTPs, previously treated patients; QW, every week; SHL, short half-life

Company's model overview

Markov model with some people modelled to have bleeds each cycle



- All people start in "No bleeds" state
- Some have bleed each cycle: either treated (1x extra FVIII) or untreated (mild bleed, no FVIII)
- 6-month cycle, half cycle correction, lifetime time horizon

Model inputs:

- Costs: use number treated bleeds / cycle
- QALYs: % with bleed each cycle + number of treated and untreated bleeds:
  - Treated bleeds = ABR (treated bleeds)
  - Untreated bleeds = ABR (any bleed) - ABR (treated bleeds).

Utilities

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

ABR, annualised bleeding rate; FVIII, factor VIII; QALYs, quality adjusted life years. Link to supplementary slides: treatment effectiveness in model; model inputs at ACM1

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Consultation responses to draft guidance summary (1)

Experience with efanesoctocog alfa: THS, clinical and patient experts

- Longer half-life, higher trough levels and less frequent administration vs. other FVIII EHLs
  - Likely also beneficial as O-D treatment but no direct comparisons vs. O-D EHL/SHLs
- Reduced risk of bleed during surgical and dental procedures and improved vein health
- Psychological benefits from maintained factor levels: “fuller life” can be led → allows daily activities and exercise towards the end of weekly cycle
- Bleed free life possible with efanesoctocog alfa

Clinical evidence: THS, UKHCDO

- Unreasonable to expect randomised controlled trial given rarity of condition
- XTEND-1 trial design consistent with other haemophilia A studies. Appropriate to:
  1. Include intra-patient comparison (participants acting as own control) due to:
     - inter-individual variability in ABRs (even within severe haemophilia A population)
     - subjective nature of reporting bleeds
  2. Exclude baseline emicizumab use: long half-life would mask treatment effect
  3. Not randomise between prior O-D and prophylaxis: O-D not standard care
- Unclear how placebo effect applies, given that all studies open-label
- XTEND-1 baseline ABRs reflect UK population.
- XTEND-Kids data should be included.

ABR, annualised bleeding rate; EHL, extended half-life; FVIII, factor VIII; O-D, on demand; SHL, short half-life; THS, The Haemophilia Society; UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation. Link to supplementary appendix: summary of stakeholder responses.

Consultation responses to draft guidance summary (2)

Modelling assumptions/parameters: THS, clinical expert, Novo Nordisk

Following not considered in the company's model:

- Impact on chronic joint damage
- Bleed types: joint vs. cutaneous
- Costs and resource for extra care of people needing FVIII injections for bleeds on emicizumab: lack experience in self-administering IV injections
- Cost and resource savings (for patients and NHS) with efanesoctocog alfa as less need for Port-A-Cath in children with weekly administration
- Adverse events

Uncaptured benefits: THS, clinical experts:

- QoL improvement from reduced administration frequency, especially in children and carers
- Committee should consider innovation of the technology and rarity of the condition

Company: following not captured in the QALY:

- benefits in long-term joint damage
- impact of near normal FVIII levels with efanesoctocog alfa.
- benefits of early FVIII tolerance as can be used in children: if have emicizumab instead and develop inhibitors they require costly and burdensome clotting FVIIa products

Switching treatments: company

- Switching treatments not common practice due to: risk of inhibitor development (especially in PUPs: risk highest in initial FVIII exposure), guidelines and policies that limit switching, stability and effectiveness of long-term prophylaxis regimens
- Switching most likely early in life, after initial FVIII exposures. After this, driven by specific clinical indications and patient preferences only.

FVIIa, factor VIIa; FVIII, factor VIII; IV, intravenous; O-D, on demand; PUPs, previously untreated patients; QALY, quality adjusted life year; QoL, quality of life; THS, The Haemophilia Society. Link to supplementary appendix: consultation responses draft guidance summary

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Summary of changes to company's modelling assumptions from ACM1

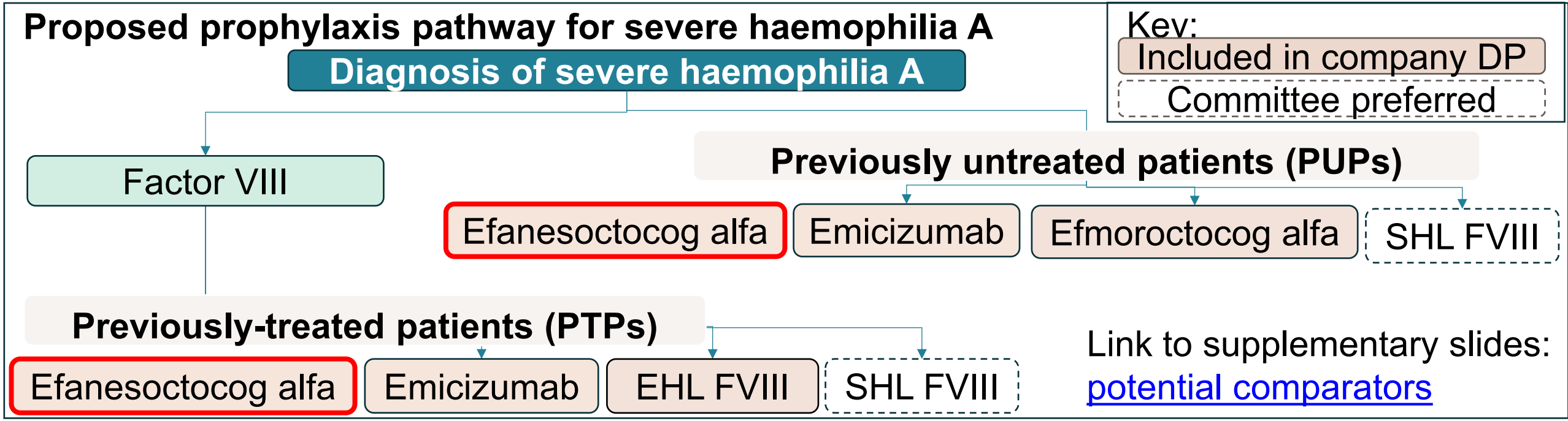
	Company base case ACM1	Company base case ACM2	Committee preferred?	ICER impact
Comparator	Emicizumab for PUPs and PTPs + EHL for PUPs	EHLs for PUPs and PTPs. Simoctocog alfa (SHL) for PUPs, no SHLs for PTPs	No	Large
ITC	MAIC vs. HAVEN-3, PSM vs. A-LONG	MAIC adjusting A-LONG and XTEND-1 to HAVEN-3	To be confirmed	Large
FVIII disutility	FVIII under 20%. Applies to 100% emicizumab arm	FVIII under 20% retained. Applies to 30% emicizumab arm	To be confirmed	Large
O-D dose	25 IU/kg efanesoctocog alfa	50 IU/kg efanesoctocog alfa	Yes	Large
Wastage costs	Octocog alfa only	All prophylactic treatments in adults. Approach for octocog alfa updated.	Yes	Minimal
Managing bleeds	Haematologists only	Include specialist nurse and phone visits	To be confirmed	Minimal
PAS	PAS in place at ACM1	Updated at ACM2	-	-

ACM, appraisal committee meeting; EHL, extended half-life; FVIII, factor VIII; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; O-D, on demand; PUPs, previously untreated patients; PAS, patient access scheme; PSM, propensity score matching; PTPs, previously treated patients; SHL, short half-life

Key issue #1 RECAP: Treatment pathway

RECAP

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



Treatment options for severe haemophilia A

Class	Treatments	Administration
SHL FVIII	Octocog alfa, moroctocog alfa, simoctocog alfa, turoctocog alfa	IV every 2 days
EHL FVIII (current)	Efmoroctocog alfa, rurioctocog alfa pegol, turoctocog alfa pegol	IV every 3-5 days
EHL FVIII (new)	Efanesoctocog alfa	IV QW
Non-factor	Emicizumab	SC QW/Q2W

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

Link to supplementary appendix: SHL and emicizumab prescribing data

Key issue #1: Comparators

Company base case includes EHLs for PTPs but include SHLs for PTPs in scenarios only

Recap: Company optimised efanesoctocog alfa use: positioned as replacement to emicizumab and, in PUPs, efmoroctocog alfa (only EHL available for under 12s)

Committee conclusion: Include as comparators: emicizumab, SHLs (octocog alfa, simoctogog alfa, morcotogog alfa), EHLs (efmoroctocog alfa; for PTPs only: turoctocog alfa pegol and rurioctocog alfa pegol)

Company: SHLs not standard care: currently minimal use and declining. Clinical experts states:

- In PUPs: SHLs (specifically simoctocog alfa) only used when high risk of developing inhibitors or CNS bleed at diagnosis: 5% of all PUPs
- UK market share data specific to people with FVIII under 1% and no inhibitors suggests few people have SHLs in the NHS

Base case: emicizumab + EHLs for PUPs and PTPs Simoctocog alfa (SHL) for PUPs.

