Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

For projector – Redacted information

Technology appraisal committee D 12th March 2025

2nd committee meeting

Chair: Raju Reddy

Lead team: Sue Wen Leo (clinical lead), Giles Monnickendam (cost lead), Carole Pitkeathley (lay lead)

External assessment group: Warwick Evidence

Technical team: Alice Pritchard, Victoria Kelly, Ian Watson

Company: Pfizer

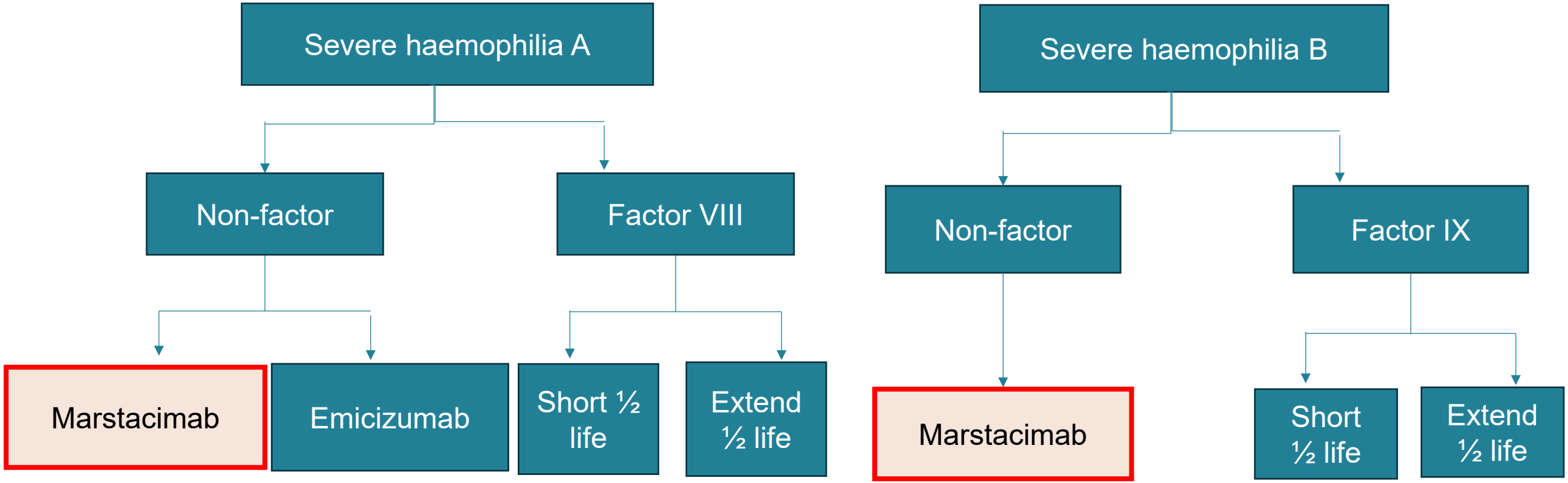
ACM 1 – draft guidance recommendation

Marstacimab is not recommended, within its marketing authorisation, for preventing bleeding episodes (prophylaxis) caused by severe haemophilia A (congenital factor VIII [8] deficiency) or severe haemophilia B (congenital factor IX [9] deficiency) in people 12 years and over, weighing at least 35 kg, without factor inhibitors (anti-factor antibodies).

- Committee concluded that the cost-effectiveness estimates were uncertain and further justifications for assumptions were needed

Treatment pathway severe haemophilia A and B

Treatment options include factor treatment or 'non-factor' treatment (emicizumab)



- GB MA not granted yet. EMA MA: For routine prophylaxis of severe (<1% factor activity) haemophilia A (congenital FVIII deficiency) without FVIII inhibitors or severe haemophilia B (congenital FIX deficiency) without FIX inhibitors, in adults and paediatric patients 12 years of age and older

Note: For haemophilia B, gene therapy (TA989) is currently available in managed access but is not a comparator in this appraisal

EMA, European Medicines Agency, FVIII, factor VIII, FIX, factor IX, IV, intravenous, MA marketing authorisation, SC, subcutaneous,

Response to draft guidance consultation

- Pfizer (company)
- CSL Behring
- Novo Nordisk
- Web comments

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Key issues from 1st Committee Meeting and Company's Response 1/2

Key issues and company response

Key issue ACM1	Committee preference	Company response
Generalisability of BASIS trial to NHS and source for baseline annualised bleed rate	• UK Haemophilia Centre Doctors' Organisation data	Yes
Dose escalation of marstacimab	• Modelled in year 2	Yes
Discontinuation of haemophilia treatments	• 6.02% rate • Requested analysis which reflects UK practice and scenario of a 10% discontinuation rate for emicizumab	Yes
Dosing of factor prophylaxis	75% of company base case	85% of recommended mid-point dose for each factor product

Abbreviations: ABR, annualised bleed rate; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Key issues from 1st Committee Meeting and Company's Response 2/2

Key issues and company response

Key issue ACM1	Committee preference	Company response
Separate or pooled modelling of haemophilia types	• Pooled ABR data from people with haemophilia A and B. Concerns not captured difference in discontinuation of A and B. Requested clarity from company	Company explained that no difference in management of haemophilia in UK, aside from treatment
Bleed disutility	• Single utility decrement 0.16, for joint and non-joint bleeds, 2.5 days	• Yes
Treatment disutility per administration	• Likely to be a difference in utility decrements between methods of administering treatment	• Further evidence provided

- All other preferences from ACM1 were adopted by the company, see supplementary slide other changes to company base case

Abbreviations: ABR, annualised bleed rate; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Key issues for committee discussion at 2nd committee meeting

Key issues outstanding at second committee meeting

	Issue	ICER impact	New evidence presented?
Cost-effectiveness	Separate or pooled modelling	Small	No
	Dosing factor prophylaxis	Moderate	No
	IQVIA market share data	Small	Yes
	Discontinuation of haemophilia treatments [in supplementary appendix]	Moderate	Yes
	Treatment disutility per administration	Large	Yes
	Blended comparator	Large	Yes

Response to DG consultation (1/2)

Summary of responses from stakeholders

Stakeholder comments (Novo Nordisk, CSL Behring)

Treatment disutility:

- Highlighted evidence from Okkels et al (2024) time trade off study. UK study estimating UK utilities associated with treatment device and dosing frequency.

Efficacy differences between haemophilia A and B:

- Cannot assume identical relationships of the tenase complex/Tissue Factor Pathway Inhibitor in people with Haemophilia A v Haemophilia B. Published study, Castaman et al (2019) available which summarises the molecular and clinical differences between Haemophilia A and B

Abbreviations: DG, draft guidance

Response to DG consultation (2/2)

Responses web comments, patient organisations Haemophilia Northern Ireland

Evidence base:

- Haemophilia Northern Ireland - need for robust clinical trial design which incorporates blinding, randomisation, appropriate comparator and UK data. Having long term data highly preferable. Given infected blood scandal – safety must be a priority

Unmet need:

- Only 1 subcutaneous option for severe haemophilia A,
  no subcutaneous option for severe haemophilia B
- People with haemophilia B and inhibitors do not have any treatment options other than immune tolerance induction, which has lower response rates than in severe haemophilia A

Abbreviations: DG, draft guidance; HNI, haemophilia northern ireland

Cost effectiveness

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Key Issue: Separate or pooled modelling of Type A and Type B

Company state that HB and HA are managed and monitored same in UK

Recap

- Haemophilia A and B grouped by company, applied no treatment specific efficacy or dose escalation. EAG noted that haemophilia B<A for treatment effect and dose escalations. Supplementary slide, separate or pooled modelling of haemophilia types.
- Committee accepted modelling based on pooled effectiveness, concerned there could be other differences between A and B not captured, asked company to explore

Company

- Haemophilia A and B managed/monitored - but not treated - identically in UK. Base case differentiates between haemophilia A and B: treatments, dosing, costs and administration, cost of treatment for bleeds, discontinuing emicizumab.

EAG comments

- EAG scenario presents separate A and B scenarios and differentiates baseline bleeding rate and relative effectiveness (does not affect direction of results)

NICE Does the model reflect relevant differences between HA and HB?

Abbreviations: ABR, annualised bleed rate; EAG, external assessment group; HA, haemophilia A; HB, haemophilia B

Key Issue: Dosing of factor prophylaxis 1/2

Committee prefer factor dosing to 75% of company base case, company lowered to 85%

Recap

- Company took mid-point dosage from summary of product characteristics (SmPC) and base case weighted by market share (IQVIA). These were higher than BASIS trial data.
- EAG analysis % of people SHL and EHL factor prophylaxis in BASIS split by haemophilia A + B. Applied weights using iQVIA market share data; also higher than BASIS values.
- Committee preferred EAG assuming factor dosing 75% of company's base case

Company

- Clinical experts stated that to achieve 0 bleed rate clinicians tend to dose at upper range of SmPC; not uncommon to prescribe even more
- Data from UKHCDO limitations; includes % of patients receiving treatment 'on-demand'.
- Apply 85% of mid-point SmPC dosing, aligns with BASIS trial

Abbreviations: EAG, external assessment group; EHL, extended half life; SHL, standard half life; SmPC, summary of product characteristics; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Key Issue: Dosing of factor prophylaxis 2/2

EAG base case of dosing of factor prophylaxis remains at 75% of company base case

EAG comments

- UKHCDO data include treatment 'on demand' as did some people in BASIS
- Original company base case dosing for FVIII ≈ [redacted] more than UKHCDO
- proportion of adolescents in the UKHCDO data may have been too high, but even among adults assumed dosing [redacted] and [redacted] higher than UKHCDO data for SHL and EHL respectively - EAG base case might be too optimistic for FVIII due to both comparison to UKHCDO adult dosing and that there will be adolescents
- EAG retains base case of 75% of company base case; scenarios of 70% + 80%.

