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

Technology appraisal committee D 5th December 2024

For Projector – redacted information

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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

Treatment pathway severe haemophilia A and B

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

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

Table: Treatment options for severe haemophilia A and B in people 12 years and over

Class	Treatments	Administration
Haemophilia A		
Non-factor (new)	Marstacimab	SC
Non-factor (current)	Emicizumab	SC
SHL FVIII	Octocog alfa, moroctocog alfa, simoctocog alfa, turoctocog alfa	IV every 2 days
EHL FVIII	Efmoroctocog alfa, rurioctocog alfa pegol, turoctocog alfa pegol	IV every 3-5 days
Haemophilia B		
Non-factor (new)	Marstacimab	SC
SHL FIX	Nonacog alpha	IV
EHL FIX	Eftrenonacog alpha, albutrepenonacog alpha, nonacogbeta pegol	IV

EHL, extended half-life, FVIII, factor VIII, FIX, factor IX, IV, intravenous, SC, subcutaneous, SHL, short half-life

Marstacimab (Hympavzi, Pfizer)

SC treatment for severe haemophilia A and B without inhibitors

Marstacimab information summary

Marketing authorisation	• For the 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 (EMA, CHMP granted September) • GB MA not granted yet; anticipated [redacted]
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

Key issues

EAG identified 7 key issues

Issue	Slide	ICER impact
1. Generalisability over the BASIS trial and its relevance to UK practice	14	Unknown
2. Information source for baseline annualised bleed rates and treatment efficacy	20	Large
3. Dose escalation of marstacimab	22	Unknown
4. Discontinuation of haemophilia treatments	23	Large
5. Dosing of factor prophylaxis	24	Large
6. Separate or pooled modelling of haemophilia types	26	Large for haemophilia B
7. Treatment disutility per administration	27	Large

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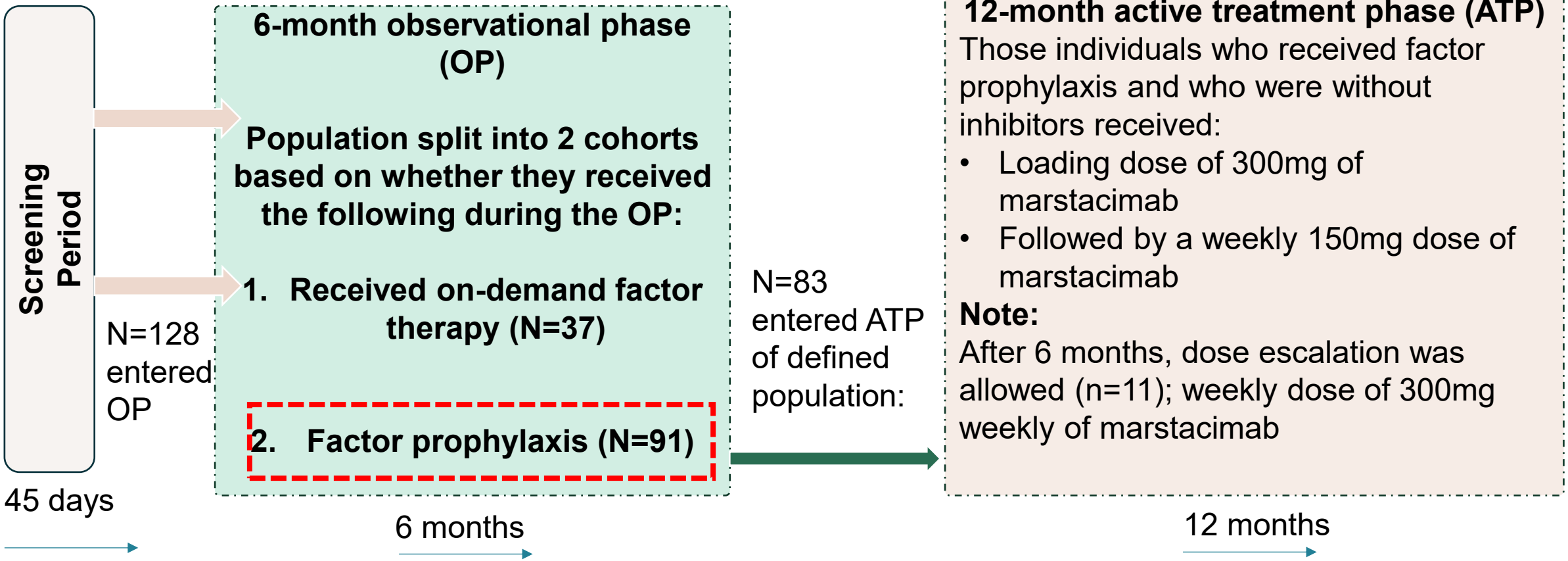
BASIS clinical trial design