Scenarios: includes SHLs for PTPs

N.B. Some EHL and SHL analyses use weighted bucket of available treatments at different prices. Weights use current published data (2023 UKHCDO annual report) in all people with haemophilia A as proxy for SHLs use in PTPs. Limitations: includes prophylactic and O-D use, all severities and inhibitor statuses, double counting where 2+ FVIII products used per year. Assumes equal effectiveness within class.

UKHCDO usage data 2023: people with FVIII <1% (defined as severe), no current inhibitors, treated prophylactically in UK

Treatment	12 and over	Under 12s
Emicizumab	[redacted]	[redacted]
SHLs	[redacted]	[redacted]
EHLs	[redacted]	[redacted]

CNS, central nervous system; DP, decision problem; EHL, extended half-life; PUPs, previously untreated patients; PTPs, previously treated patients; UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation; SHL, short half-life.

Key issue #1: Comparators

EAG: SHLs remain a relevant comparator as currently used in NHS practice

EAG: any current treatment is a comparator, even if only a small % have in clinical practice → company's evidence in decision problem population confirms that SHL FVIII is a relevant comparator for this appraisal.

- Small % expected to have SHLs for some years to come. Octocog alfa most common SHL.

Other considerations:

Novo Nordisk: haemophilia A treatments fall under NHS tender so, in practice, efanesoctocog alfa would be competitively ranked against other EHLs: EHLs only relevant comparator

UKHCDO: Emicizumab has highest clinical effectiveness and market share

- ABRs in both clinical trials and real-world settings for SHLs and EHLs consistently worse than emicizumab and efanesoctocog alfa
- Some prefer SHL and EHL, but infrequently used in PUPs. Reluctance to switch to pegylated FVIII (turoctocog and rurioctocog alfa pegol) as non-pegylated FVIII restricted

THS: company not justified in excluding FVIIIs as relevant comparators in PTPs

Clinical experts: Only ~10% with FVIII activity level under 1% (defined as severe) use SHLs as prophylaxis and use diminishing rapidly: mainly used for O-D, surgery and intercurrent bleeding.

- Emicizumab and EHL FVIII products designed for prophylaxis and should be the appropriate comparator.

Has the committee seen evidence or rationale to reconsider the inclusion of SHLs as a comparator for efanesoctocog alfa?

EHL, extended half-life; FVIII, factor VIII; PUPs, previously untreated patients; PTPs, previously treated patients; SHL, short half-life; THS, The Haemophilia Society; UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation

Key issue #1: Comparators

Different NHS usage data available for FVIII replacement therapies

Different sources of UKHCDO usage data for FVIII therapies in the NHS

Class	SHLs				EHLs		Application in model
Therapy	Simoctocog alfa	Moroctocog alfa	Turoctocog alfa	Octocog alfa	Efmorotocog alfa	Turoctocog alfa pegol	**Base case:** - Company + EAG: simoctocog alfa for PUPs (expert opinion). Separate EHLs. - EAG only: basket of SHLs for PTPs. **Scenarios:** - Company: basket of SHLs + EHLs for PTPs. - EAG: basket of EHLs + SHLs using additional UKCHDO data sources
Company and EAG ACM2, UKHCDO annual report 2023: all people with haemophilia A (all ages and severities), treated prophylactically + on-demand April 2022-March 2023							
PUPs	100%	0%	0%	0%	100%	0%	
PTPs	5%	30%	12%	53%	50%	50%	
EAG scenario ACM1, UKHCDO data request: FVIII under 1% (defined as severe haemophilia A), split by age (under and over 12 years old), treated prophylactically + on-demand April 2022-March 2023							
PUPs	27%	17%	0%	56%	98%	3%	
PTPs	2%	38%	0%	60%	41%	59%	
UKCHDO data provided to NICE pre-ACM2: FVIII under 1% (defined as severe haemophilia A), split by age (under and over 12 years old), treated prophylactically during 2023							
PUPs	40%	16%	0%	44%	95%	5%	
PTPs	3%	31%	21%	45%	48%	52%	

Turoctocog alfa pegol licenced in 12 years+.

If SHLs are a relevant comparator, should company approach (UKHCDO annual report data) or EAG scenario (UKHCDO data request) be used? Which data source best represents the population in the decision problem?

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

Key issue #2 RECAP: Company's ITC methods at ACM1

RECAP

Committee considered MAIC vs emicizumab uncertain → requested alternative ITC approaches

Separate ITCs for comparators using trials in PTPs aged 12+ with severe disease, no inhibitors.

Comparator and approach	Preferred arms	Committee conclusion
EFA vs. efmo: unanchored PSM • Adjusted both trial populations	**Company and EAG:** pooled arms from each trial	• ABR for any bleed not recorded in A-LONG so not included in analysis. • Uncertainty in adjusted variables but informative in the context of evidence available
EFA vs. emi: unanchored MAIC • XTEND-1 adjusted to HAVEN-3 population	**Company** (prior O-D arms): HAVEN-3 Arm B, XTEND-1 Arm B **EAG** (prior prophylaxis arms): HAVEN-3 Arm D, XTEND-1 Arm A	MAIC unlikely to provide reliable estimates: • Unanchored MAIC uncertain: assumes all prognostic variables and effect modifiers adjusted • People in HAVEN-3 had higher baseline ABR than in XTEND-1 but not adjusted for: likely prognostic • Inconsistency in matched covariates and outcomes depending on arms used • Small ESS after adjustment with company's arms **Requested alternative ITC approaches**

ABR, annual bleeding rate; ACM, appraisal committee meeting; EFA, efanesoctocog alfa, efmo, efmoroctocog alfa; emi, emicizumab; ESS, effective sample size; FVIII, factor VIII; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; O-D, on demand; PSM, propensity score matching; PTPs, previously treated patients; SHL, short half-life

Key issue #2: ITC methods (1)

Link to supplementary slides: company's MAIC methodology

Company base case: MAIC including all company comparators adjusted for baseline ABR

Committee requested: MAIC adjusting both A-LONG and XTEND-1 to HAVEN-3 aggregate data

Company: provided requested MAIC adjusting XTEND-1 Arm A (IPD) and pooled arms of A-LONG (IPD) to HAVEN-3 Arm D aggregate data (efa and efmo data adjusted to emicizumab population)

- Adjustment for age, weight, race, presence of target joints
- Not appropriate to adjust for pre-study ABR but include in model as committee preferred
  - ❖ Not marker of severity as driven by prior treatments which vary across trials: EHL use in XTEND-1 pre-study = 44%, HAVEN-3 pre-study = 18%
  - ❖ XTEND-1 more recent → lower baseline ABR vs. HAVEN-3 as standard care improved

Company modelled (#1a): adjustment for baseline ABR; ***Scenario (#1b):*** no adjustment for baseline ABR

NB. Company refers to analysis #1b as base case but results from analysis #1a used in model.

EAG: adjusting for pre-study ABR [redacted] IRRs of efanesoctocog alfa vs. both comparators → suggests prognostic so relevant to include

- Results may not be generalisable to NHS if improved standard care has reduced baseline ABRs in clinical practice vs. trials
- Treatment effect may also vary with baseline ABR, but unanchored ITC assumes not

Other considerations: UKCHDO: HAVEN-3 included countries where prophylaxis not optimised

THS: baseline ABRs vary between trials likely due to prior regimen not population severity

ABR, annual bleeding rate; EHL, extended half-life; FVIII, factor VIII; ITC, indirect treatment comparison; IPD, individualised patient data; IRR, Incidence rate ratios; MAIC, matching-adjusted indirect comparison; THS, The Haemophilia Society

Key issue #2: ITC methods (2)

Link to supplementary slides: company's methodology

Company provide committee requested analyses using intra-patient comparisons

Committee requested: using intra-patient comparison to inform outcomes

Company: ***Scenarios***: Intra-patient comparison from XTEND-1 (N=78) used to:

1. directly inform outcomes for efanesoctocog alfa vs. SHLs and EHLs
   - Higher ABRs expected with SHL than EHL prophylaxis → subgroup analysis for efanesoctocog alfa vs prophylaxis with pre study: a) SHL, b) EHL, c) mixed SHL and EHL
2. anchor an ITC: weighted rate ratios for pre-study (mixed EHL and SHL) vs. on-study treatment from XTEND-1 and HAVEN-3 compared in an ITC
   - Only matched on prior ABRs → no other baseline data for HAVEN-3 pre-study

Pre-studies only collected ABR for treated bleeds so ABR for any bleed not considered

EAG: Pros and cons to using intra-patient comparisons:

- Pro: no confounding by characteristics pre-study (same people pre- and on- study)
- Con: pre-study regimen may affect on-study outcomes. But, refuted by [redacted] ABR IRRs in:
  - ❖ MAIC from ACM1: pre-study O-D vs. prophylaxis arms of XTEND-1 and HAVEN3
  - ❖ Subgroup analyses for XTEND-1 intra-patient comparison by pre-study SHL/EHL use
- Regression to mean (people recruited when condition already improving) seems unlikely given long (1 year) pre-study period.

