External Assessment Group's Critique of Company Comments on Draft Guidance following AC1 [ID6342]

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1 Committee draft recommendations and consultation responses

This section summarises elements of the Committee draft recommendation together with responses from one or more consultees:

- the company Pfizer,
- CSL Behring, the manufacturer of Idelvion EHL FIX, and
- the Haemophilia NI board as represented by William McKeown.

Where relevant these are followed by an EAG response.

Comments were also received from Novo Nordisk but these relate mainly to the wording of the draft guidance and are of limited relevance to what follows.

1.1 *Section 1: Recommendations*

Committee: Marstacimab is not recommended.

1.2 *Section 3.2: Treatment pathway*

Committee: Current treatments do not always prevent bleeds and are associated with administration challenges, particularly among the young and the elderly.

1.3 *Section 3.6: Generalisability of trial results*

Committee: The marstacimab trial, BASIS, had no UK sites. Patients in other countries may have a different prophylaxis history than UK patients which could mean much higher background bleed rates. UK patients typically have very low bleed rates.

Haemophilia NI: There is a need for robust trial design incorporating blinding, randomisation, appropriate comparator(s) and UK data where possible. Long term data is highly preferable. In the light of the infected blood scandal safety must be a priority.

1.4 *Section 3.7: Comparison with emicizumab*

Committee: The indirect comparison with emicizumab was highly uncertain but the available evidence did not suggest that the effectiveness of marstacimab is markedly different from that of emicizumab.

1.5 *Section 3.9: Modelled baseline bleed rates*

Committee: UKHCDO bleed rates for factor prophylaxis and for emicizumab are preferable to those of BASIS and the indirect treatment comparison with emicizumab.

Pfizer: The company revised base cases apply the UKHCDO bleed rates for factor prophylaxis and for emicizumab.

CSL Behring: Bleed rates among BASIS FIX patients are significantly higher than in other trials targeting the same patient groups and do not represent UK experience. UKHCDO bleed rates should be used for modelling.

1.6 *Section 3.10: Marstacimab dose escalation*

Committee: The proportion of marstacimab patients who will dose escalate from 150mg to 300mg is uncertain and could be higher or lower than that assumed by the company. Dose escalation may occur after the first year. The base case should include the EAG's year 2 dose escalation.

Pfizer: The company revised base cases apply the BASIS ATP (Active Treatment Phase) and OLE (Open Label Extension) dose escalation rates, in line with the EAG's year 1 and year 2 dose escalation. Company experts suggest that dose escalation is likely to be in line with BASIS but could be lower due to UKHCDO bleed rates for factor prophylaxis being lower than during the BASIS OP (Observation Phase).

EAG: The ATP saw [redacted] dose escalation among those remaining on marstacimab treatment. During the OLE a further [redacted] dose escalated. The OLE proportion eligible for dose escalation was [redacted] Over time dose escalation may exceed that observed during the BASIS ATP and OLE October 2023 Data Cut.

1.7 *Section 3.11: Treatment discontinuation*

Committee: Clinical experts suggest that around 10% of emicizumab patients discontinue their emicizumab. The company should submit UK relevant scenarios that explore discontinuations from emicizumab, including 10% discontinuing.

Pfizer: The company ACD base case applies the marstacimab 6.02% discontinuation rate to emicizumab as there is no reason for discontinuation rates to

differ. The company also provides a scenario of a 10% emicizumab discontinuation rate. The effect is relatively minor at list prices.

EAG: Committee views the relative effectiveness of marstacimab and emicizumab as uncertain but there was no evidence of a marked difference, as per section 1.4 above. In the light of this assuming the same discontinuation rate for emicizumab and marstacimab seems most reasonable for the base case. The effect may be larger when FVIII cPAS discounts are included.

1.8 *Section 3.12: Factor prophylaxis dosing*

Committee: The company method may have overestimated factor prophylaxis dosing compared to UKHCDO data, which is representative of NHS practice. The EAG base case that applies 75% of the company factor prophylaxis dosing is appropriate.