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

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

Key clinical trials

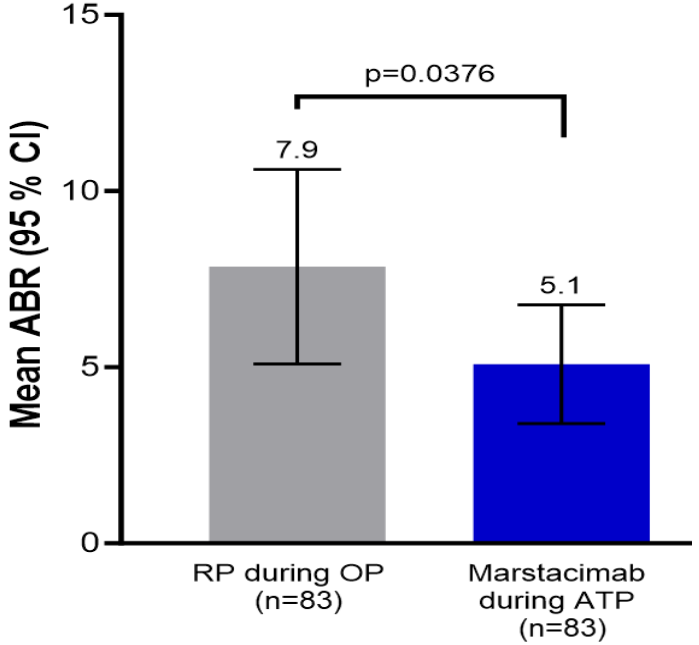
	BASIS (N= 128)	Open Label Extension (N=88)
Design	Phase 3, one-way, cross-over, multicentre	Phase 3, interventional, open-label extension
Population	• Men aged 12 to <75 years with severe haemophilia A or moderate/severe haemophilia B • Haemophilia A defined as <1% FVIII activity, moderate/severe Haemophilia 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]

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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]

Are the ITC methods the company used appropriate? Are the results reliable due to the differences in the trials?

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

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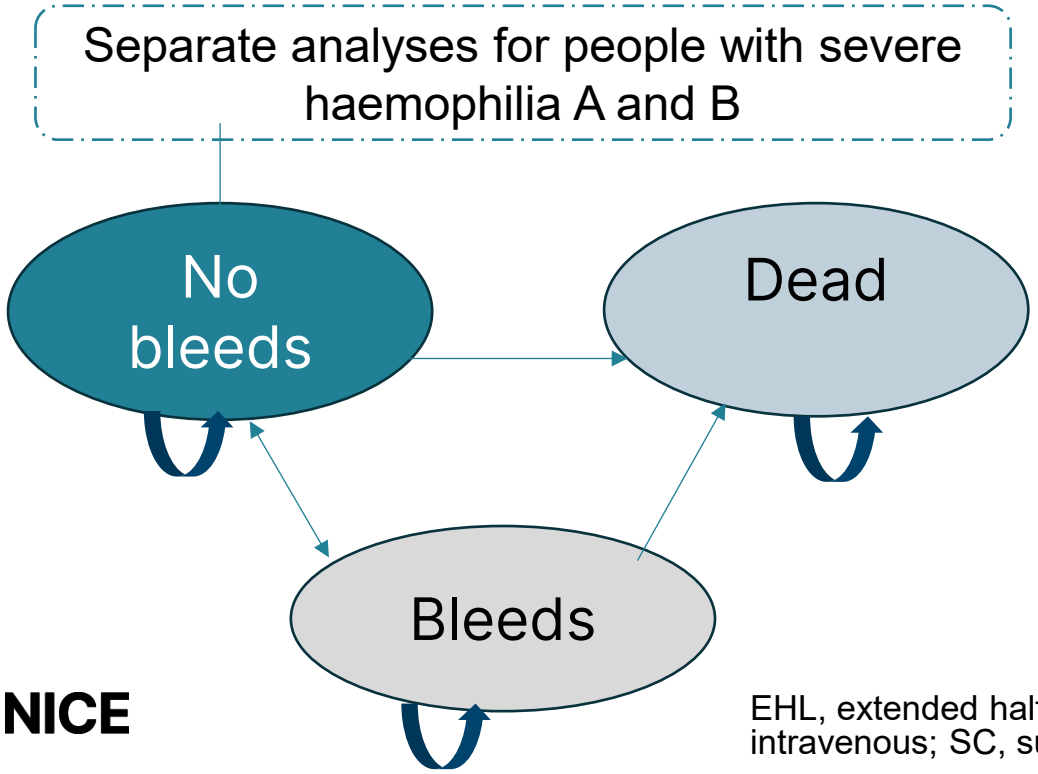
Company's model overview