What is the most appropriate assumption for dosing of factor prophylaxis?

Abbreviations: EAG, external assessment group; FVIII, factor VIII; FIX, factor IX; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Key Issue: Market Share

Company prefer IQVIA market share data

Abbreviations: EAG, external assessment group; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Recap

- Company preferred IQVIA market share data
- EAG and committee preferred UKHCDO

Company

- Opted for IQVIA report specific to UK and more recent to July 2024 than UKHCDO to March 2024.
- Reports a scenario of 2024 UKHCDO market share data

EAG comments

- Retain preference of UKHCDO market share data.

Market share data comparison: small ICER impact

Factor VIII market share data	2023		2024	
	IQVIA	UKHCDO	IQVIA	UKHCDO
Advate	[redacted]	28%	[redacted]	25%
RefactoAF	[redacted]	16%	[redacted]	14%
NovoEight	[redacted]	8%	[redacted]	5%
Nuwiq	[redacted]	3%	[redacted]	2%
Esperoct	[redacted]	23%	[redacted]	28%
Elocta	[redacted]	20%	[redacted]	23%
Adynovi	[redacted]	2%	[redacted]	2%
FIX market share data				
BeneFix	[redacted]	23%	[redacted]	19%
Alprolix	[redacted]	47%	[redacted]	51%
Idelvion	[redacted]	15%	[redacted]	14%
Refixia	[redacted]	15%	[redacted]	15%

Which is the most appropriate market share data to apply for factor prophylaxis?

Key Issue: Treatment disutility per administration 1/2

Company provided further evidence for treatment disutility per administration, maintain base case

Recap

- Company modelled disutility (Johnston et al) for administering IV (0.0003) and SC (0.0002) treatments. Concerns over no confidence intervals, and time trade off captures differences in administration and effects of treatments
- Committee: requested company provide further evidence and modelling.

Company

- Results from Lu et al (2024) cross-sectional, web-based survey, discrete choice experiment, n=194 of which n=44 in UK, identifying patient preference regarding prophylaxis treatment and administration.
- Results: Changing from IV to SC injection via pre-filled pen has a relative attribute importance of 12.1% ($p<0.001$). Company maintain original decrement values.
- Company suggest when considering net health benefit impact of treatment disutility is not significant.

Abbreviations: CI, confidence interval; SC, subcutaneous; DCE, discrete choice experiment; IV, intravenous; TTO, time trade off; n, number

Key Issue: Treatment disutility per administration 2/2

Literature review supports values obtained by Johnson et al

EAG comments

Conducted literature review, EAG literature review summary treatment administration

- Okkels et al (2024), sponsored by Novo Nordisk, time trade off online survey – superior methods to Johnston et al
- Okkels et al and Johnston et al are among general public and not people with haemophilia
- EAG previously highlighted bias in Johnston et al. estimates but Okkels et al. estimates provide some support to Johnston et al.
- Okkels et al suggest there could be additional gains from prefilled subcutaneous pen (administration of marstacimab) compared to single use subcutaneous syringe (administration of emicizumab)
- EAG retains Johnston et al utility decrements in base case

Are the Johnston et al utility decrements appropriate for decision making?

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Abbreviations: SC, subcutaneous; EAG, external assessment group; IV, intravenous; TTO, time trade off

Uncaptured benefits

Company stated that treatment administration has carer benefit

Background

- Previously committee did not identify uncaptured benefits

Company

- SC injection compared to IV injection benefits carers
- Consulted clinical experts who agreed, notably for carers of adolescents
- Family/carer quality of life improvement not captured in utility decrements.

EAG comments

- EAG clinical expert stated the 90% to 95% of adult patients self-administer; children begin training in self-administration from very early age
- % of patients requiring carer assistance likely low
- No carer decrements have been quantified.

Is there an uncaptured carer benefit needed to be factored into decision making?

Abbreviations: EAG, external assessment group; IV, intravenous; SC, subcutaneous

Company further analysis: Blended comparator analysis 1/2

Background

- Alongside pairwise comparison-present scenario with a blended comparator across HA and HB (provides alternative way of considering the cost-effectiveness impact of the introduction of marstacimab

Company

- Most patients in the NHS expected to receive marstacimab would have HB-Unmet need for people with HB
- Weighting of HA and HB based on expected uptake of marstacimab in patients in UK clinical practice (NHS England's estimates).
- Updated data from UKHCDO shows uptake of emicizumab continues to rise: estimated 60-70%

EAG comments

- UKHCDO report shows 59% not 70% receiving emicizumab. Company's choice 70% unreasonable.
- Rate of increased uptake of emicizumab diminishing over time: 2022/2023 uptake increased by only 6%.
- May be better to consider types of haemophilia cost effectiveness estimates separately

Abbreviations: EAG, external assessment group; HA, haemophilia A; HB, haemophilia B

Company further analysis: Blended comparator analysis 2/2

Distribution of population expected to receive marstacimab	Company estimate	EAG estimate (assuming all patient switch to mars – using UK proportions)
Haemophilia A	[redacted] *	83% (UKHCDO 2023)
Haemophilia B	[redacted] *	17% (UKHCDO 2023)
Emicizumab market share	70% (estimated based on UKHCDO nov 2024 report)	59% + scenario at 64% (UKHCDO)

*NHS England Budget Impact Analysis Submission for Marstacimab

Is a blended comparator appropriate? If so, what are the appropriate proportions for HA and HB and emicizumab share?

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Abbreviations: EAG, external assessment group; HA, haemophilia A; HB, haemophilia B; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Company and EAG base case assumptions 1/2

Issue	Company base case	EAG base case
Generalisability BASIS + baseline ABR	UKHCDO ABR baseline	
Dose escalation of marstacimab	Dose escalation of marstacimab applied in year 2 model	
Discontinuation of haemophilia treatments	6.02% discontinuation rate applied to emicizumab and marstacimab arm (10% scenario)	
Dosing factor prophylaxis	85% of company base case	75% of company base case.
Separate or pooled modelling	Pooled	Pooled: Scenario for separate modelling
Utility decrement bleeds	Utility decrement of 0.16 applied over 2.5 days	
Utility decrement	Subcut utility decrement of 0.0002, IV of 0.0003 applied per administration	
Market share data	IQVIA 2024 market share	UKHCDO

Abbreviations: ABR, annualised bleed rate; EAG, external assessment group; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Company and EAG base case assumptions 2/2

Issue	Company base case	EAG base case
Emicizumab dosing cap	Capped at 100kg body weight	
Dosing factor product following a bleed	Align to UKHCDO data	
20% of bleeds incur hospital resource use benefit	Applied	
FIX/FVIII ABR for BASIS observational phase of study	All patients	Those in observational phase
Blended comparator scenario	Blended comparator weighted by expected marstacimab uptake (haemophilia A: [redacted], haemophilia B: [redacted]) 70% market share emicizumab	Blended comparator weighted by prevalence (HA 83%, HB 17%) 59% market share emicizumab

Abbreviations: kg, kilogram; EAG, external assessment group; HA, haemophilia A; HB, haemophilia B; OP, observational phase; OLE, open label extension

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential commercial arrangements for the intervention and comparators

Analyses considered	Results
Company preferred base case (pairwise):	• Marstacimab is more expensive with less QALYs gained compared with emicizumab in haemophilia A (dominated) • Marstacimab is more expensive with more QALYs gained compared with FVIII basket in haemophilia A (ICER > 1 million per QALY gained) • Marstacimab is cheaper with more QALYs gained compared with FIX basket in haemophilia B (dominates)
EAG base case (pairwise):	• Results are similar in the EAG base case
Scenario with blended comparator:	• In company scenario marstacimab dominates the blended comparator • In EAG scenario the ICER for marstacimab compared with the blended comparator is > £1 million

EAG, external assessment group; HA, haemophilia A; HB haemophilia BFVIII, factor VIII; FIX, factor ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life-year; UKHCDO, UK haemophilia centre doctors' organisation

Key issues for committee discussion at 2nd committee meeting

Key issues outstanding at second committee meeting

	Issue	ICER impact
Cost-effectiveness	Separate or pooled modelling	Small
	Dosing factor prophylaxis	Moderate
	IQVIA market share data	Small
	Discontinuation of haemophilia treatments [in supplementary appendix]	Moderate
	Treatment disutility per administration	Large
	Blended comparator	Large

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Supplementary appendix

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Key Issue: Discontinuation of haemophilia treatments

Company modelled same discontinuation rate for emicizumab and marstacimab

Recap

- People can stop marstacimab and switch to factor prophylaxis. Company did not apply discontinuation rate for emicizumab. Committee heard ≈ 10% who receive emicizumab in UK discontinue.

Company

- Clinical expert stated discontinuation rate for emicizumab in range of 2-10%
- Discontinuation rate of 6.02% applied to emicizumab and marstacimab in base case
- Scenario where discontinuation rate of 10% applied to emicizumab and marstacimab

EAG comments

- Assuming the same discontinuation rate, of 6.02%, for emicizumab and marstacimab seems reasonable for base case. Increasing to 10% in each arm has little effect on the ICER.