Pfizer: The original company base case applied the mid-point of the SmPC dose range per kg. In practice there is wide variation and some clinicians prescribe in excess of SmPC recommendations. UKHCDO data includes patients receiving on-demand regimens which will reduce the average dose. Dosing during BASIS was around 85% of the original company base case, so the company applies a 85% adjustment factor in its revised base case.

EAG: The data is reviewed in more detail in section 5.3.2 of the original EAG report.

The UKHCDO dosing data may include patients receiving on-demand treatment. As outlined in section 2.2.1 of the original EAG report it seems that some patients in BASIS may also have been receiving on-demand treatment.

The original EAG report noted that the original company base case dosing for FVIII was around [redacted] more than UKHCDO data. The proportion of adolescents in the UKHCDO data may have been too high, but even among adults the assumed dosing was [redacted] and [redacted] higher than UKHCDO data for SHL and EHL respectively. Given that there are adolescent patients, the EAG base case of a 75% adjustment factor may be too optimistic for FVIII. The EAG report notes that for FIX based upon UKHCDO data an adjustment factor of [redacted] may be more reasonable.

Given the above the EAG retains its base case 75% adjustment factor, also supplying scenarios of 70% and 80%.

1.9 *Section 3.13: Separate or pooled modelling of Type A and Type B*

Committee: Pooling bleed rates across Type A and Type B is acceptable. But there may be other differences between Type A and Type B, such as discontinuation rates. The company should provide further clarity on whether the model captures different treatment pathways and parameters for haemophilia A and B.

Pfizer: Other than the different types of treatment Type A and Type B are managed and monitored identically in the UK. The company revised base case differentiates treatment costs, administration disutilities and bleed treatment costs between Type A and Type B.

CSL Behring: Studies are available that summarise the molecular and clinical differences between Type A and Type B. Comparator therapies have conducted studies with extensive patient sample sizes, notably among Type B patients. It is unclear why similar considerations were not applied in BASIS. Pfizer should submit more evidence specific to Type B. When assessing cost effectiveness data specific to Type A and to Type B should be taken into account.

EAG: The model has the facility to differentiate all clinical effects between Type A and Type B, such as discontinuation rates, baseline bleed rates, bleed relative risks and dose escalation rates. If pooling baseline bleed rates for FVIII and FIX is acceptable to Committee it is unclear what other clinical parameters Committee thinks should or could be differentiated between Type A and Type B. The EAG will present results that differentiate baseline bleed rates and relative effectiveness between Type A and Type B.

1.10 *Section 3.14: Bleed disutilities*

Committee: Joint and non-joint bleeds may have different disutilities. No evidence was presented that measured these together. The company should provide further information and justification for their assumed disutilities. In the absence of further evidence, the EAG preference for a common disutility of 0.16 lasting 2.5 days should be applied.

Pfizer: The original company approach was aligned with TA989. But the company acknowledges the data uncertainties and aligns its revised base case with the original EAG base case.

EAG: The effects become relatively minor due to the low UKHCDO baseline bleed rates meaning that reducing bleeds further has only a small effect upon QALYs.

1.11 *Section 3.15: Administration disutilities*

Committee: There are patient benefits from subcutaneous administrations compared to intravenous infusions. The company evidence had limitations and may have overestimated these benefits. There was insufficient evidence to justify the company treatment administration disutilities.

Pfizer: The modelled QALY gains are small while the differences in treatment costs and to a lesser extent bleed costs are large. This means that the net health benefits are little affected by changes to the QALY gains and are driven by the differences in treatment costs. The company cites an additional paper as ranking the preferences of haemophiliacs for injection frequency and subcutaneous over intravenous infusion, frequency being more important than route of administration. The company retains its original treatment disutilities as sourced from Johnston et al.

EAG: The EAG has a preference for reporting net health benefits when a technology is estimated to dominate another, but reverts to the more usual ICER when this is not the case.