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]	

Which are the preferred data sources for efficacy of prophylaxis treatment?

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]

Should the model include dose escalation beyond year 1 and, if so, for how long?

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?

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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

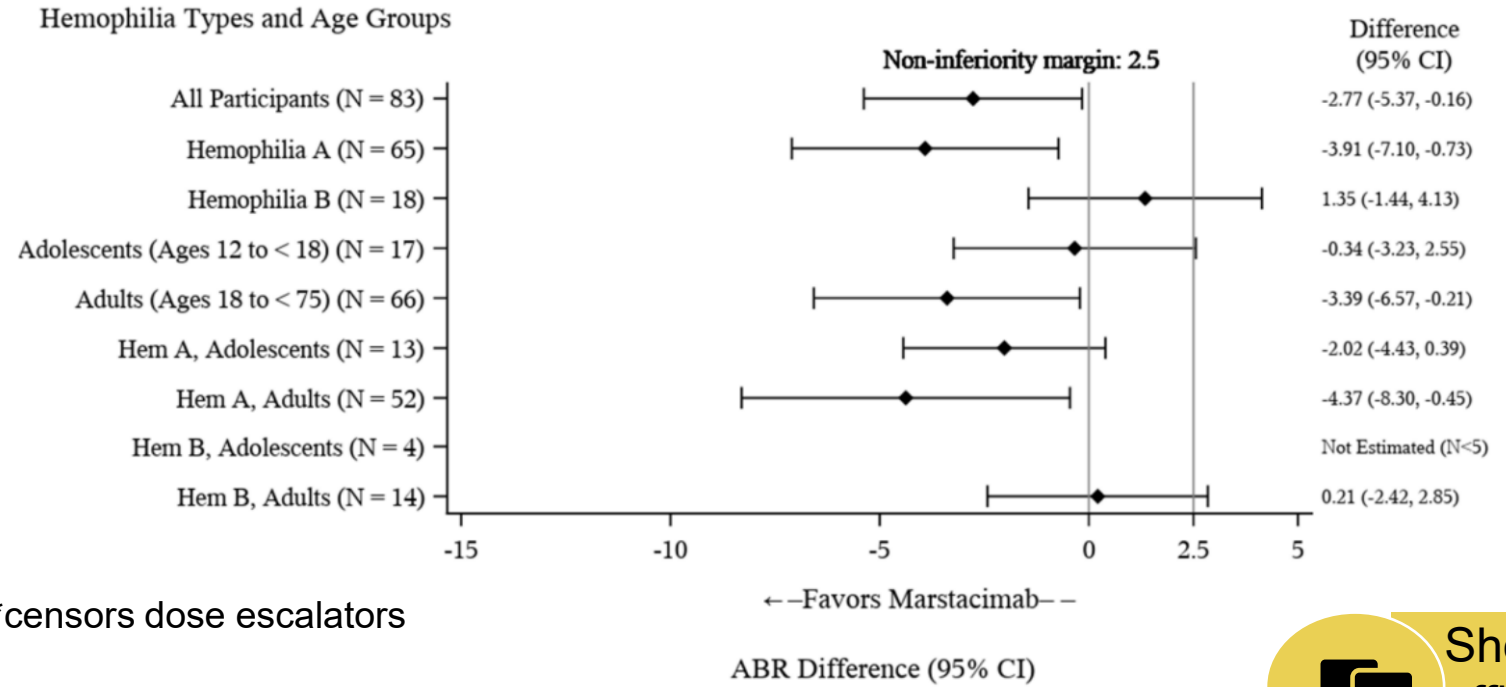
Key Issue: Separate or pooled modelling of haemophilia types