Committee requested: analyses using the O-D arms of each trial to anchor the ITC

Company: not provided: see supplementary appendix for further details

ABR, annual bleeding rate; EHL, extended half-life; FVIII, factor VIII; ITC, indirect treatment comparison; IRR, Incidence rate ratios; MAIC, matching-adjusted indirect comparison; O-D, on-demand; SHL, short half-life

ITC results: comparison of approaches

Results favour efanesoctocog alfa vs. comparator (IRR under 1) but magnitude of effect differs

Company: IRRs [redacted] across different approaches.

- Slight variations in IRRs explained by underlying methodological differences.

IRRs for efanesoctocog alfa vs. comparators using company's different approaches to ITC

	Mean ABR, IRR (95% CI)	Company base case ACM1	#1a: MAIC adjusting to HAVEN-3 population + adjust ABR	#1b: #1a without adjustment for ABR	#2: intra-patient comparison anchors ITC (weighted)
EFA vs efmo	Treated bleeds	**0.29 (0.17, 0.51)**	[redacted]	[redacted]	–
EFA vs emi	Any bleed	**0.28 (0.10, 0.81)**	[redacted]	[redacted]	–
	Treated bleeds	**0.47 (0.15, 1.44)**	[redacted]	[redacted]	[redacted]
Efmo vs emi	Treated bleed	–	[redacted]	[redacted]	–

Modelled ABRs (IRRs from MAIC applied to ABR from HAVEN3 Arm D)

	Modelled ABRs (#1a)			ABRs scenario #1b		
ABR	EFA	Efmo	Emi	EFA	Efmo	Emi
All bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup analyses for intra-patient comparison (EFA vs efmor, unweighted mean ABR (95% CI):

- Prior SHLs: IRR [redacted]
- Prior EHLs: IRR [redacted]

ABR, annual bleeding rate; ACM, appraisal committee meeting; CI, confidence interval; EFA, efanesoctocog alfa; efmor, efmoroctocog alfa; EHL, extended half-life; emi, emicizumab; ITC, indirect treatment comparison; IRR, Incidence rate ratios; MAIC, matching-adjusted indirect comparison; SHL, short half-life

Which approach is preferred? Do the results have face validity when applied in the model?

Key issue #3: Utility decrements for bleeds (1)

Link to supplementary appendix: Utilities in the company model

Company: frequency has a greater impact on QoL than route of administration

Recap: Company based disutilities for immediate (7 days) and long-term impact (6 months) of bleeds on TOBIT model using EQ-5D-5L data from XTEND-1. No treatment specific utilities.

Committee conclusion: approach inappropriate.

- Company should consider QoL impact from: a) differences in treatment administration and bleeds between treatments; b) chronic pain from subclinical bleeds
- Company should justify preferred TOBIT model and parameter values for utility decrements

Company

1. Treatment administration: Little research into patient preference for IV vs SC
   - Muhlbacher et al. evaluated QoL impact in haemophilia A of varying both:
     - ❖ Mode: no significant difference in preference weights between IV and SC route
     - ❖ Frequency: more important than route. Supported by QoL decrement for more frequent infusions identified in CHESS II study.
   - Clinical experts: preference for IV vs. SC varies, especially as emicizumab used with IV SHL for bleeds on prophylaxis
     - ❖ UKHCDO data: [redacted]% people on emicizumab also issued SHL.

***Scenario*:** CHESS study utilities for treatment administration between –0.027 and –0.107

2. Severity, type and location of bleeds: cannot use trial data → number of bleeds low for effective treatments and limited number of EQ-5D measurements.
   - Not expected that bleed location impacts ICER: Minimal difference in ITC between joint and non-joint treated bleeds

IV, intravenous; QoL, quality of life; SC, subcutaneous, SHL, short half-life; UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation.

Key issue #3: Utility decrements for bleeds (2)

Company update base case to use treatment specific utilities for FVIII activity levels over 20%

Company (continued)

3. Impact of chronic pain: modelled through correlation with FVIII levels.
   - Likely conservative: statistically significant difference in PROMIS Pain Intensity scores in Arm A (prophylaxis) and Arm B (O-D) in XTEND-1 → reduced pain vs. EHLs/SHLs
   - No specific pain measures in HAVEN-3: cannot compare pain vs. emicizumab
4. Justification for TOBIT models: prevents ceiling effect of ED-5D data (utilities over 1).
   - Specific TOBIT model (#2) chosen for: a) best fit, b) disutility for FVIII activity levels under 20%, aligned with expert advice

Update after postponed ACM2

- Confirmed no change to data set informing TOBIT models at ACM1 and 2 → just additional models provided
- Provided EAG requested information on TOBIT and linear models, including number in analysis and approach to missing data, standard error and confidence intervals for coefficients.

***Base case*:** uses treatment specific baseline data (from XTEND-1, A-LONG and ASPIRE) for FVIII over 20%. Utility decreases proportionally with general population decline.

***Scenario*:** Age adjustments using age coefficient in TOBIT models; linear models for utility

Technical team: TOBIT models based on XTEND-1, ALONG and ASPIRE trials for FVIII therapy:

- HAVEN-3 (emicizumab) not included in TOBIT models so questionable relevance to emicizumab → differences in treatment administration and mode of action

ACM, appraisal committee meeting; FVIII, factor VIII; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; O-D, on demand. Link to supplementary appendix: Utilities in the company model

Key issue #3: Utility decrements for bleeds (3)

EAG: identify several issues with company's updated TOBIT models

EAG: company arguments for not including route of administration, bleed type / location and chronic pain reasonable. Welcome use of trial data but several concerns remain:

1. Company confirmed that models based on the same data as at ACM1: XTEND-1 study (efanesoctocog alfa; N= 127), A-LONG (efmoroctocog alfa; N = 81) and ASPIRE studies (efmoroctocog alfa; N = 127).
2. Company's chosen model (#2) same as for ACM1 and does not have best fit to data
3. Days since treatment initiation disregarded by company in economic model so should use TOBIT models (#5 to #8) that exclude this.
   - Prefer #8 for base case (includes disutility for FVIII activity under 5%: best fit to data for a model that aligns with patient reports that QoL affected by low FVIII)

Other considerations: **Novo Nordisk:** model should include: a) disutilities related to dosing frequency and administration method, b) caregiver disutilities as appraisal includes children.

THS: Some prefer IV injections as all previous haemophilia treatments use this route

- Emicizumab can be more painful to administer than FVIII as is a viscous substance

Should the model include utilities for a) different routes and frequency of treatment administration, b) treatment specific bleeds, c) chronic pain from subclinical bleeds?

Should the company's updated TOBIT models be used in the model and, if so, which?

ACM, appraisal committee meeting; FVIII, factor VIII; IV, intravenous; QoL, quality of life; THS, The Haemophilia Society

Key issue #4: Utility decrement for FVIII activity levels (1)

Company defends application of disutility for FVIII activity levels under 20%

Recap: Company applied a disutility for FVIII activity levels under 20% → captures anxiety and changes to daily activity from higher risk of bleeds

Committee conclusion: disutility for low FVIII levels likely but company approach unsuitable:

- FVIII activity of 20% = relatively low bleed risk: people unlikely to amend daily activities
- Emicizumab does not replace FVIII so cannot use FVIII activity to measure bleed protection

Requested: justification for link between FVIII levels and QoL, scenario with disutility for FVIII activity under 15%

Company:

1. Disutility for low FVIII activity justified and supported by XTEND-1 exit interviews and improvements in pain and joint health whilst having efanesoctocog alfa
2. Emicizumab: limited fluctuation between doses but bleeds may still limit daily life
    - In animal models, FVIII-like activity stabilised at around 20%
    - Kizilocak et al. (N=10 on emicizumab with severe haemophilia A): 100% had FVIII-like activity above 10%, 30% had FVIII-like activity 10-20%.
3. Applying disutility for 15% FVIII activity levels: 15% unlikely to have spontaneous bleeds.
    - Disutility applies to threshold where people limit activity not those linked to bleeds
    - Updated TOBIT models found significant disutilities for FVIII levels below 5, 15 and 20%
4. PROPEL study: FVIII activity levels 20% and over associated with lower total, spontaneous, spontaneous joint, and traumatic ABRs compared with FVIII activity levels below 20%

ABR, annual bleeding rate; FVIII, factor VIII; N, number; QoL, quality of life. Link to supplementary appendix: Utilities in the company model, analysis of ABR by FVIII concentration

Key issue #4: Utility decrement for FVIII activity levels (2)

Company updates base case assumption for emicizumab and explores other FVIII thresholds

Company cont.:
Base case: 30% emicizumab patients have FVIII activity between 10–20%
Scenarios: a) no disutility for low FVIII levels, b) no disutility for emicizumab arm only, c) disutilities at 5%, 15% and 20%, d) disutility for FVIII below 5%, with separate disutility for FVIII between 5% and 20%

EAG: Agree QoL affected by low FVIII levels but unclear at what threshold this should apply.
- Useful to have scenarios comparing a range of thresholds

Other considerations:
Novo Nordisk: Irrelevant to consider disutility by FVIII activity level for emicizumab
UKHCDO: Emicizumab provides constant level of protection equivalent to ~20% FVIII levels, but inter-individual variability expected.