The EAG accepts that patients have a preference for fewer administrations and for subcutaneous over intravenous infusions. The company appears to suggest that there is a stronger preference for fewer administrations than for subcutaneous over intravenous infusions.

As reviewed in greater detail in section 5.2.2 of the original EAG report the EAG thinks that the vignettes of Johnston et al., funded by the manufacturer of emicizumab, are biased against intravenous infusion. Intravenous infusion is described as having "*significant risks of complications including injury, infections and internal bleeding*". The infusion time of "*up to 30 minutes*" may be too high. In time patients "*may be able to*" self-administer, when in practice it is highly probably. These appear designed to bias the analysis against intravenous infusion, and it should be borne in mind that the study was conducted among members of the general public who would not be expected to have any experience of factor infusions.

The EAG presents a brief literature review of relevant quality of life papers in Appendix 1 below. The EAG thinks that the studies with utility estimates provide some support to the values of Johnston et al., despite the vignettes of Johnston et al. being biased. Some caution needs to be exercised due to the quality of life values being estimated from the general population rather than haemophiliacs. The discrete choice experiments suggest that administration frequency is not as important as other treatment attributes in determining patient preferences between treatments, and may be relatively unimportant.

1.12 *Section 3.17: Committee preferred modelling assumptions*

Committee: The base case should apply the following:

1. UKHCDO bleed rates for factor and for emicizumab
2. Year 2 dose escalations for marstacimab
3. Factor prophylaxis dosing 75% of company base case
4. Pooled clinical effectiveness estimates for Type A and Type B
5. A common bleed disutility of 0.16 for 2.5 days
6. Fix model errors identified by EAG
7. UKHCDO factor use for bleeds
8. Cap emicizumab dosing at that for a patient weight of 100kg
9. Only 20% of bleeds incur hospital resource use
10. Apply UKHCDO market share data for factor prophylaxis

Pfizer: The company revised base case applies 1, 2, 4, 5, 6, 7, 8 and 9. Under 3 it applies 85% factor prophylaxis dosing compared to its previous base case. Under 10 it updates the market share data to be from the IQVIA 2024 data, and further increases emicizumab use to 70% through extrapolation. When combining Type A and Type B the company assumes [redacted] Type A and [redacted] Type B.

Committee: The following analyses should be presented by the company:

1. Emicizumab discontinuations, including a 10% discontinuation rate

2. Further justify the evidence on bleed disutilities
3. Further justify the evidence on administration disutilities
4. Further explore the treatment pathways and model parameters split by Type A and Type B.

Pfizer:

1. Emicizumab discontinuations are modelled, in the revised base case assuming them to be equal to those of marstacimab.
2. The company adopts the EAG approach.
3. An additional paper is summarised as showing a patient preference for fewer administrations and for subcutaneous over intravenous infusion, the former being the more important.
4. Clinical parameters are not differentiated by Type A and Type B.

1.13 *Section 3.21: Uncaptured benefits*

Committee: No uncaptured benefits were identified in the economic modelling.

Pfizer: Subcutaneous administration compared to intravenous infusions also has a carer benefit.

Haemophilia NI: There is no subcutaneous option for haemophilia type B. Haemophilia NI also expresses concerns about those with inhibitors and rare factor disorders but since these are outside the license the EAG has not presented them.

EAG: The 2022 NICE methods guide section 4.3.17 states that "*Evaluations should consider all health effects for patients, and, when relevant, carers. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a* ***substantial effect*** [EAG emphasis] *on carer's health-related quality of life and how the technology affects carers*." How substantial the carer effect needs to be is not defined.