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

Summary of company and EAG base case assumptions

Main differences: source of efficacy of comparators, dose escalation modelled beyond one year, factor therapy dose estimates

Summary of company and EAG base case assumptions

EAG model change	Assumption	Company base case	EAG base case	
		Assumption	Assumption	Rationale
EAG01	Fixing errors	-	Corrected errors in company model	
EAG02	Dose escalation	Dose escalation in first year only based on observed dose escalation in 12 month ATP	Updated ATP dose escalation for discontinuers and added OLE dose escalation in year 2	Beyond 12 month time period of ATP, in the OLE, dose escalation continued
EAG03	Dosing of factor prophylaxis	Factor therapy dose estimates from summary of product characteristics	FVIII/FIX prophylaxis dose reduced to 75% of company base case	Factor therapy dose estimates in company model higher than UK average doses per person per year and higher than in BASIS

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ATP, active treatment phase; FVIII, factor VIII; FIX, factor IX; OLE, open label extension

Summary of company and EAG base case assumptions

Main differences: source of efficacy of comparators, dose escalation modelled beyond one year, factor therapy dose estimates

Summary of company and EAG base case assumptions

EAG model change	Assumption	Company base case	EAG base case	
		Assumption	Assumption	Rationale
EAG04	FVIII/FIX administered for bleeds	Assumption that FVIII/FIX treatment of bleeds is weighted average basket of FVIII/FIX	UKHCDO data, this increases the FVIII/FIX per bleed and assume FVIII/FIX used for bleeds same as prophylaxis	UKHCDO data more reflective of NHS
EAG05	Emicizumab dosing	As patients weight exceeds 100kg, their dose of emicizumab would continue to increase	Cap emicizumab dosing at the dose for a 100kg	EAG expert opinion that doses are capped to 100kg weight
EAG06	Hospital resource use estimate	Assumed resource use of average 2.12 non-IP visits and 0.29 IP admissions, yields average cost per bleed £545	Assume only 20% bleeds incur company hospital resource use	EAG expert: most bleeds managed at home without need for hospital visit

ATP, active treatment phase; EAG, external assessment group; ITC, indirect treatment comparison;UKHCDO, UK Haemophilia Centres Doctor's Organisation

Summary of company and EAG base case assumptions

Main differences: source of efficacy of comparators, dose escalation modelled beyond one year, factor therapy dose estimates

Summary of company and EAG base case assumptions

EAG model change	Assumption	Company base case	EAG base case	
		Assumption	Assumption	Rationale
EAG07	Disutility	Disutility of 0.16 applied for non-joint bleed, and 0.28 for joint bleed. Average time lasting for 4.5 days	Assume disutility for both joint and non-joint bleeds of 0.16, average time for 2.4 days	Data sources used by company for target joints, not joint bleeds.
EAG08(A)	UKHCDO efficacy data	Efficacy estimates of factor therapy taken from BASIS. Efficacy estimate of emicizumab from ITC.	Efficacy estimates of factor therapy/emicizumab from UKHCDO	UKHCDO data reflects NHS prophylaxis usage. BASIS did not include centres in UK.
EAG08(B)	Separate or pooled modelling of haemophilia types	Pooled clinical effectiveness estimates for haemophilia A and B - Scenario provided for separate clinical effectiveness estimates.	EAG base case uses pooled clinical effect estimates. Scenario for separate clinical effectiveness estimates for haemophilia A and B	Different clinical effectiveness ABR treat in haemophilia A and B. Different rate of dose escalation in BASIS.