Should the model include a disutility for low FVIII activity levels?
If so, how? Apply a disutility by FVIII activity level (5%, 15%, 20%, other), to all treatments or only FVIII replacement therapies? At what rate for emicizumab?

FVIII, factor VIII; QoL, quality of life UKHCDO, United Kingdom Haemophilia Centre Doctors Organisation. Link to supplementary appendix: Utilities in the company model

Summary of company and EAG base case assumptions

Main differences: choice of TOBIT model for utilities, inclusion of SHLs as comparator

Assumption	Company base case	EAG base case
Comparators	EHLs for PUPs and PTPs. Simoctocog alfa (SHL) for PUPs, no SHLs for PTPs.	All SHLs relevant comparator for PUPs and PTPs
ITC	MAIC adjusting A-LONG and XTEND-1 populations to HAVEN-3, adjusting baseline ABR	As per company
Utilities for bleeds	TOBIT model #2	TOBIT model #8
FVIII disutility	Disutility for FVIII under 20% retained. Applies to 30% emicizumab arm	Unclear but preferred model has disutility for FVIII activity levels under 5%
Wastage costs	Included for all prophylactic treatments in adults. Approach for octocog alfa updated.	As per company
Managing bleeds	Include specialist nurse and phone visits	As per company

ABR, annual bleeding rate; EHL, extended half-life; FVIII, factor VIII; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PUPs, previously untreated patients; PTPs, previously treated patients; SHL, short half-life

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: efanesoctocog alfa is dominant against emicizumab and efmoroctocog alfa in PUPs and PTPs but not cost effective against turoctocog alfa pegol in PTPs

EAG base case:

- PUPs: efanesoctocog alfa is dominant over efmoroctocog alfa, simoctocog alfa (only SHL included by company) and emicizumab using company's preferred comparators
- PTPs: efanesoctocog alfa is not the most cost-effective treatment vs comparators

N.B dominant treatments are less costly and produce more QALYs than the dominated comparator

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PTPs, previously treated patients; PUP, previously untreated patients; QALY, quality adjusted life-year; SHL, short half-life

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

RECAP

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: population • XTEND-1 only included 12 years and over but people any age included in anticipated MA. • 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	• Company should use current SoC rather than future trends • Emicizumab and efmoroctocog alfa not used together in PUPs

NICE

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

XTEND-1: key results

Link to: main slides, XTEND-1 trial overview

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	Prophylaxis N=133	Arm B	
		O-D N=26	Prophylaxis N=26
Bleeds in past 12 months, mean (SD)	3.2 (5.4)	35.7 (22.2)	35.7 (22.2)
Mean ABR treated bleeds (SD)	**0.71** [redacted]	21.42 (7.41)	0.69 (1.35)
Mean ABR 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 with 0 bleeds per year (%)	86 (65)	0	20 (77)

- Difference in mean ABR (Arm A, treated bleeds) vs pre study prophylaxis at week 52: -2.27, 95% CI -3.44, -1.10; p<0.0001).
- Post injection FVIII levels maintained to week 26

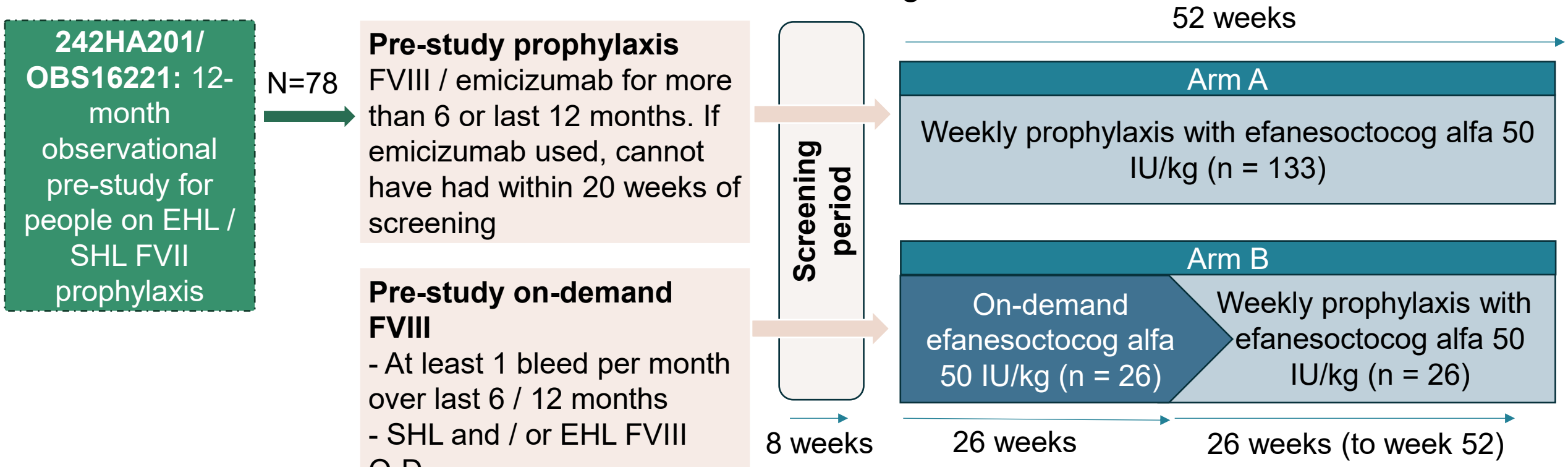
ABR, annualised bleeding rate; CI, confidence interval; FAS, full analysis set; FVIII, factor VIII; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; N, number; O-D, on-demand; SD, standard deviation. **Bold** = used in company model

XTEND-1 clinical trial design

RECAP

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

Summary of stakeholder responses

Stakeholders who responded to consultation on the draft guidance	
Company	Sobi
Patient organisations	The Haemophilia Society (THS)
Clinical organisations	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)
Clinical experts	x1
Commentators	Novo Nordisk (company for turoctocog alfa pegol) Roche (company for emicizumab)
Web comments	x1

Link to: main slides

Consultation responses to draft guidance summary

Population: THS, Roche

- Should be available for people with FVIII levels over 1% (defined as moderate or mild haemophilia A) with severe bleeding phenotype: same pathway of referral, diagnosis and management.
- Efanesoctocog alfa unlikely used if long term inhibitors but may be for immune tolerance induction (regular and prolonged high dose FVIII) in PUPs who develop inhibitors on FVIII.
- No requirement for PUPs studies: recommended to include PUPs in phase 4 studies only