The company base case estimates lifetime patient gains due to administrative disutilities of [redacted] QALYs for FVIII, [redacted] QALYs for FIX and a loss of [redacted] QALYs compared to emicizumab. Annual gains are estimated to be [redacted] QALYs for FVIII, [redacted] QALYs for FIX and a loss of [redacted] QALYs compared to emicizumab. These need to be read alongside the EAG concerns about the source of the administrative

disutilities as summarised in section 1.11 above. EAG expert opinion suggests that the vast majority, 90% to 95%, of adult patients self-administer, and that children begin training in aspects of self-administration from a very early age. The proportion of patients requiring carer assistance is likely to be low.

2 Additional Pfizer model revisions

The company has made a number of minor revisions to the EAG base case clinical effect estimates. The EAG broadly accepts these with the exception of the FIX/FVIII ABR for the BASIS OP which is used to calculate the relative effectiveness of marstacimab. The company prefers the all patient value while the EAG prefers the value for the subset who entered the BASIS OLE, this being the more relevant figure for extrapolation. More detail is provided in Appendix 2 below. The effects of these changes are minor, as outlined in Table 7 below.

The company has updated the market share data to be from 2024 sources.

Table 1: Company revised market shares: FIX

	2023		2024	
	IQVIA	UKHCDO	IQVIA	UKHCDO
Advate	[redacted]	28%	[redacted]	25%
Refacto AF	[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%

Table 2: Company revised market shares: FIX

	2023		2024	
	IQVIA	UKHCDO	IQVIA	UKHCDO
BeneFix	[redacted]	23%	[redacted]	19%
Alprolix	[redacted]	47%	[redacted]	51%
Idelvion	[redacted]	15%	[redacted]	14%
Refixia	[redacted]	15%	[redacted]	15%

The company further argues that the emicizumab market share among those with severe type A haemophilia continues to increase. The UKHCDO 2024 report shows it increasing to 59%[1], with the company citing an additional presentation at the November 2024 UKHCDO annual meeting as estimating it to be between 60% and 70%. The company applies a 70% market share for emicizumab.

The EAG thinks that the extrapolation to 70% is unreasonable. The absolute rate of increase is slowing over time and only increased by 6% between 2022/23 and 2023/24. The EAG does not have access to the November 2024 data so applies the 2023/24 59% market share, also providing a scenario of a 64% market share.

When pooling Type A and Type B results, the company assumes [redacted]% Type A and [redacted]% Type B. The EAG has previously pooled assuming all patient switch to marstacimab, so 83% Type A and 17% Type B, which is also consistent with the company approach which pools emicizumab and FVIII. The EAG retains this approach. This does highlight that pooling results across Type A and Type B is questionable and it may be better to consider their cost effectiveness estimates separately. A further argument for considering their cost effectiveness estimates separately is that they are wildly different.

3 COST EFFECTIVENESS RESULTS

3.1 *Cost basis*

The results of this report only include the marstacimab PAS. This has been increased from [redacted] to [redacted] resulting in annual costs of [redacted] for 150mg and [redacted] for 300mg. First year dose escalation results in a weighted average annual cost of [redacted] while second year dose escalation results in a weighted average annual cost of [redacted] It should be borne in mind that during the BASIS OLE considerably more patients were eligible for dose escalation than escalated during the OLE, around [redacted] of those who remained on 150mg at the start of the OLE. Should [redacted] of all marstacimab patients dose escalate over time the weighted average annual cost increases to [redacted]

There are commercial agreements in place for all comparators with the exception of Novo Eight which is no longer part of the MPSC framework. Other treatments are

[1] Figure 7, Page 41

costed using list prices and where appropriate the publicly available CMU EMIT prices. A confidential cPAS appendix that summarises and applies the comparator price discounts has been supplied.

3.2 *Company base case cost effectiveness results*

The revised company base case results in the following costs and benefits for haemophilia type A.

Table 3: Company base case: Costs and QALYs: Type A

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
Advate	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]
Adynovi	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 4.

Table 4: Company base case: Net Costs, net QALYs and cost effectiveness: Type A

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	..	..	..	..	..
Advate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adynovi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The revised company base case for haemophilia type B is presented below.

Table 5: Company base case: Costs and QALYs: Type B

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 6.