Which is the most appropriate scenario to model discontinuation of emicizumab?

Abbreviations: ICER, incremental cost-effectiveness ratio

Other changes to company base case

Model change proposed during ACM1	Committee preference	Adopted by company in response?
Emicizumab dosing capped at 100kg	• Capped at 100kg	Yes
Dosing factor product following a bleed	• Align to UKHCDO data	Yes
20% of bleeds incur the hospital resource use benefit	• 20% of bleed incur the hospital resource use benefit	Yes

Link to: main slides, key issues from ACM1 and company response

Kg, kilogram; UKHCDO, UK Haemophilia Centre Doctors' Organisation

EAG literature review summary treatment administration

EAG literature review found further studies which support values obtained by Johnson et al

Summary of additional studies from literature review exploring treatment administration and quality of life

Study	Study description	EAG comment
Carlsson et al	TTO, n=184 haemophilia, n=1,233 general population. Estimate of -0.00026 decrement (for haemophiliacs) and -0.00036 (general population) per IV injection	Aligns with Johnston et al
Furlan et al	DCE, Haemophilia patients HA n= 89, HB n=32.	Frequency of infusion most important attribute
Chiou et al	DCE, n=51, found type of treatment, FVIII versus non-factor VIII and risk of thromboembolic events most important determinants of preferences	SC compared to IV treatment administration followed
Fifer et al	DCE, n=56 haemophilia patients, bleeds, side effects, injection site reactions, use of rescue therapy and storage determines patient choices	Different to outcomes by Furlan et al (2015)

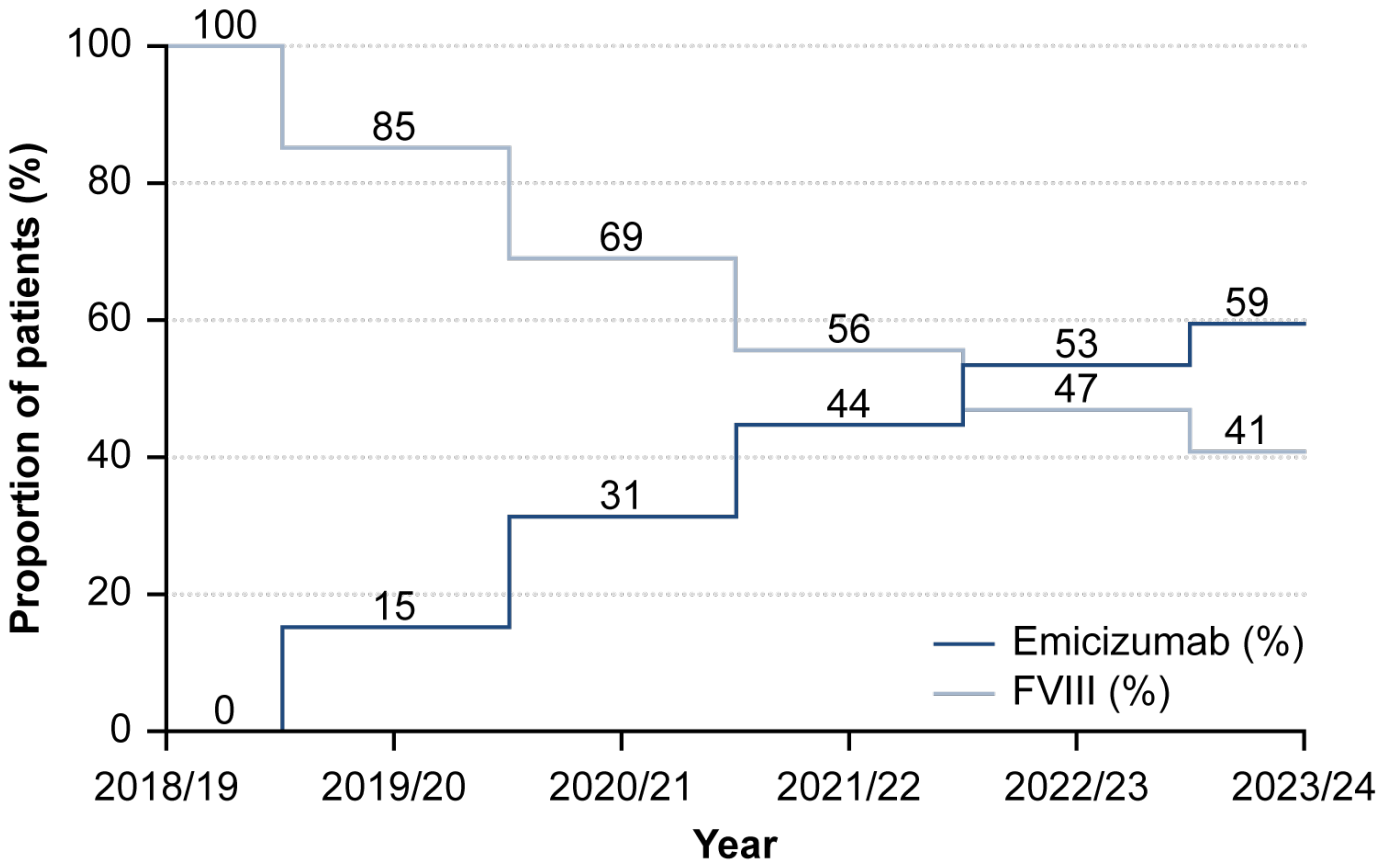
Abbreviations: DCE, discrete choice experiment; FVIII, factor VIII; HA, haemophilia A; HB, haemophilia B; TTO, time trade off; n, number. Link to main slides, treatment disutility

Emicizumab uptake, UKHCDO annual report

Background

- Data presented in UKHCDO annual report 2024

Proportion of patients with severe congenital haemophilia A, no inhibitors, issued primary treatment



Link to: main slides, Company further analysis blended comparator

Abbreviations: FVIII, factor VIII; UKHCDO, UK Haemophilia Centre Doctors' Organisation

Blended haemophilia A and haemophilia B comparator displacement weightings

Company's estimates for blended comparator

Distribution of population expected to receive marstacimab		
Severe haemophilia A[1]		Severe haemophilia B[1]
[redacted]		[redacted]
FVIII prophylaxis[2]	Emicizumab[2]	FIX prophylaxis[1]
[redacted]	[redacted]	[redacted]

[1]NHS England Budget Impact Analysis Submission for Marstacimab [ID6342], [2]UKHCDO Annual Meeting, 2024.

EAG's estimates for blended comparator

Distribution of population expected to receive marstacimab		
Severe haemophilia A[1]		Severe haemophilia B[1]
83%		17%
FVIII prophylaxis[2]	Emicizumab[2]	FIX prophylaxis[1]
34%	49%	17%

[1]UKHCDO 2023 report table 1 [2]UKHCDO Annual Meeting, 2024.

Link to: main slides, Company further analysis blended comparator

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Abbreviations: EAG, external assessment group; HA, haemophilia A; HB, haemophilia B

Marstacimab (Hympavzi, Pfizer)

SC treatment for severe haemophilia A and B without inhibitors

Marstacimab information summary

Marketing authorisation	• GB MA not granted yet; [redacted] • EMA, CHMP granted September 2024: For routine prophylaxis of severe (<1% factor activity) haemophilia A (congenital FVIII deficiency) without FVIII inhibitors or severe haemophilia B (congenital FIX deficiency) without FIX inhibitors, in adults and paediatric patients 12 years of age and older
Mechanism of action	• Marstacimab inhibits the tissue factor pathway inhibitor, which enhances the extrinsic pathway of clot formation and reduces the need for replacement factor therapies
Administration	Administered as subcutaneous injection, for people who are 12 years of age and older and weigh at least 35kg: • Recommended loading dose is 300 mg • Followed by weekly dose of 150 mg [dose adjustment up to 300 mg permitted in patients 50 kg or more when bleeding events judged to be inadequate]
Price	• List price: [redacted] per 150mg pack • List price for 12 months of treatment: a weekly dose of 150 mg [redacted] per patient, for receiving a weekly dose of 300mg weekly [redacted] per patient • A patient access scheme has been agreed

FVIII, factor VIII; FIX, factor IX; kg, kilogram; mg, milligram

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

ACM 1 slides

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Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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

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Background on haemophilia A and B

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

Causes: Inherited disorder causing mutations in genes encoding FVIII for haemophilia A and FIX for haemophilia B, leads to deficiency / absence of FVIII or FIX

- Results: Impairs fibrin production → Delayed clot formation → excessive bleeding

Epidemiology: ~2,230 people treated for severe haemophilia A and ~374 treated for severe haemophilia B for people aged 12 and over

Diagnosis and classification: Company submission is focused on severe form only

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

Abbreviations: dL, deciliters, FVIII, factor VIII, Factor IX, factor IX, IU, international unit

Patient perspectives

Submission from the Haemophilia Society

Affects quality of life:

- Risk of bleeds affects daily life: lack confidence in crowded areas/social settings, limits careers and sports.
- Treatments can be time consuming: people with severe haemophilia plan life around treatment
- Many people feel anxious or depressed. Anxiety around treatments due to contaminated blood scandal
- Can develop joint damage which requires rehabilitation

SC administration is valued by patients

- Accessing veins is difficult when there is damage to veins or joints
- Burden due to frequent IV infusions. People with haemophilia B will have a SC option for the first time
- People with joint mobility issues may struggle to self-infuse

"There is a substantial burden of treatment and anxiety in managing treatments which may be eased through subcutaneous treatments such as this product and emicizumab"

"People with severe haemophilia still have painful bleeds requiring additional treatment and often rehabilitation"

IV, intravenous; SC, subcutaneous

Clinical perspectives

Submission from clinical experts

- Treatment aim: prevent bleeds, lower mortality and preserve joint health. Children and men with complicated haemophilia B have recurrent painful bleeds and may become wheelchair dependent in their second decade
- Marstacimab addresses unmet needs of:
    - SC treatment option for severe haemophilia B
    - Effective prophylactic treatment for people with inhibitors with severe haemophilia B
    - Treatment option for people with severe haemophilia A who have developed anti-drug antibodies against emicizumab (very small patient numbers), or for whom emicizumab has not provided best bleed prevention

Reduces treatment burden:

- Carers would be able to administer SC easily. SC much easier than finding a vein, which becomes harder with time

"Subcutaneous administration may lead to earlier independence of management of their own condition for adolescents and particularly for individuals with additional medical or social communication diagnoses, many of whom may never be able to administer their own intravenous treatment, but who can master subcutaneous treatment rapidly."