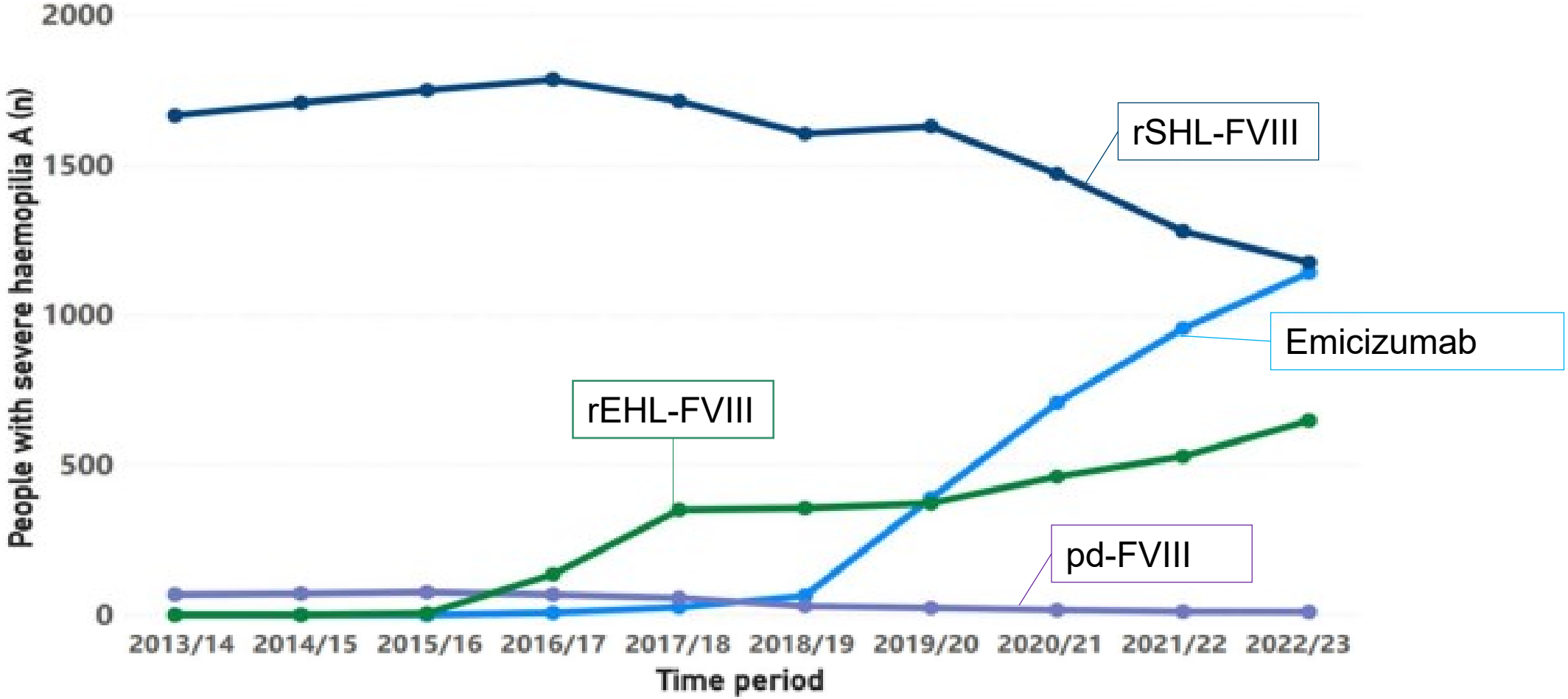
Link to: main slides, consultation comments

FVIII; factor VIII; PUP, previously untreated patients; PTPs, previously treated patients; FVIII, factor VIII; THS, The Haemophilia Society

SHL and EHL use, UKHCDO annual report 2022/23

Data supports falling SHL and increasing emicizumab use, but large proportion still have SHLs

Number of people with severe haemophilia (FVIII levels of 1% or under) issued product 2013/14 – 2022/23



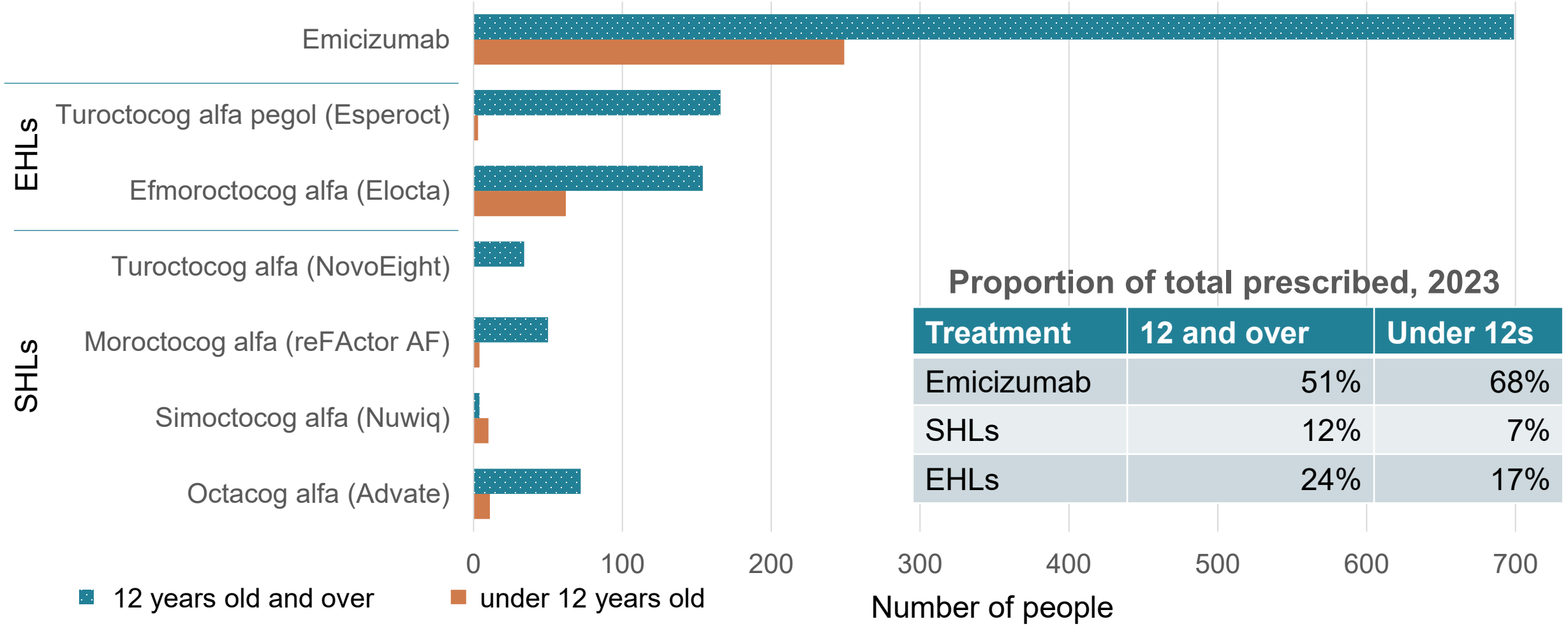
EHL, extended half-life; FVIII, factor VIII; pd, plasma derived; r, recombinant; SHL, short half-life.

Link to: main slides, SHLs as comparators

UKCHDO prescribing data, 2023 (provided to NICE Aug 2024)

New data for ACM2 shows prophylactic use of haemophilia products in the population of interest

Products issued to people with haemophilia A and FVIII >1% and no inhibitors, treated prophylactically in 2023



Proportion of total prescribed, 2023

Treatment	12 and over	Under 12s
Emicizumab	51%	68%
SHLs	12%	7%
EHLs	24%	17%

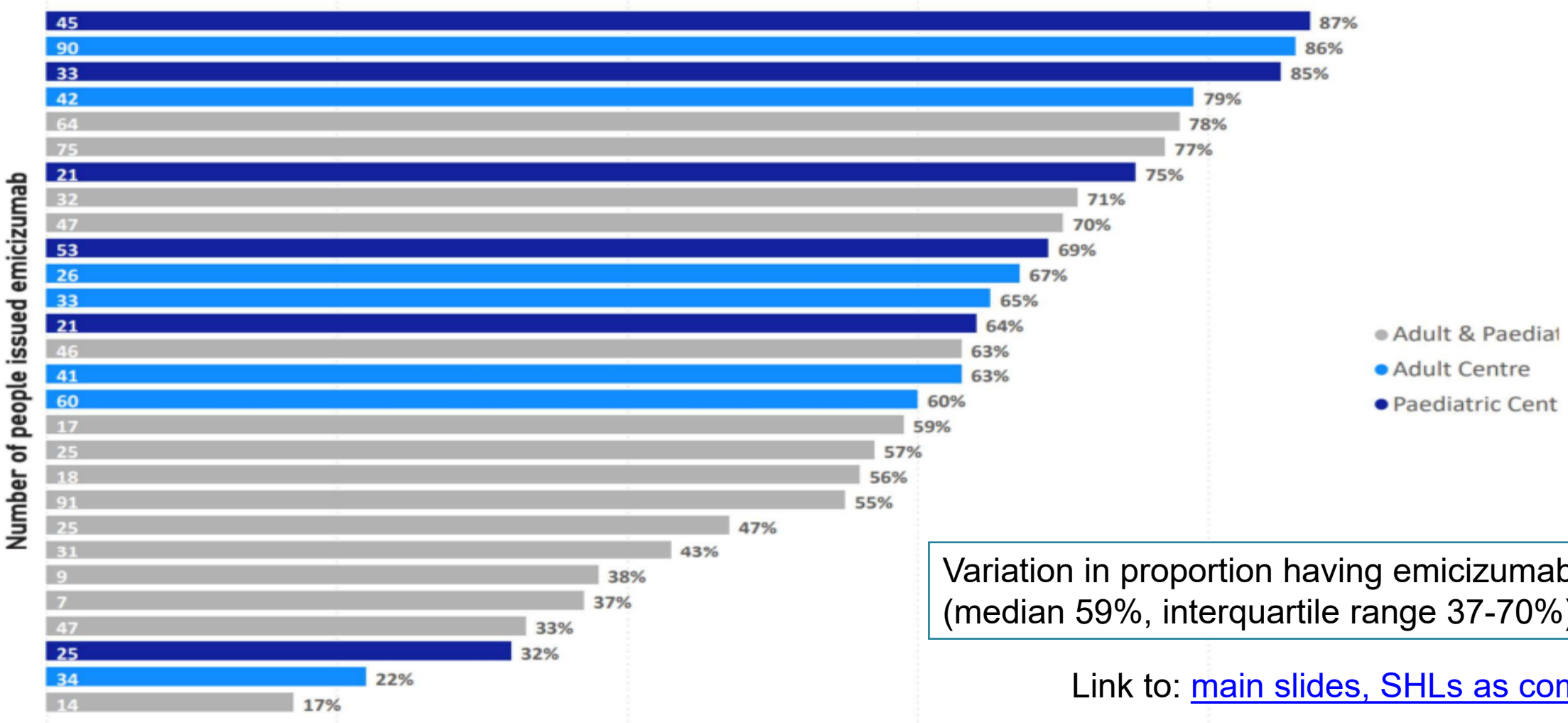
EHL, extended half-life; FVIII, factor VIII; SHL, short half-life.