Table 6: Company base case: Net Costs, net QALYs and cost effectiveness: Type B

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	..	..	..	..	..
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pooling results assuming 70% emicizumab among Type A and [redacted] Type A and [redacted] Type B results in net health benefits of [redacted] QALYs at a willingness to pay of £20,000 and [redacted] QALYs at a willingness to pay of £30,000.

A variety of scenario analyses are presented in Appendix 1 of the company consultation response.

4 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

4.1.1 EAG model revisions

The EAG revised base case differs from the company revised base case in the following.

- EAG01: 75% FVIII/FIX dose adjustment rather than 85%
- EAG02: UKHCDO market share data rather than IQVIA
- EAG03: Minor revisions to clinical inputs

Table 7: EAG model changes effects upon NHB of marstacimab: WTP £20,000

Comparator	Section	Emicizumab	FVIII	FIX
Company BC	3.2	[redacted]	[redacted]	[redacted]
EAG01	1.8	[redacted]	[redacted]	[redacted]
EAG02	2	[redacted]	[redacted]	[redacted]
EAG03	2	[redacted]	[redacted]	[redacted]
EAG01-EAG03		[redacted]	[redacted]	[redacted]

The revised EAG base case results in the following costs and benefits for haemophilia type A.

Table 8: EAG base case: Costs and QALYs: Type A

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
Advate	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]
Adynovi	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 9.

Table 9: EAG base case: Net Costs, net QALYs and cost effectiveness: Type A

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Advate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adynovi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pooling across emicizumab and FVIII results in estimates of net health benefits of [redacted] QALYs at a willingness to pay of £20,000 and [redacted] QALYs at a willingness to pay of £30,000.

The revised EAG base case for haemophilia type B is presented below.

Table 10: EAG base case: Costs and QALYs: Type B

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 11.

Table 11: EAG base case: Net Costs, net QALYs and cost effectiveness: Type B

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	-	-	-	-	-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pooling across Type A and Type B results in estimates of net health benefits of [redacted] QALYs at a willingness to pay of £20,000 and [redacted] QALYs at a willingness to pay of £30,000.

4.1.2 EAG scenario analyses

The EAG supplies the following scenario analyses:

- SA01: Reducing the administration disutilities to 50% and 0% of their base case values.
- SA02: Varying the FVIII/FIX dose adjustment from 75% to 70% and 80%.
- SA03: Applying the year 2 dose escalation percentage to subsequent years until 50% of marstacimab patients have dose escalated.
- SA04: 10% emicizumab discontinuation rate
- SA05: emicizumab 64% Type A market share
- SA06: Type A and Type B specific bleed rates, treatment effectiveness and dose escalation.

Table 12: EAG scenarios: NHB for WTP £20,000: QALY gains

Comparator	Emic.	FVIII	Type A	Type B	All
EAG BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01a: Admin disutility 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01b: Admin disutility 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SA02a: FVIII/FIX 70% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA02b: FVIII/FIX 80% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA03: Dose escalation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA04: 10% emic. disc.	[redacted]	..	[redacted]	..	[redacted]
SA05: 64% emic. market	..	..	[redacted]	..	[redacted]
SA06: Type specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: EAG scenarios: NHB for WTP £30,000: QALY gains

Comparator	Emic.	FVIII	Type A	Type B	All
EAG BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01a: Admin disutility 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01b: Admin disutility 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA02a: FVIII/FIX 70% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA02b: FVIII/FIX 80% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA03: Dose escalation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA04: 10% emic. disc.	[redacted]	..	[redacted]	..	[redacted]
SA05: 64% emic. market	..	..	[redacted]	..	[redacted]
SA06: Type specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 Appendix 1: Literature review of quantitative studies of administrative quality of life values.

The EAG has provided an extensive review of the estimates of the disutilities of subcutaneous administration and intravenous infusion of Johnston et al. in section 5.2.2 of its original report. It views the health state vignettes as biased against intravenous infusion. There are also concerns around the poor reporting of the statistical analyses and the disutility estimates only being reported to one significant figure.