SC, subcutaneous

Equality considerations

Considerations raised during scoping include the use of animal derived blood products

The remit has been kept broad and includes all people with severe haemophilia A and B.

It was also noted during scoping that:

- Some people cannot have FVIII replacement treatments that include blood products derived from humans, animals or animal cells because of religious faith or beliefs.

It was noted in the clinical expert submissions that:

- Severe haemophilia almost universally occurs in men and boys, but in very rare situations may also occur in women and girls. So, marstacimab should be available irrespective of gender
- Some people with joint damage, or who have a disability in addition to haemophilia, may struggle to self-administer IV infusions

Any relevant equality issues should be explored by the committee.

FVIII, factor VIII; IV, intravenous

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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

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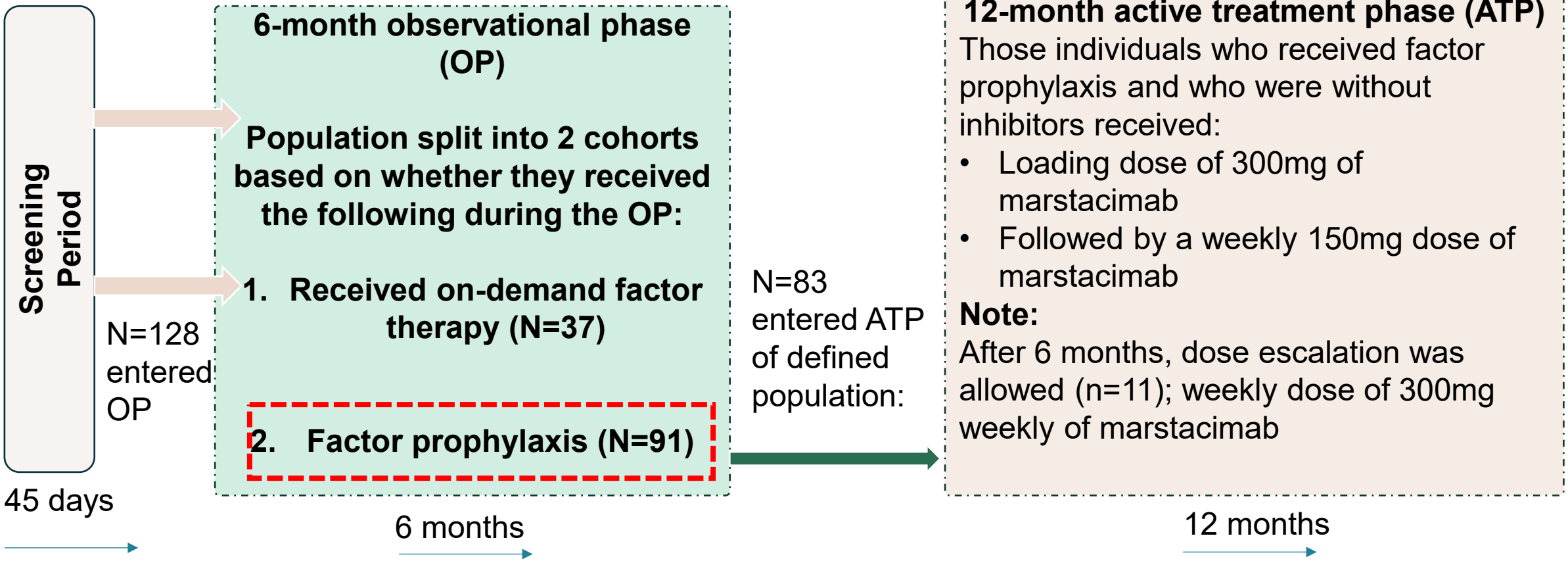
BASIS clinical trial design

18 month trial consisting of 6 month OP and 12 month ATP

BASIS clinical trial structure



- During the 6-month OP people received SOC prophylactic.
- The ABR of ATP was compared to OP

ABR, annualised bleed rate, ATP, active treatment phase, mg, milligram, N, number, OP, observational phase, SOC, standard of care

Key clinical trials

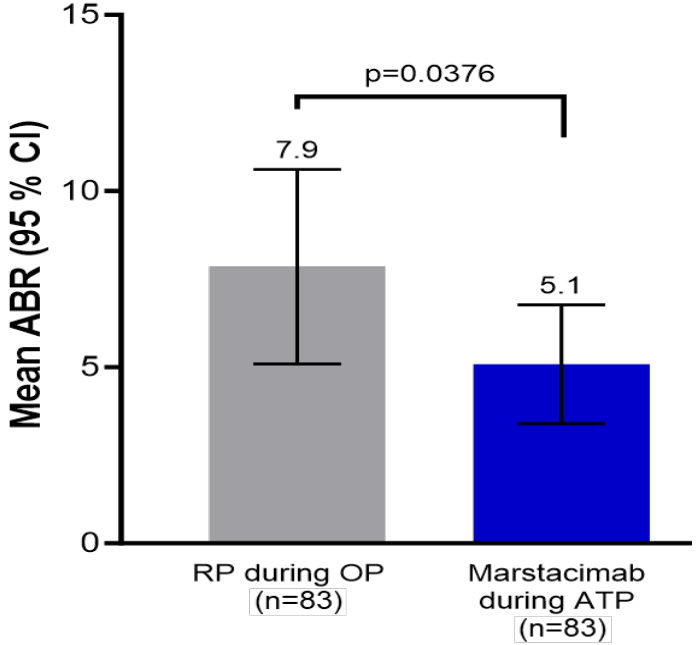
	BASIS (N= 128)	Open Label Extension (N=88)
Design	Phase 3, one-way, cross-over, multicentre	Phase 3, interventional, open-label extension
Population	• Men aged 12 to <75 years with severe haemophilia A or moderate/severe haemophilia B • Haemophilia A defined as <1% FVIII activity, moderate/severe Haemophilia B* defined as ≤2% FIX activity (with or without inhibitors).	
Number of participants	• 179 screened • 128 entered the OP • 116 entered the ATP	• 111 completed BASIS study • 108 planned to participate in OLE • 88 entered the OLE as of the interim data cut-off of 10th March 2023
Intervention	Marstacimab; 300 mg SC loading dose followed by 150 mg once weekly	
Comparator(s)	Prior SOC treatment in 6 month OP phase	Not applicable
Duration	12 month ATP, 1 month follow up safety	Planned follow up 7 years.
Primary outcome	ABR for treated bleeding events (involved counting all treated bleeds experienced by patients and was defined as the number of treated bleeding episodes during the 12-month ATP.)	
Key secondary outcomes	ABR for treated joint bleeds, ABR for spontaneous bleeds, ABR for total bleeds, ABR for treated target joint bleeds, change in joints (HJHS), number of patients with no treated bleeds	
Locations	19 countries, sites in Europe, no UK sites	
Used in model?	Yes	No

ABR, annualised bleed rates; ATP, active treatment phase; FVIII, factor VIII; FIX, factor IX; HJHS, haemophilia joint health score; OP, observational phase; SOC, standard of care *all recruited patients for haemophilia B had severe [<1% FIX]

BASIS- key results: 17 April 2023 data cut-off; mITT analysis set)

Lower ABRs with marstacimab prophylaxis than routine prophylaxis

BASIS trial results: Mean ABR treated*



***Note:** Bleeding records on or after dose escalation are censored for people who dose escalated (n=11)

ABR, annualised bleed rates; ATP, active treatment phase; OP, observational phase; RP, routine prophylaxis; SE, standard error. Link to supplementary slides: treatment effectiveness censored and uncensored, OLE October 2023 data-cut results

- **EAG** requested data from 1st 6 months to reduce bias from differing follow up lengths. As dose escalation could only occur after 6 months, censoring is not an issue in these analyses.