Link to: main slides, SHLs as comparators

Emicizumab use, UKHCDO annual report 2022/23

Considerable centre-to-centre variation in proportion having emicizumab across NHS

Proportion of people with severe haemophilia A without an inhibitor who were issued emicizumab, by centre, in 2022/23



Variation in proportion having emicizumab (median 59%, interquartile range 37-70%)

Link to: main slides, SHLs as comparators

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

ITC results: comparison of approaches

Company use 3 different approaches to determine the clinical effectiveness of efanesoctocog alfa vs. comparators.

	Base-case MAIC	Updated MAIC adjusted for pre-study ABR	Anchored MAIC through pre-study regimen
Method	Unanchored MAIC	Unanchored MAIC	Anchored MAIC (pre-study prophylaxis as common reference)
Reference population	A-LONG vs efmoroctocog alfa HAVEN 3 vs emicizumab	HAVEN 3	HAVEN 3
Patient data	• ARM A XTEND-1 (IPD) • A-LONG (aggregate) • Arm D HAVEN 3 (aggregate)	• ARM A XTEND-1 (IPD) • A-LONG (aggregate) • Arm D HAVEN 3 (aggregate)	Only pre-study XTEND-1 and HAVEN 3 patients included: • 78 from group A of XTEND-1 • 48 from group D HAVEN 3
Characteristics for adjustment	Age, body weight, race, target joint at baseline	Age, body weight, race, target joint at baseline, pre-study ABR	Pre-study ABR
Interpretation of the relative effect	IRR in comparator study population (XTEND-1 population adjusted to A-LONG or HAVEN-3)	IRR between in the population of HAVEN 3	IRR between in the population of HAVEN 3 (adjustment only for pre-study ABR)

Link to: main slides, company's ITC

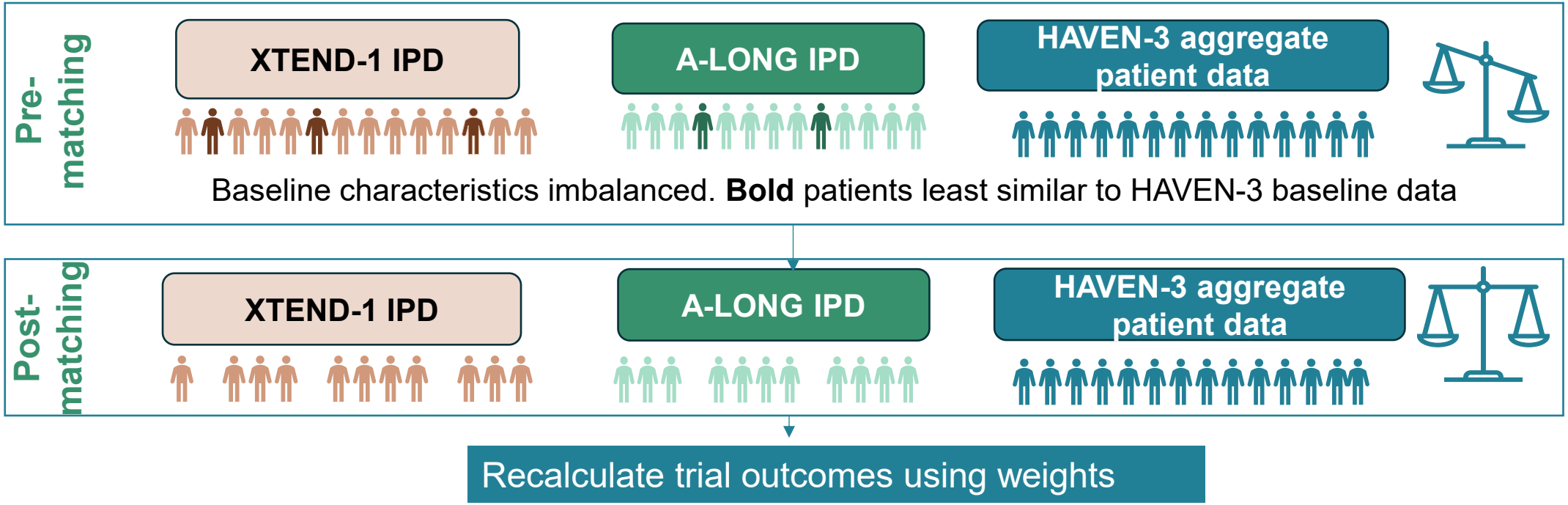
ABR, annualised bleed rate; IPD, individualised patient data; MAIC, matching adjusted indirect comparison

Link to: main slides, company's updated MAIC

Company's MAIC methodology (base case, analysis #1a)

MAIC adjusts XTEND-1 and A-LONG trials to HAVEN-3 IPD aggregate patient data

Methodology of the MAIC



MAIC adjusts for age, weight, race, presence of target joints. Scenario also adjusts for baseline ABR

ESS in the company's MAIC

ESS	XTEND-1 Arm A		A-LONG pooled arms		HAVEN-3 Arm D
Adjust for pre-study ABR?	No	Yes (base case)	No	Yes (base case)	N/A
Before matching	119	108	81	80	63
After matching	76	63	51	36	N/A

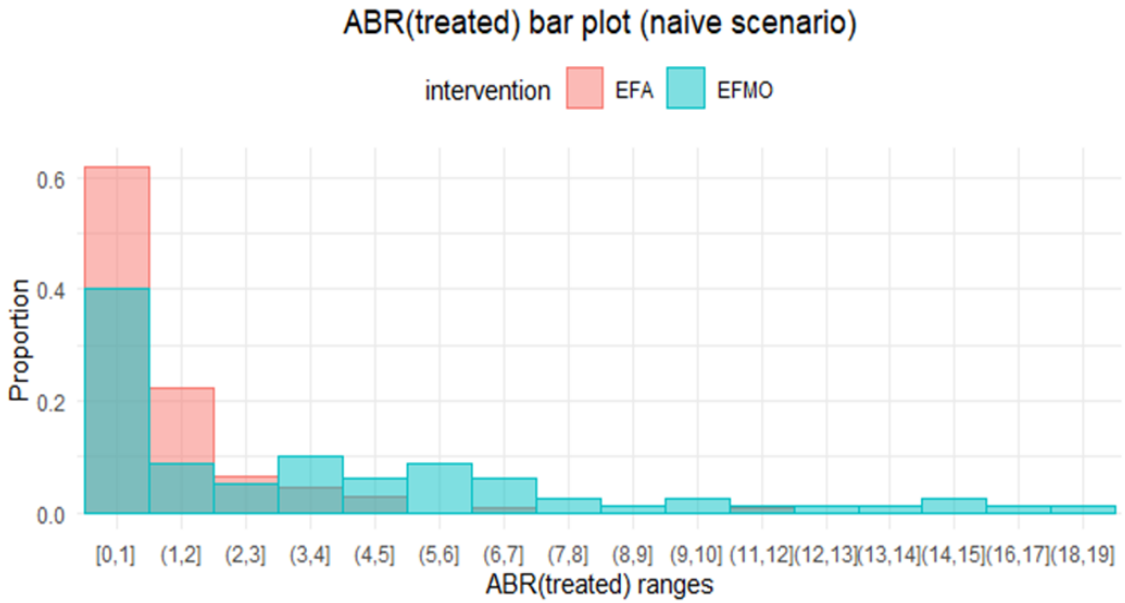
ABR, annualised bleeding rate; ESS, effective sample size; IPD, individual patient data; MAIC, matching-adjusted indirect comparison