Okkels et al. (2024), sponsored by Novo Nordisk, undertook a time trade off exercise through an online survey among members of the UK, Canadian and USA male general public. Long form health state descriptors were initially presented to participants but for most of the survey short form summaries were presented. Unfortunately, the short form summaries are largely not presented. Haemophilia was not mentioned.

Respondents who would not trade off any survival or all their future survival were asked why. Respondents who stated that ethical or religious beliefs led to their trading behaviour or that they did not understand the question were excluded from the analysis. The reason for excluding those with ethical or religious reasons is unclear. Excluding those who said they did not understand the question appears to exclude noise from a particular direction so may bias the analysis. Around a fifth of respondents were excluded though not solely for these reasons.

Within one block of the three blocks of surveys treatments could be characterised as having no injections site reactions or always having an injection site reaction within 48 hours, this being mild rash, redness, bruising, itching or discomfort. It is unclear how or to which health states the injection site reactions were associated with. Most vignettes appear to have assumed no injection site reactions.

The prefilled pen for subcutaneous injection is described as taking 1 minute, the vial with single use syringe for subcutaneous injection is described as taking 5 minutes while single use syringe for intravenous infusion is described as taking 10 minutes.

The EAG thinks that the vignettes of Okkels et al. are both reasonable and superior to those of Johnston et al.

The utility gains of Okkels et al. can be compared with those implied by the estimates of Johnston et al., assuming that prefilled and single use syringe for subcutaneous injection involve the same disutility of -0.0002. For monthly prefilled subcutaneous versus weekly prefilled subcutaneous Okkels et al. estimate a utility gain of 0.012 compared to 0.008 for Johnston et al. For monthly prefilled subcutaneous versus weekly intravenous Okkels et al. estimate a utility gain of 0.049 compared to 0.013 for Johnston et al.

Okkels et al. also raise the possibility of prefilled subcutaneous resulting in gains compared to single use syringe subcutaneous. While not entirely unambiguous it appears that monthly prefilled subcutaneous compared to monthly single use syringe subcutaneous resulted in a utility gain of 0.031.

It is tempting to assume a constant disutility per administration to infer disutilities per administration for use in the modelling. But this results in estimates that are inconsistent with one another, suggesting that a constant disutility per administration is invalid.

Despite the apparent bias in the vignettes of Johnston et al. the estimates of Okkels et al. provide some support to the estimates of Johnston et al. They also suggest that there could be additional gains from prefilled subcutaneous such as marstacimab compared single use syringe subcutaneous such as emicizumab.

Carlsson et al. (2017), funded by Sobi Swedish Orphan Biovitrium AB, performed a time trade off study among 184 Swedish haemophiliacs and 1,233 members of the Swedish general population. This rated four health states:

1. injection frequency every other day, can participate in physical activity, 1 – 2 bleeds per year
2. injection frequency every other day, cannot participate in physical activity, 1 – 2 bleeds per year
3. injection frequency every fifth day, can participate in physical activity, 1 – 2 bleed per year
4. injection frequency every fifth day, can participate in physical activity, 5 - 6 bleed per year

Injections are described as taking 20-30 minutes including preparation. EAG expert opinion suggests that 10-25 minutes might be a more usual average for FVIII/FIX plus an additional 5 minutes for Haemtrack recording. Haemophiliac respondents rated each of the four health states considerably higher than members of the general public, with an increment of around 0.15. The differences between mean health states were more consistent, haemophiliac respondents suggesting a differences between (1) and (3) of 0.3 while the general public suggested a difference of 0.4. Assuming a constant disutility per intravenous injection, further regression results of Carlsson et al. suggests a haemophiliac estimates of a -0.00026 decrement and -0.00036 from the general public, which are broadly aligned with the estimate of Johnston et al.