BASIS first 6-month results from ATP for marstacimab

	Routine prophylaxis (n=83)	Marstacimab (n=83)
All participants		
Percentage with zero bleeds	[redacted]	[redacted]
Mean ABR treated (SE)	[redacted]	[redacted]
Mean ABR joint treated (SE)	[redacted]	[redacted]
Mean ABR total treated (SE)	[redacted]	[redacted]
Excluding those with zero bleeds		
Mean ABR treated (SE)	[redacted]	[redacted]
Mean ABR joint treated (SE)	[redacted]	[redacted]
Mean ABR total treated (SE)	[redacted]	[redacted]

Key issues: Generalisability to NHS

Different NHS usage data for EHL and SHL therapies compared to BASIS

Background

- BASIS trial was used as evidence for clinical effectiveness for marstacimab to inform the model
- BASIS was a multi-centre phase 3 trial and included sites across Europe but included no UK patients

Company

- Used data from BASIS trial in analysis, no adjustments for differences between BASIS vs NHS practice

EAG comments

- BASIS cohort had [redacted] individuals who received EHL therapies compared to UK practice. Clinical experts stated participants in the BASIS trial were not on prophylaxis comparable to UK SOC
- Baseline bleed rates were higher during the prophylactic period compared to NHS patients
- Calculated real-world UK specific ABR baseline treated ABR ([redacted]), combined reported ABR from UKHCDO with use of SHL /EHL in BASIS, - used to apply relative effects estimated from BASIS to derive efficacy of marstacimab

Summary of prophylaxis regimen in BASIS vs UK data

	BASIS OP Routine Prophylaxis (n=83)	UKHCDO (n=901)
Proportion of people on type of prophylaxis (%)		
SHL	[redacted]	[redacted]
EHL	[redacted]	[redacted]
Emicizumab	[redacted]	[redacted]
Mean ABR (SHL and EHL for BASIS. SHL, EHL, emicizumab for UKHCDO)	[redacted]	[redacted]

SHL, standard half-life; SOC, standard of care; UKHCDO, UK haemophilia centre doctors' organisation. Link to supplementary slides: Treatments used for bleeding events in BASIS, baseline characteristics

Does trial provide information of how marstacimab performs in UK setting against current comparators?

Summary of company ITC

Company did an ITC to compare marstacimab and emicizumab

Background

- No direct trials comparing marstacimab and emicizumab, so company did an ITC

Company

- ITC compared marstacimab and emicizumab using data from HAVEN-3. No IPD for HAVEN trial
- Company chose unanchored STC. STC compared the control of bleeding events people with severe haemophilia A, without inhibitors who received prior prophylaxis

Summary of data sources included in the ITC

Intervention	Marstacimab		Emicizumab	
Trial	BASIS haemophilia A subgroup (n=65)		HAVEN-3 (cohort D, n=63, cohort D is only relevant cohort)	
Regimen	Prior regimen	Trial regimen	Prior regimen	Trial regimen
Prior prophylaxis	-SHL or EHL for 6 months in OP of study	Initial loading dose of 300mg, followed by weekly disease of 150mg	- SHL or EHL FVIII prophylaxis for over 24 weeks prior to study	D: 1.5 mg/kg SC QW (n=63)

EHL, extended half life; FVIII, factor VIII; IPD, individual patient data; ITC, indirect treatment comparison; OP, observational phase; SHL, standard half life; STC, simulated treatment comparison; QW, weekly; mg, milligram Link to supplementary slides: Baseline characteristics summary for ITC

Key Issue: Efficacy estimation for emicizumab 1/2

EAG and company used different covariates in ITC

Company

- Ruled out an anchored ITC due to the single arm cross-over design of the BASIS study. Anchored ITC using intrapatient comparison data not feasible due to differences in studies.
- Compared 5 efficacy outcomes: ABR_{total}, ABR_{treat}, $AJBR_{treat}$, percentage with zero total bleeding events and percentage with zero treated bleeding events
- Effect modifiers were: Prior ABR total, target joints, age, BMI, race and ethnicity
- Emicizumab was favourable across the 5 efficacy outcomes, but no outcomes were statistically significant

EAG comments

- Concerned whether BASIS is similar enough to either of the HAVEN trials to be compared in an ITC.
- Requested additional analysis based on those published by Astermark et al. (a study which identified medically relevant covariates from HAVEN 3). Covariates identified were: age, % white, BMI, baseline ABR, proportion with <9 bleeds in prior 24 weeks and proportion receiving SHL FVIII. Company also added target joints in STC adjustment.
- EAG preferred source of efficacy is UKHCDO data, but if an ITC is done, prefers to include variables from Astermark
- Conducted NMA - Estimates from NMA consistent with ITC. See supplementary slides: NMA results

ABR, annualised bleeding rate; ABR_{treat}, annualised bleeding rate of treated bleeds; $AJBR_{treat}$, annualised bleed rate of treated joint bleeds; BMI, body mass index; FVIII, factor VIII; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; SHL, standard half life; STC, simulated treatment comparison

Key Issue: Efficacy estimation for emicizumab 2/2

No significant differences in efficacy found between marstacimab and emicizumab

EAG comments contd:

- Analysis used 33 weeks of follow-up data in BASIS for consistency with reported follow up in HAVEN 3
- Point estimates suggest a small benefit of emicizumab but none were statistically significant.
- EAG requested indirect comparison to HAVEN-4, and the results did not find a statistical difference

Summary of ITC results

	Comparing marstacimab to emicizumab using HAVEN 3		
	Naive rate ratio	Company preferred STC adjusted rate ratio	STC using Astermark covariates + Target joints
ABR total	[redacted]	[redacted]	[redacted]
ABR treat	[redacted]	[redacted]	[redacted]
AJBR treat	[redacted]	[redacted]	[redacted]
Proportion zero treated bleeds (OR)	[redacted]	[redacted]	[redacted]

ABR, annualised bleeding rate; ABR_{treat}, annualised bleeding rate of treated bleeds; $AJBR_{treat}$, annualised bleed rate of treated joint bleeds; ITC, indirect treatment comparison, OR, odds ratio, STC, simulated treatment comparison

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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

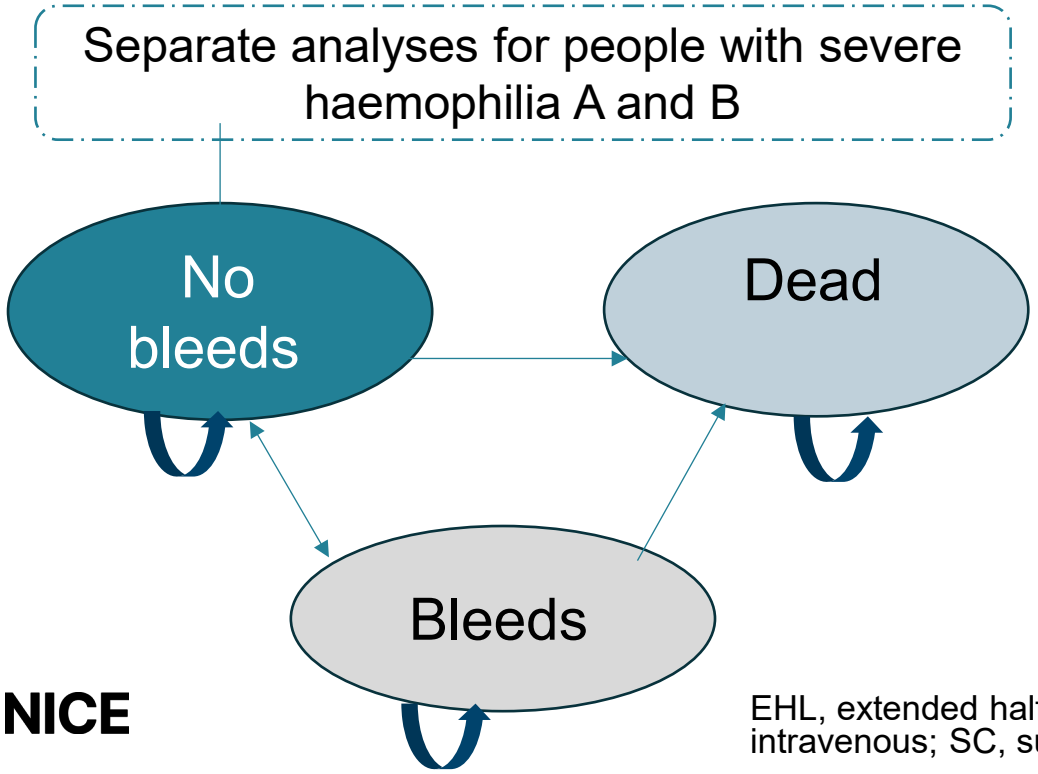
NICE National Institute for Health and Care Excellence

Company's model overview

Markov model with treated bleeds being modelled in each cycle

- Lifetime time horizon (64 years), cycle length 1 year, 3.5% discount rate
- BASIS trial EQ-5D applied, QALY decrements for joint bleeds and non-joint bleeds, sub cut and IV treatments
- No treatment waning included

3-state Markov model: bleeds, no bleeds, dead



- Marstacimab affects QALYs by:
  - Reduced annualised treated bleed rate
  - SC vs IV SHL/EHL prophylaxis
  - Reduced annual number of administrations
- Marstacimab affects costs by:
  - Changing costs of treatments and treating bleeds
- Assumptions with greatest effect on ICER:
  - Mean dose of prophylaxis and wastage calculations
  - Marstacimab dose escalations
  - Pooling vs separate clinical effectiveness assumptions, dose escalation rates
  - Whether clinical effectiveness estimates for 2nd year and beyond based on BASIS open label or BASIS

EHL, extended half life; EQ-5D, euroqol 5 dimensions; ICER, incremental cost effectiveness ratio; IV, intravenous; SC, subcutaneous; SHL, standard half life; QALY, quality adjusted life year

Key Issue: Baseline annualised bleed rates and efficacy

Treatment effectiveness based on ABR and AJBRs

Background:

- At model entry, patients are distributed among the "No bleeds" and "Bleeds" health states.
- ABRtreat used in the efficacy analysis (previous models in haemophilia used ABRtotal) to align with BASIS outcomes and to reflect that bleed events in model incur treatment costs
- Within the "bleeds" health state both joint and non-joint treated bleeds are considered
- Estimates for emicizumab are derived by applying the ITC odds ratio of no bleeding to the marstacimab odds of no bleeding, and the rate ratios for ABRT and AJBRT.