ABR distributions for company's base case MAIC

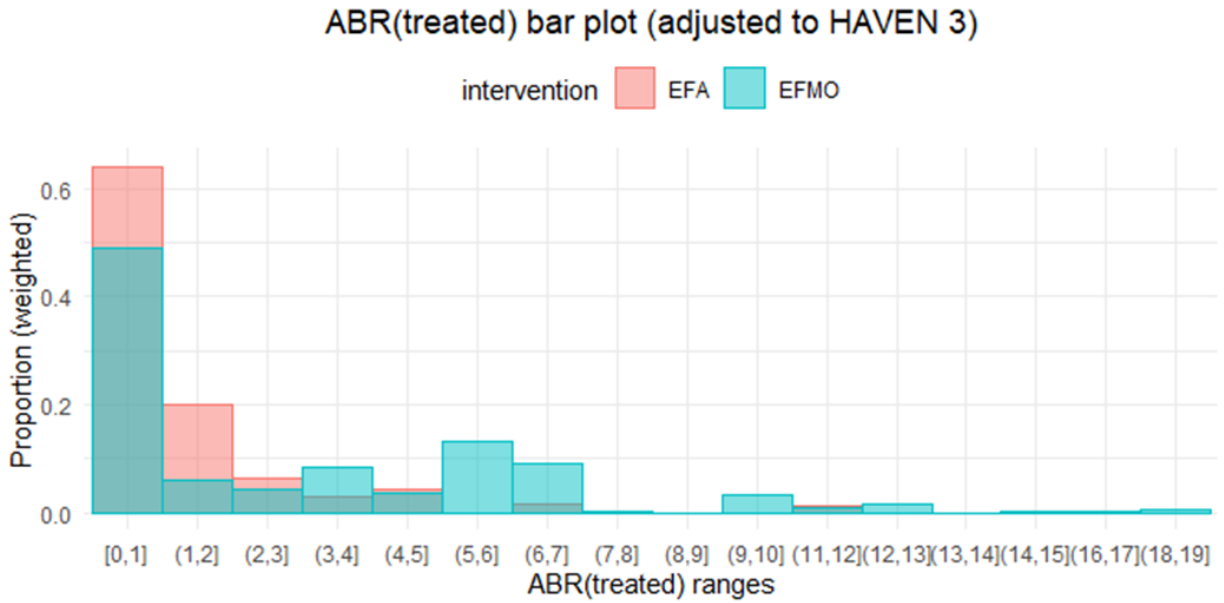
% with no and low bleeds ABRs 0 to 2 higher with efanesoctocog alfa than efmoroctocog alfa

Histogram for any treated bleeds, efanesoctocog alfa and efmoroctocog alfa

Before matching



After matching



HAVEN-3 reported ABRs as the output of negative binomial model: cannot produce histogram for emicizumab

Link to: main slides, company's updated MAIC

ABR, annualised bleed rate; EFA, efanesoctocog alfa; EFMO, efmoroctocog alfa

Link to: main slides, company's updated MAIC

Company's intra-patient comparison analyses

Company uses pre-post approach to compare ABRs for efanesoctocog alfa and emicizumab

STEP 1: Pre-study populations adjusted using MAIC

Pre-matching

Baseline characteristics imbalanced. **Bold** patients least similar to HAVEN-3 baseline data

Post-matching

Recalculate trial outcomes using weights

MAIC adjusts only for baseline ABR: no other outcomes reported in HAVEN 3 pre-study.

STEP 2: Pre-study ABRs compared with on-study ABRs for each patient

1. ABRs of [redacted] XTEND-1 patients (both pre- and on-study) re-estimated both with and without MAIC weights using separate negative binomial regression models.
   - After weighting, estimated pre-study ABR for treated bleeds in XTEND-1 [redacted] from [redacted] to align with ABR for HAVEN 3 pre-study ([redacted]).
   - Estimated on-study ABRs remained [redacted] after weighting.
2. IRR vs pre-study ABRs estimated using negative binomial regression models (both unweighted and weighted).
3. Weighted rate ratio between XTEND-1 and HAVEN 3 calculated

ABR, annualised bleeding rate; ESS, effective sample size; IPD, individual patient data; IRR, Incidence rate ratios; MAIC, matching-adjusted indirect comparison

Key issue #2: ITC methods (3)

Link to: main slides, company's updated MAIC

Company: using O-D arms to anchor ITC inappropriate, no analyses submitted

Committee requested: analyses using the O-D arms of each trial to anchor the ITC

Company: Not provided as:

- Populations having prophylaxis FVIII different to those having O-D FVIII: non overlapping
  - ❖ prior ABR and risk of joint bleed correlates with regimen: cannot balance using a PSM
- People having prior prophylaxis in HAVEN3 could not be randomised to prior O-D arms (A, B and C): non comparable
- Also assumes O-D arms of each trial equivalent: Unlikely given:
  - ❖ The variation in SHL and EHL use between trials and differing PK by half life
  - ❖ That people having O-D in XTEND-1 had efanesoctocog alfa, in HAVEN-3 had prior FVIII replacement product
  - ❖ That not supported by XTEND-1 results: lower ABR for Arm B during O-D period vs. baseline suggests O-D efanesoctocog alfa more effective than other SHLs or EHLs.

EAG:

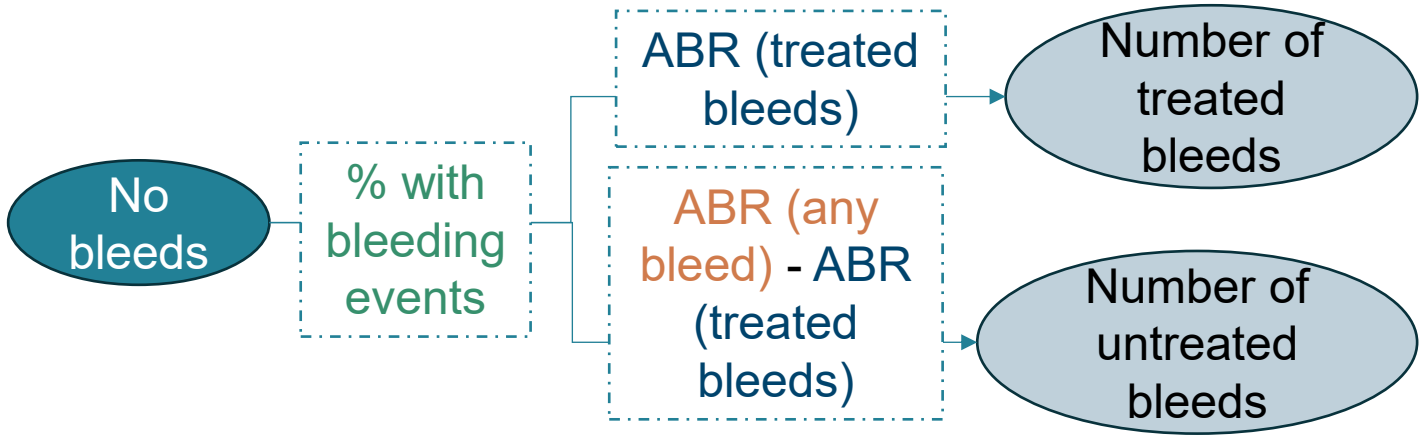
- Unclear why flaws with using O-D arms any worse than those in other approaches
- Reiterate that unclear if prior therapy affects prognosis
- Company could have provided results of people having prior O-D FVIII who were randomised to Arm D HAVEN3 (prophylaxis) to support claim

ABR, annual bleeding rate; EHL, extended half-life; FVIII, factor VIII; ITC, indirect treatment comparison; O-D, on-demand; PK, pharmacokinetic; PSM, propensity score matching; SHL, short half-life