ABR, annualised bleed rates; EAG, external assessment group, UKHCDO, UK Haemophilia Centres Doctor's Organisation

Summary of company and EAG base case assumptions

Main differences: source of efficacy of comparators, dose escalation modelled beyond one year, factor therapy dose estimates

Summary of company and EAG base case assumptions

EAG model change	Assumption	Company base case	EAG base case	
		Assumption	Assumption	Rationale
Additional scenarios	Market share data of FVIII/FIX basket	iQVIA market shares applied	Scenarios using UKHCDO and iQVIA market share. Further analysis with baskets split by EHL and SHL	UKHCDO market shares more reflective of NHS setting
	Discontinuation of haemophilia products	Discontinuation of marstacimab in year 1 only. No discontinuation rate for emicizumab	Discontinuation of marstacimab in year 1 only. No discontinuation rate for emicizumab. Scenario for no discontinuation of marstacimab	no data available for discontinuation of emicizumab-probable bias
	Disutility for treatment administration	Disutility per SC administration was 0.0002, disutility per IV 0.0003	EAG provide scenarios for which disutilities for treatment administration are halved and when they are not applied	Disutility estimates are provided at 4 decimal places, uncertainty around the values

EAG, external assessment group; EHL, extended half life; SC, subcutaneous; SHL, standard half life; UKHCDO, UK Haemophilia Centres Doctor's Organisation

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 base case: • Haemophilia A: Fully incremental marstacimab against emicizumab and FVIII basket of comparators weighted by iQVIA market share • Haemophilia B: Pairwise analyses vs basket of FIX comparators weighted by iQVIA market share	• Haemophilia A: marstacimab is dominated by emicizumab and against FVIII basket the ICER is >£1million per QALY gained • Haemophilia B: marstacimab is dominant against FIX basket
EAG base case: Comparisons same as company and additional scenario using UKHCDO usage data	• Haemophilia A: marstacimab is dominated by emicizumab and against FVIII basket the ICER is >£1million per QALY gained • Haemophilia B: Against FIX basket the ICER is >£1million per QALY gained [small reduction in ICER using UKHCDO usage data]
EAG scenario analyses	No EAG scenarios result in ICERs below £1 million per QALY gained

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

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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Key issues

EAG identified 7 key issues

Issue	Slide	ICER impact
1. Generalisability over the BASIS trial and its relevance to UK practice	14	Unknown
2. Information source for baseline annualised bleed rates and treatment efficacy	20	Large
3. Dose escalation of marstacimab	22	Unknown
4. Discontinuation of haemophilia treatments	23	Large
5. Dosing of factor prophylaxis	24	Large
6. Separate or pooled modelling of haemophilia types	26	Large for haemophilia B
7. Treatment disutility per administration	27	Large

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EAG, external assessment group

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

Supplementary appendix

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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]

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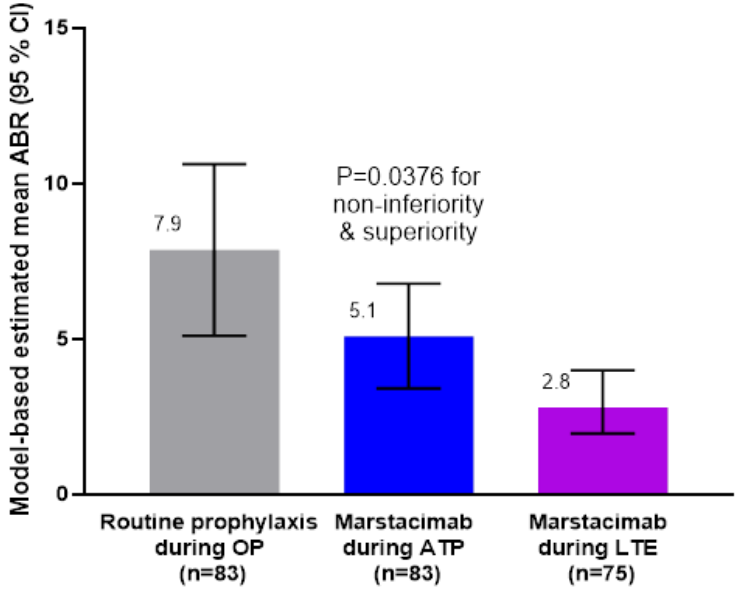
ABR, annualised bleed rates; ATP, active treatment phase; EAG, external assessment group; OP, observational phase; OLE, open label extension. Link to: main slides, BASIS key results

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]

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]

NICE *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 %)

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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