EAG comments: prophylaxis received in OP is not reflective of NHS SOC

- BASIS trial used to inform efficacy, prophylaxis treatments in BASIS OP are not reflective of NHS SOC: BASIS had a greater proportion of people who were receiving SHL therapy, compared to in NHS [See key issue: generalisability to NHS]
- UKHCDO is a real-world database relating to treatments used in the NHS.
- In BASIS compared to NHS (see UKHCDO baseline annualised bleed rates and efficacy for full data):
  - % receiving EHLs is [redacted]
  - % having treatment of breakthrough bleeds is [redacted]
  - ABR for SHL products was [redacted] and proportion with no bleeds was [redacted]
- EAG updated base case assumptions to use ABRs based on UKHCDO data

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ABR, annualised bleed rate; ABR_{treat}, annualised bleeding rate of treated bleeds; AJBR, annualised joint bleed rate; $AJBR_{treat}$, annualised bleed rate of treated joint bleeds; EAG, external assessment group; ITC, indirect treatment comparison; STC, simulated treatment comparison; SOC, standard of care Link to supplementary slides: Treatment effectiveness in company model

Comparison of BASIS vs UKHCDO

[redacted] *people received SHL treatment in UKHCDO dataset compared to BASIS*

	Basis			UKHCDO			iQVIA market share data
Treatment	**% people receiving treatment**	**Bleed rates %**	**ABR mean**	**% people receiving treatment**	**Bleed rates %**	**ABR mean**	**% people receiving each treatment**
FVIII SHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII EHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emicizumab	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
FIX SHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIX EHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All prophylaxis (FIX and FVIII)		[redacted]	[redacted]		[redacted]	[redacted]	

Key Issue: Dose escalation of marstacimab

Dose escalation continued after 12 months, a small proportion of those eligible had dose escalated

Background

- Dose escalation in BASIS trial is allowed after 6 months in the ATP and can continue in OLE
- People that dose escalate have their dose of marstacimab increased from 150mg to 300mg
- Clinicians decide whether a person can have their dose increased, providing a set criteria is met (weigh ≥50kg and experience two spontaneous bleeds over 6 month period)

Company

- Only included dose escalation in the first year of model
- 13.25% escalated their dose in the ATP of BASIS trial
- [redacted] days average time on 150mg in ATP for dose escalators

EAG comments

- Some patients may be ineligible for dose escalation due to <50kg
- Adjusted dose escalation percentage to [redacted] to reflect that nobody whose dose was escalated discontinued
- People dose escalated in OLE. This is not captured in company model. Mean duration of treatment in OLE for dose escalators is [redacted] days. EAG argues for 1 of the following to be applied:
  - OLE dose escalation year 2 of [redacted] (current EAG base case)
  - Annual ongoing escalation rate of [redacted] and cap at 50% (in EAG scenario analysis)

Comparing proportion eligible for dose escalation to proportion whose dose did escalate

Dose escalation	Eligible %	Actual %
ATP all patients	[redacted]	[redacted]
OLE Oct 2023	[redacted]	[redacted]
OLE Oct 2023 adjusted for ATP dose escalators	[redacted]	[redacted]

ATP, active treatment phase; EAG, external assessment group; OLE, open label extension; mg, milligram.
Link to supplementary slides: impact of dose escalation

Key Issue: Discontinuation of haemophilia treatments

Discontinuation of marstacimab applied but no discontinuation for emicizumab

Background

- People can discontinue marstacimab and switch to factor prophylaxis

Company

- Applied a one-off discontinuation rate for marstacimab of 6.02% in the first cycle due to discontinuation of treatment in BASIS
- No discontinuation of emicizumab was applied due to lack of data

EAG comments

- Discontinuation is not modelled for emicizumab due to the absence of data. This is a source of uncertainty and probable bias
- EAG provide a scenario where there are no discontinuations for marstacimab

Should the model include a discontinuation rate for marstacimab and/or emicizumab? If, so how many cycles should this be applied for?

ATP, active treatment phase; FVIII, factor VIII; FIX, factor IX; WTP, willingness to pay

Key Issue: Dosing of factor prophylaxis 1/2

Company base cases uses different sources to estimate dosage and efficacy of factor prophylaxis

Company

Company base case uses different sources to estimate dosage and efficacy of factor prophylaxis:

- ❖ Relative efficacy estimates from BASIS
- ❖ Dosage information was taken from summaries of product characteristic documents

- Base case assumes SmPC weighted by market share
- Assumed drug wastage and all dosing was rounded up

Mean total factor prophylaxis dose from different sources

Source	Mean total prophylaxis dose (IU/kg/year)	Change from BASIS value
BASIS OP (routine prophylaxis)	[redacted]	-
SmPC doses x IQVIA market share - **company base case**	[redacted]	+18%
BASIS OP doses x IQVIA market share	[redacted]	+21%
UKHCDO 2023 annual report	3,500	[redacted]

ABR, annualised bleed rate; IU, international unit; kg, kilogram; OP, observational phase; SmPC, summary of product characteristics; UKHCDO, UK haemophilia centre doctors' organisation

Key Issue: Dosing of factor prophylaxis 2/2

UKHCDO total FVIII issued per person over one year was lower than company base case

EAG comments

Differences in mean total factor prophylaxis may be due to:

1. Dosing during BASIS was less than in NHS, may imply suboptimal treatment during BASIS and that BASIS was biased in favour of marstacimab
2. FVIII/FIX dosing for routine prophylaxis in the model is too high. EAG can only explore this possibility

- In the table, company base case for SHL is [redacted]% more and EHL [redacted]% more than UKHCDO data in haemophilia A. Note that adolescents contribute to 28% of UKHCDO data.
- Haemophilia B average annual dose [redacted]% of the company base case
- EAG base case reduces FVIII/FIX dosing to 75% of company base case. Explored scenarios: 85% and 100% of the company base case

FVIII dosing per person, per year in company model vs UKHCDO annual report (Adult and adolescent data)

Total FVIII issued per person per year	Company base case [routine prophylaxis]	UKHCDO annual report 2023 [routine prophylaxis + treating bleeds]
SHL	[redacted] IU	259,574 IU
EHL	[redacted] IU	271,697 IU

What is the most appropriate assumption for dosing of factor prophylaxis?

EAG, external assessment group; EHL, extended half life; FVIII, factor VIII; FIX, factor IX; IU, international unit; SHL, standard half life; UKHCDO, UK haemophilia centre doctors' organisation. Link to supplementary slides: Adolescent factor prophylaxis dosing

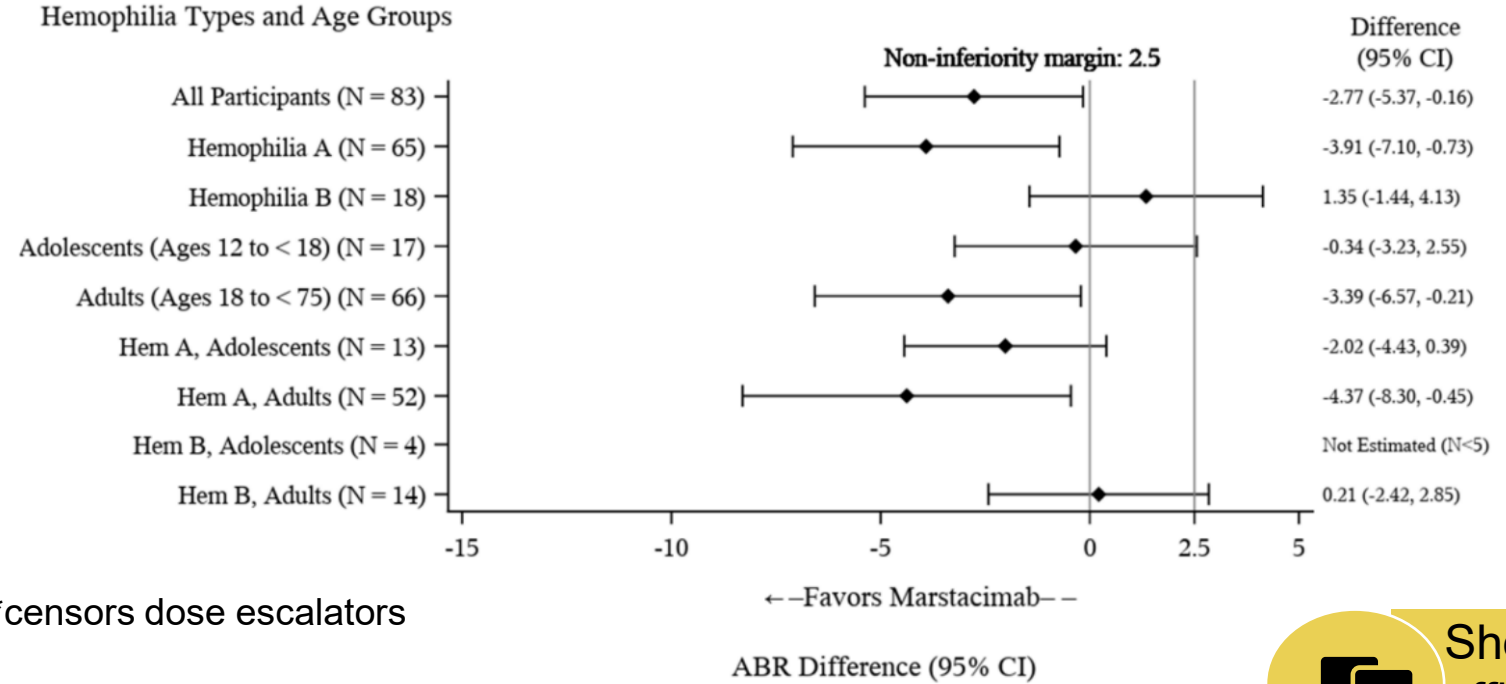
Key Issue: Separate or pooled modelling of haemophilia types