Treatment effectiveness in model at ACM1

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 at ACM1

RECAP

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

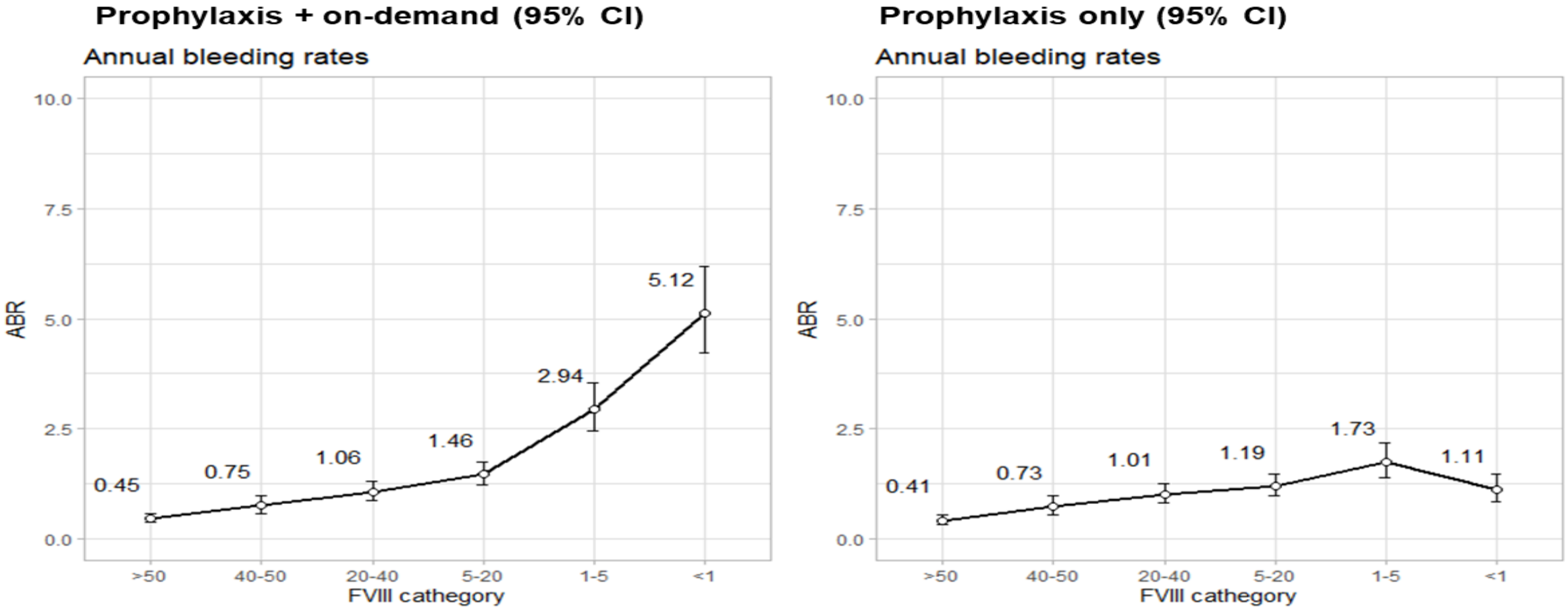
AE, adverse event; BNF, British National Formulary; FVIII, factor VIII; O-D, on-demand; PTPs, previously treated patients; PUP, previously untreated patients; US, United States

Analysis of ARBs by FVIII concentration

Combined trial data for prophylaxis + OD therapies suggests link between FVIII levels and ABR

Company ran a poisson regression combining data on FVIII and ABR from XTEND-1, A-LONG + ASPIRE trials.
Estimated ABR relatively low for FVIII activity >20% but increased with lower FVIII activity.
Pre-study prophylaxis: association between ABR and FVIII concentration not very clear.

ABRs by FVIII concentration



ABR, annualised bleeding rate; FVIII, factor VIII. Link to: main slides, disutility for low FVIII levels

Utilities in the company model at ACM2

Base case utility regression models: combined data from XTEND-1, A-LONG and ASPIRE (prophylaxis only)

		Results of the regression coefficients, TOBIT model, any bleed							
Model		1	2	3	4	5	6	7	8
Intercept		0.4119	0.4868	0.4851	0.4864	0.3849	0.4675	0.4613	0.4491
Baseline utility		0.8092	0.7692	0.7690	0.7642	0.8151	0.7747	0.7747	0.7762
7d_bleed_disutility		–0.0676	–0.0663	–0.0661	–0.0649	–0.0789	–0.0760	–0.0757	–0.0738
6m_bleed_disutility		–0.0396	–0.0435	–0.0434	–0.0432	–0.0479	–0.0447	–0.0446	–0.0441
Days since study initiation		–0.00005	–0.00007	–0.00007	–0.00007	Not used	Not used	Not used	Not used
Age		–0.0047	–0.0053	–0.0053	–0.0052	–0.0047	–0.0053	–0.0053	–0.0052
Proportion of time in <5%		Not used	Not used	Not used	–0.0782	Not used	Not used	Not used	–0.1231
Proportion of time in <15%		Not used	Not used	–0.0299	Not used	Not used	Not used	–0.0728	Not used
Proportion of time in <20%		Not used	–0.0277	Not used	Not used	Not used	–0.0728	Not used	Not used
Model fit	BIC	137.641	169.365	169.250	167.688	151.738	187.544	187.167	184.840
	AIC	95.750	123.101	122.986	121.424	115.083	146.420	146.043	143.717

Utility values in the company's model

Health state	Value	Source
FVIII>20% and no bleed in last 6 months	0.7784	TOBIT models. Updated at ACM2 to include trial baseline utility data
FVIII<20% and no bleed in last 6 months	0.7349	
FVIII>20% and a bleed in last 6 months	0.7507	
FVIII<20% and a bleed in last 6 months	0.7072	
Short-term disutility for a bleed	–0.0663	
Disutilities for frequent injections (scenario only)	-0.074, -0.027 and -0.107	CHESS study (include highest and lowest values)

Company conducted TOBIT and linear regression models to estimate values for both treated and any bleeds. Results comparable regardless of whether bleed was treated. Model 2 (red) used in company base case

AIC, Akaike Information Criterion:, BIC Bayesian Information Criterion; d, day; FVIII, factor VIII; m, month.

Key issue #5: Wastage costs

Company updated base case to include all prophylactic treatments in adults

Recap ACM1: company assumed wastage costs only for octocog alfa (O-D treatment for bleeds on emicizumab)

- wastage costs N/A for prophylactic treatments: doses used rounded up to a full vial.

Committee concluded: wastage costs uncertain: include for all prophylactic treatments to capture wasted drug from "rounding up" of doses

Company:

1. Wastage costs included for all prophylactic treatments for adults only, because:
   - Modelling weight-based treatments hard in people under 18, especially in very young.
     - ❖Assessed 6 monthly → weight varies as children grow: vial use does not always reflect weight increase
   - Not expected to have large effect on ICER as all comparators use weight-based dosing
2. Approach to modelling wastage costs for octocog alfa updated:

Assume people have enough SHL at home to treat bleed (2 x 25 IU/kg vials) = 4,175 IU for average weight patient (previously 6000 IU) → Apply cost per unit of SHL → Apply this cost to % with no bleed in 2 years (shelf life of SHLs)

Scenarios: a) no SHL wastage, b) SHL wastage halved.

EAG: agrees with company's approach to modelling wastage.

Other considerations: **Novo Nordisk:** appropriate to include wastage for prophylactic treatments

- Unclear why 6,000 IU were chosen as O-D dose of octocog alfa at ACM1.
- Likely some patients with no bleeds will use octocog alfa within 2 years as can use for minor surgeries

Roche: emicizumab associated with high zero bleed rate so use of extra FVIII likely to be low

ACM, appraisal consultation committee; FVIII, factor VIII; ICER, incremental cost-effectiveness ratio; IU, international units; kg, kilogram; O-D, on-demand; SHL, short half-life

Key issue #6: Cost of managing bleeds

Company updates cost of managing bleeds based on clinical advice of NHS pathway

Recap ACM1: company included the costs for 1.11 outpatient visits per bleed: assumed that all bleeds managed by specialists not nurses
EAG: mild and moderate bleeds will be resolved by phone by nurses: costs overestimated.

- Submitted scenarios where resource use split 50:50 specialist: nurse visits

Committee conclusion: cost of bleed management unclear

Company: further expert opinion suggests typical bleed management in NHS typically includes clinical review even if resolved by phone:

Base case: 1.11 contacts per bleed but costs weighted across consultant and non-consultant led face-to-face and phone outpatient contacts. Likely conservative as assumes equal costs for each arm: people on emicizumab may need more assistance as 'deskilled' at IV injections
Scenarios: a) all bleeds resolved over phone with no follow up (1 x non-consultant-led, non-face-to-face contact), b) no resource use for treating bleeds

EAG: agrees with company's approach to modelling bleed management costs

A and E, accident and emergency; FVIII, factor VIII; IV, intravenous; MDT, multidisciplinary team

Summary of company scenarios

Company scenarios submitted at consultation

Scenario	Scenario
Treatment effect	**Utilities**
EHLs = 100% efmoroctocog alfa (PTPs only)	Utility model 6 (includes time in study)
EHLs = 100% turoctocog alfa pegol (PTPs only)	Linear model for utility
Baseline ABRs from XTEND-1 with treatment effects for EHLs and emicizumab from the extended MAIC	No FVIII decrement
Using treatment effects for EHLs from XTEND-1 intra-patient comparison and emicizumab from the intra-patient ITC • In full XTEND-1 population • Using pre-study EHL only subgroup	a) FVIII <15% and b) FVIII <5% for utility decrement
	a) No FVIII decrement for emicizumab, b) a + FVIII threshold <15%; c) a + linear model d) a+ b + c (**EAG corrected)**
Baseline ABR from HAVEN-3, with treatment effect from the MAIC without adjustment for prior bleeds	Utility decline with age from model
	Frequent infusion disutility of a) -0.027, b) -0.0745 and c) -0.107
Excluding untreated bleeds: rate of treated bleeds from HAVEN-3 as the baseline ABR	**Cost and resource use**
	1x outpatient contact per bleed (£345.90)
	No resource use for treating bleeds

ABR, annualised bleeding rate; EHL, extended half-life; FVIII, factor VIII; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PUPs, previously untreated patients; PTPs, previously treated patients