Turning to discrete choice experiments, Furlan et al. (2015), sponsored by Biogen, conduct what appears to be a similar survey of patient preferences as that of the Lu et al. (2024) abstract cited by Pfizer in its consultation response. Haemophilia patients, 89 type A and 32 type B, were asked about their likelihood of switching between different treatment scenarios, these varying by administration frequency, number of bleeds, vials per infusion, diluent volume, whether the device did or did not premix and manufacturer. The manufacturer could be either new to haemophilia and unfamiliar to the patient, or one the patient was familiar with both it and its haemophilia products. Frequency of infusion was the most important attribute, 47%, followed by breakthrough bleeds, 25%, and manufacturer, 19%. Whether the device premixed was relatively unimportant at around 3% which contrast with the results of Okkels et al.

Chiou et al. (2025) in a series of discrete choice experiments among 51 Taiwanese haemophiliacs found type of treatment, Factor VIII vs non-Factor VIII, and risk of thromboembolic events to be the most important determinants of preferences. This was followed by whether treatment was subcutaneous or intravenous. Administration frequency and bleed rates followed, then long term evidence on safety being available and monitoring requirements.

Fifer et al. (2020), sponsored by Roche Products, also conducted discrete choice experiments among 56 haemophilia patients, treatment attributes including time per administration, < 5 minutes, 5-15 minutes and > 5 minutes, and administration frequency, daily, weekly, fortnightly and monthly. Other attributes were bleed

frequency, whether the treatment could be used as rescue treatment, risk of developing inhibitors, side effects, severe side effects, injection site reactions, storage requirements and prescription collection/delivery options. In contrast to Furlan et al. the frequency of administration and time taken for administration are of 0% relative importance. Bleeds, side effects, injection site reactions, use as rescue therapy and storage determining patient choices.

Naraine et al. (2002) in an unsponsored study used the standard gamble to estimate quality of life values for haemophilia health states among 30 health adults, 30 parents of children with haemophilia and 28 adults with haemophilia. The health state vignettes encompassed bleeds which varied with the treatment received: on demand therapy, FVIII weekly, FVIII twice weekly and FVIII every other day. Median utilities for each health state are presented rather than means, with those of the general population being the lowest. In contrast to parents of children with haemophilia and adults with haemophilia, the median responses from the general population were non-monotonic; i.e. they did not steadily decline over the health states. The difference between the best and the worst health state for the general population was 60% higher than that of parents of children with haemophilia and of adults with haemophilia.

Naraine et al. in their conclusions note that subjects with experience of haemophilia generated higher median scores and that this mirrors other results such as those of Boyd et al. This also mirrors the results of Carlsson et al. reviewed above. Naraine et al. suggest that parents of children with haemophilia and adults with haemophilia have experienced some elements of the scenarios involved and so were less willing to take the risk of death within the standard gamble; i.e. having experience of haemophilia health states including varying treatment frequencies meant they viewed them less negatively than the general population. This may give some pause for thought about estimates from members of the general population, such as those of Johnston et al. and Okkels et al.

The EAG thinks that the studies that provide utility estimates provide some support to the values of Johnston et al., despite the vignettes of Johnston et al. being biased. The discrete choice experiments in general suggest that administration frequency is not as important as other treatment attributes and may be relatively unimportant.

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6 Appendix 2: EAG review of company changes to clinical inputs

	Company	EAG	Description
AJBR Proportion (Cell B6)	[redacted]	[redacted]	When cell F98 is corrected to [redacted] company aligns with EAG of [redacted]
Year 1 Rate Ratio (Cell B13)	[redacted]	[redacted]	Company estimate comes from raw data rather than EAG estimates from a combining different sources and rounded numbers. Company estimate likely correct.
Year 2 Rate Ratio (Cell C13)	[redacted]	[redacted]	EAG calculation of long term rate based on OLE population only, excluding those who drop out, whilst use pre-OLE estimate for all people, including those who do not reach OLE. As estimate is relevant for OLE period and population, EAG maintain their preference.