Haemophilia A and B have different treatment effect and rates of dose escalation in BASIS

Background

- Company base case groups haemophilia A and B together
- Company base case applied no treatment specific efficacy or dose escalation for haemophilia A and B

Comparison of ABR $_{treat}$ for haemophilia types during the OP (routine prophylaxis) and after 12 months* of marstacimab prophylaxis in ATP



*censors dose escalators

Company

- BASIS had small sample sizes (haemophilia A n=65; haemophilia B n=18) and was not powered to detect subgroup differences

EAG comments

- Smaller treatment effect and different dose escalations for haemophilia B than haemophilia A

Should the model include separate or pooled efficacy estimates and dose escalation rates for haemophilia A and B?

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ABR $_{treat}$, annualised bleed rate treated, ATP, active treatment phase, Hem A, haemophilia A, Hem B, haemophilia B, OP, observational phase

Link to supplementary slides: Separate or pooled modelling: dose escalation rates

Key Issue: Treatment disutility per administration

Disutilities applied for treatment administration have large effects on the ICER

Background

- Disutilities were applied in model for IV and SC treatment administration. In the company model they provide 75% of modelled QALY gain in the FVIII treatment arm, and 50% QALY gain in FIX arm.

Company

- The utility decrement per SC administration was 0.0002, and 0.0003 per IV. Disutilities from Johnson et al
- Statistically significant preference for SC administration

EAG comments

- Johnson et al, sponsored by Hoffman-la Roche (manufacturer of emicizumab):
  - ❖ Performed TTO study → vignettes presented for 6 health states. Vignette for IV not accurate as in UK patients self-administer after a few administrations. Risks for IV listed were internal bleeding, but this not quantified or placed in context. No risks for SC were listed in vignette. Design of TTO might be biased against IV administration. Preference may arise due to differing ABRs for SC (1-2) and IV (4-5)
- Disutility estimates are provided at 4 decimal places, actual mean for IV administration disutility may be between 0.00025 to 0.00035, mean for SC administration disutility could be from 0.00015 to 0.00025. No CI reported, EAG think that CI's could overlap.
- Scenarios for disutility: Halve disutility applied for SC and IV administration and no disutility applied. EAG base case, the baseline bleeds were reduced for FVIII/FIX, these scenarios have large effect on ICER.

NICE Should the model apply disutility for treatment administration? If so, what assumption should be made?

ABR, annualised bleed rates; EAG, external assessment group; FVIII, factor VIII; FIX, factor IX; IV, intravenous; SC, subcutaneous; TTO, time trade off

Link to supplementary slides: treatment disutility: study vignettes

BASIS- results: Comparison of censored and uncensored analysis

Effect difference reduces when the impact of dose escalation is included for OLE results

- EAG requested analyses that were not censored for dose escalation
- Data from ATP shows that relative benefit of marstacimab [redacted] when impact of higher dosing accounted
- OLE data has unexpected result that effect difference reduces when impact of dose escalation is included
- EAG prefers uncensored estimates of efficacy as this more representative of NHS use of marstacimab

Results for BASIS using first 6 months of data from ATP for marstacimab

	ATP (n=83)	OLE (n=75)
With censoring for dose escalation	[redacted]	[redacted]
Without censoring for dose escalation	[redacted]	[redacted]
Reported or estimated ABR for OP (routine prophylaxis)	7.88	[redacted]
Reported or estimated ABR for marstacimab	[redacted]	[redacted]
Derived ABR ratio using censored estimates values OP (routine prophylaxis)	[redacted]	[redacted]

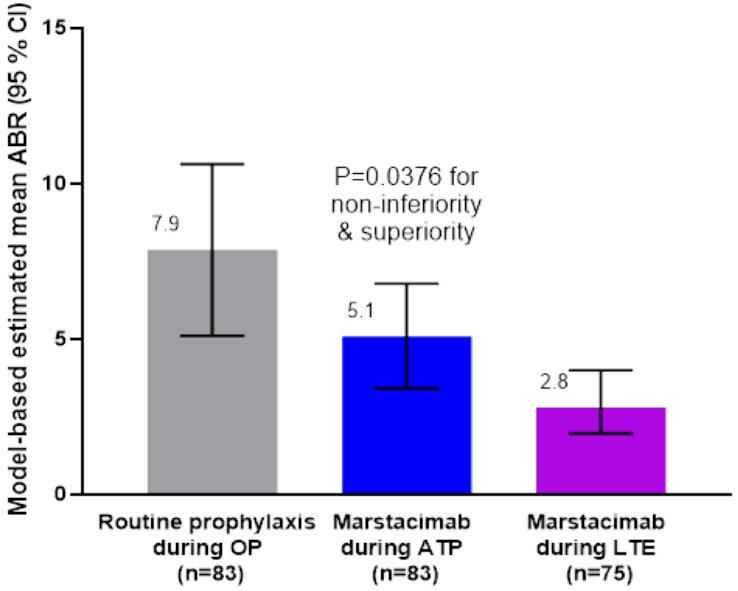
NICE

ABR, annualised bleed rates; ATP, active treatment phase; EAG, external assessment group; OP, observational phase; OLE, open label extension. Link to: main slides, BASIS key results

OLE October 2023 data-cut results

Key results of BASIS and OLE using latest data-cut

BASIS trial and OLE results: model derived ABR_{treat} for routine prophylaxis, 12 months Marstacimab in ATP of BASIS and after Marstacimab in OLE



***Note:** Bleeding records on or after dose escalation are censored for people who dose escalated (n=11)

BASIS 12-month results from ATP for Marstacimab and OLE results October 2023

	Marstacimab prophylaxis BASIS trial ATP April 2023 data-cut [mITT analysis]	Marstacimab during OLE October 2023 data-cut [Safety analysis set]
ABR_{treat}		
Mean (SD)	5.17 (8.041)	2.88 (5.50)
Model-derived ABR_{treat}		
Estimate (95% CI)	5.08 (3.40, 6.77)	2.79 (1.95, 3.98)

ABR, annualised bleed rates; ATP, active treatment phase; CI, confidence interval; OLE, open label extension; SD, standard deviation. Link to: main slides, BASIS key results:17 April 2023 data cut off, mITT analysis

Treating bleeding events during BASIS

During BASIS SHL and EHL are used more frequently to treat bleeds compared to NHS

BASIS results using first 6 months of data from ATP for marstacimab

	OP Routine prophylaxis (n=83)	ATP Marstacimab (n=83)
% participants with bleeds	[redacted]	[redacted]
Number bleeds	[redacted]	[redacted]
% treated bleeds	[redacted]	[redacted]
Treatments used (%)		
Blood coagulation factors	[redacted]	[redacted]
Damoctocog alfa pegol	[redacted]	[redacted]
Efmoroctocog alfa	[redacted]	[redacted]
Eftrenonacog alfa	[redacted]	[redacted]
Moroctocog alfa	[redacted]	[redacted]
Nonacog alfa	[redacted]	[redacted]
Octocog alfa	[redacted]	[redacted]
Rurioctocog alfa pegol	[redacted]	[redacted]
Turoctocog alfa	[redacted]	[redacted]

Background

- Breakthrough bleed treatment provided by company during OP and ATP in BASIS

ATP, active treatment phase; EHL, extended half life; SHL, standard half-life; OP, observational phase; SOC, standard of care. Link to: main slides, generalisability to NHS

Baseline Characteristics in BASIS

Summary of baseline characteristics of participants in BASIS

Baseline characteristics of participants in BASIS. 100% participants male with severe haemophilia

	Patients treated with prior factor prophylaxis in OP (n=83)
Mean Age (years)	32.6
Race (%)	
Asian	43.4
Black or African American	1.2
White	54.2
Mean BMI	23.6
Haemophilia type (%)	
Haemophilia A	78.3
Haemophilia B	21.7
Number target joints at baseline (%)	
0	43.4
1	22.9
2	18.1
≥3	15.7

BMI, body mass index; cm, centimetre; kg, kilogram; OP, observational phase

Link to main slides: generalisability to NHS

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Baseline characteristics summary for ITC

Baseline characteristics differed between BASIS and HAVEN 3

- Some comparisons are difficult to make due to reporting differences
- BASIS participants were younger and had a lower BMI compared to HAVEN 3
- The proportion with a target joint in BASIS was higher compared to HAVEN 3

Summary of baseline characteristics of studies used in ITC

Baseline characteristics	BASIS	HAVEN-3
Age/years	31.63	36.4
Ethnicity : % White % Latino	 52.3 13.9	 74.6 11.1
BMI	23.91	25.6
% with target joint	56.92	41.3
Mean prior ABR treated	9.2	-

ABR, annualised bleeding rate; ITC, indirect treatment comparison, NR, not recorded, STC, simulated treatment comparison,

Link to: main slides, summary of ITC arms for haemophilia A

Back up slide for NMA results

NMA results consistent with those from ITC

EAG comments

- NMA conducted by EAG in addition to ITC
- Took relative effects data from Mehlangu (2018) which was an emicizumab study (HAVEN 3)
- BASIS 6 month data cut was used

Summary of NMA inputs and outputs

Inputs	Number of people without bleed	Treated ABR
BASIS factor prophylaxis (N=83)	N with no bleed= [redacted]	Mean= [redacted] SE= [redacted]
BASIS Marstacimab (N=83)	N with no bleed= [redacted]	Mean= [redacted] SE= [redacted]
HAVEN 3 Factor (N=48)	No with no bleed= 19	Rate ratio vs factor: 0.32 (95% CI: 0.20, 0.51)
HAVEN 3 emicizumab (N=48)	N=26	
Output	Odds ratio for zero bleeds = [redacted] (95% CI: [redacted]	ABR treated ratio= [redacted] (95% CI= [redacted]

NICE

CI, confidence interval; EAG, external assessment group; N, number; NMA, network meta-analysis; SE, standard error Link to: main slides, efficacy estimation for emicizumab

Treatment effectiveness in company model

Treatment effectiveness based on ABR and AJBRs

- Within the bleed health state:
  - Patients experience an average number of bleeds that are treated annually
  - Joint and non-joint bleeds were modelled separately to obtain costs and utility decrements
  - Treated bleeds were modelled as treatment specific
  - **Note:** treated non-joint ABR is the residual: $AnJBR_T = ABR_T - AJBR_T$

Summary of clinical effect estimates

Efficacy measure	Marstacimab		Factor Prophylaxis		Emicizumab	
	Source	Value	Source	Value	Company source	Company value
ABR, any bleed treated	BASIS	7.53	BASIS	13.09	STC ITC • Simulated rate ratios obtained from STC, HAVEN 3 trial (cohort D), were applied to marstacimab ABR_{treat} and $AJBR_{treat}$	[redacted]
AJBR, treated		6.09		9.43		[redacted]
Non-joint ABR, treated		1.44		3.66		[redacted]
% experiencing bleeds	BASIS	62.65	BASIS	60.24		[redacted]

ABR, annualised bleed rate; ABR_{treat}, annualised bleeding rate of treated bleeds; AJBR, annualised joint bleed rate; $AJBR_{treat}$, annualised bleed rate of treated joint bleeds; EAG, external assessment group; ITC, indirect treatment comparison; STC, simulated treatment comparison; SOC, standard of care Link to: main slides, Baseline annualised bleed rates and efficacy

UKHCDO baseline annualised bleed rates and efficacy

Prophylaxis efficacy during observational phase in BASIS is different to NHS data

Summary of treatment efficacy estimates for SHL, EHL and emicizumab. Haemtrack self-reporting

Diagnosis	Age group, years	Product group	ABR mean	AJBR mean	ASBR mean	% with no bleeds
HA	12-17	Emicizumab*	[redacted]	[redacted]	[redacted]	[redacted]
		EHL	[redacted]	[redacted]	[redacted]	[redacted]
		SHL	[redacted]	[redacted]	[redacted]	[redacted]
	18+	Emicizumab*	[redacted]	[redacted]	[redacted]	[redacted]
		EHL	[redacted]	[redacted]	[redacted]	[redacted]
		SHL	[redacted]	[redacted]	[redacted]	[redacted]
HB	12-17	EHL	[redacted]	[redacted]	[redacted]	[redacted]
	18+	EHL	[redacted]	[redacted]	[redacted]	[redacted]
		SHL	[redacted]	[redacted]	[redacted]	[redacted]

*Note emicizumab is prophylaxis treatment for HA only ABR, annualised bleed rate, AJBR, annualised joint bleeding rate, ASBR, annualised spontaneous bleeding rate; EHL, extended half life; HA, haemophilia A; HB, haemophilia B; SHL, standard half life, UKHCDO, UK haemophilia centre doctors' organisation. Link to: main slides, key issue baseline annualised bleed rates and efficacy

Impact of dose escalation of marstacimab

Long term benefits of dose escalation may need to be accounted for

EAG comments

- Company base case includes effect of dose escalation during ATP in BASIS
- Any consideration of dose escalation in OLE may need to consider for effects of the dose escalation in OLE
- If those who had their dose escalated during ATP, retained a lower ABR_T during OLE phase, extrapolating using the ATP ABR_T will not include these long term benefits
- For haemophilia A patients whose dose escalated during ATP, ABR_T increases during OLE. Patient numbers are small.
- The same can be applied to those who had dose escalation during OLE, however this dose escalation may have been due to worsening ABR during OLE

Marstacimab dose escalation: ABR_T before and after escalation

	150 mg			300mg		
	N	Days	ABRT	N	Days	ABRT
ATP escalators: ATP data n=83						
Haemophilia A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemophilia B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATP escalators OLE data October 2023 data cut (n=75)						
Haemophilia A	-	-	-	[redacted]	[redacted]	[redacted]
Haemophilia B	-	-	-	[redacted]	[redacted]	[redacted]
All patients	-	-	-	[redacted]	[redacted]	[redacted]
OLE escalators: OLE data October 2023 (n=75)						
Haemophilia A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemophilia B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE ABR_T, annualised bleed rates that are treated, ATP, active treatment phase, EAG, external assessment group, N, number; OLE, open label extension, mg, milligram

Link to: main slides, key issue dose escalation of marstacimab

Adolescent factor prophylaxis dosing

Adolescents required less FVIII compared to adults

EAG comments

- Adolescents on average issued with less FVIII per year compared to adults

Total FVIII issued per person per year for adolescents. UKHCDO data includes routine prophylaxis and treatment of bleeds

Total FVIII issued per person per year	Company base case	UKHCDO annual report 2023 Adolescent data only
SHL	[redacted] IU	242,094
EHL	[redacted] IU	187,836

EHL, extended half life; FVIII, factor VIII; IU, international unit; SHL, standard half life; UKHCDO, UK haemophilia centre doctors' organisation. Link to: main slides, dosing of factor prophylaxis

Separate or pooled modelling: Dose escalation rates

Dose escalation rates were higher in haemophilia B

EAG comments

- Dose escalation occurred after 6 months. Dose escalation weekly dose 300mg
- BASIS ATP, dose escalation rates were higher in those who had haemophilia B

Haemophilia B uncertainty is greater:

- ❖ Smaller number of patients in BASIS
- ❖ UKHCDO estimates for bleed rates on small number of patients
- Effect of modelling separately haemophilia A and B on cost effectiveness results due to differing treatment efficacy and dose escalation between haemophilia A and B are:
- ❖ Haemophilia A: Cost effectiveness of marstacimab improves*
- ❖ Haemophilia B: Cost effectiveness of marstacimab worsens*

*Note: effect of above reduces if dose escalation is the same across both groups

Comparison of ABR treat for haemophilia A and B

	ABR_{treat}	
Data source	**Haemophilia A**	**Haemophilia B**
OP (routine prophylaxis) BASIS	9.16 (n=65)	3.26 (n=18)
ATP BASIS 12 months	5.30 (n=60)	4.71 (n=12)
UKHCDO data	[redacted]	[redacted]

Proportion of dose escalators for haemophilia A and B

BASIS ATP phase after 12 months	Haemophilia A n=65	Haemophilia B n=18
Dose escalation, n (%)	5 (7.7%)	6 (33.3 %)

NICE

ABR_{treat}, annualised bleed rate treated; ATP, active treatment phase; mg, milligram; n, number; OP, observational phase

Link to: main slides, key issue separate or pooled modelling of haemophilia types

Treatment disutility: study vignettes

EAG believes vignettes are biased against IV administrations

Background

- Vignettes for 6 health states presented to 82 people:
  - On demand routine treatment with ABR 36
  - IV prophylaxis 2-3 times p/w, ABR 4-5
  - IV prophylaxis 2-3 times p/w. ABR 10
  - IV prophylaxis 7 times p/w, ABR 4-5
  - SC prophylaxis once weekly, ABR 1-2
  - SC prophylaxis 4 times p/w, ABR 1-2

EAG comments

- IV treatment in UK is administered first few times in clinic, then carers administer treatment
- Risks for IV are not quantified /placed in context. EAG expert opinion internal bleeding does not happen from IV administration

Vignette descriptors for each mode of administration

Category	IV treatment description	SC treatment description
Administration	• Have to go to hospital/clinic to receive IV • Over time may be able to do do this yourself • Through vein in arm	Needle under skin administering dose Takes less than 2 minutes
Challenges	Pain, burning, scarring at injection site→ making it difficult to find vein, infusion may take multiple attempts In addition to above, parents administering to child: parents giving painful treatment is difficult experience,	Burning sensation as medication injected
Risks	Significant risk of complication, including injury, infection and internal bleeding	No risks

ABR, annualised bleed rates; EAG, external assessment group; FVIII, factor VIII; FIX, factor IX; IV, intravenous; SC, subcutaneous; TTO, time trade off; Link to: main slides, Key issue: main slides, treatment disutility per administration