Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende etranacogene dezaparvovec til behandling af hæmofili B

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. etranacogene dezaparvovec
2. Forhandlingsnotat fra Amgros vedr. etranacogene dezaparvovec
3. Ansøgers endelige ansøgning vedr. etranacogene dezaparvovec

CSL Behring

May 24, 2024

Response document: Medicinrådets anbefaling vedr. etranacogene dezaparvovec (Hemgenix) til behandling af hæmofili B

The Danish Medicine Council (DMC) has assessed the gene therapy etranacogene dezaparvovec (Hemgenix) for the treatment of moderate severe and severe Haemophila B in adult patients with no history of factor IX inhibitors. Please find CSL Bering response on the DMC assessment below.

I. Implications of the updated durability analysis using 36-months data

The inclusion of the updated durability analysis, encompassing a 36-month follow-up period, not only affirms the findings of the initial 24-month analysis, but also enhances the extrapolation of durability. This extended duration of observation allows for a more comprehensive understanding of the long-term impacts of Hemgenix on patient outcomes and resource utilization, which are pivotal factors in health economic assessments. CSL Behring emphasizes that the overall uncertainties in the health economic analysis are lowered, further supporting the case for introducing Hemgenix for Danish patients.

II. Regarding the DMC scenario analyses on durability in Figure 10

A key driver of the cost-effectiveness results, as well as incremental cost results, is the duration of the treatment effect of Hemgenix. It is therefore appropriate to explore how sensitive the results are to alternative durability assumptions. Conducting these exercises, it is however important to acknowledge that they should be based on biologically and clinically relevant assumptions.

In the pivotal HOPE-B trial, participants treated with Hemgenix sustained FIX activity levels with a mean endogenous FIX activity of 38.6 IU/dL (SD; min, max = ±17.8; 4.8-80.3) at 36 months [A]. However, studies prove that the effects of rAAV based gene therapy can be maintained over long periods of time. The three first patients to receive Hemgenix have now been followed for 48 months after treatment [B]: Mean ± SD FIX activity was stable at 45 ± 2.76%. The durability of treatment effect for Hemgenix can also be inferred by the stable factor levels seen at 6-year follow-up of the phase I/II study on the Hemgenix predecessor AMT-060 [C, D]. Further, it is now more than 12 years since the first haemophilia B patients received AAV based gene therapy targeting hepatocytes in the scAAV2/8-LP1-Hfixco gene therapy study at the St Jude Hospital [E]. Follow-up data presented at the ASH meeting in December 2023 [F] demonstrated still stable and therapeutic FIX activity levels. In addition, Bayesian and Frequentist linear mixed models predicted that more than 80% of Hemgenix patients would remain free from prophylactic FIX replacement products 25.5 years post-infusion [G]. Based on these studies, Hemgenix therapeutic effect can be conservatively expected to have long-term durability of at least 10 years, with sustained, and in most cases normal or near normal FIX activity.

Furthermore, the assumption for the shape the curve would take after a hypothetical landmark point is of key importance. We challenge the DMC on this point regarding the scenario analyses. From a clinical and biological perspective, a more realistic evolution of FIX levels after a landmark point would be a gradual decline, rather than an immediate linear drop to 0%. Scenario analyses would greatly benefit from considering clinically plausible changes in FIX levels after the landmark point.

III. Regarding DMC risk mitigation considerations

CSL Behring wants to emphasize that the submitted cost-utility analysis in the base case takes a conservative approach already. CSL Behring notes that in the revised cost-utility analysis, DMC has taken an even further conservative approach. CSL Behring believes that pushing this very conservative scenario is unnecessary and detrimental to Hemgenix in comparison to Refixia in the cost-effectiveness (CE) results. For example, in the by us submitted analysis:

- Adverse events (AEs) for Refixia have not been included in the cost-utility analysis; we took this conservative approach since it was not possible to obtain relevant AE data for Refixia. If costs for AEs related to Refixia had been included, as CSL Behring suggested in the initial application, Hemgenix treatment would have proved even more cost-saving than in the base-case analysis.
- CSL Behring has not included increased risk of complications during surgery and increased costs for pre- and post-operative treatment as DMC also mentions in the report. If these aspects had been included in the base case cost-utility analysis, the comparison vs. Refixia would have been even more favorable to Hemgenix.

The suggested outcomes-based risk sharing agreement addresses many of the concerns and conservative scenarios identified by the DMC regarding Hemgenix. CSL Behring underscores that the cost-utility analysis submitted is already conservative in the base case.

With this context in mind, the proposed outcomes-based risk sharing agreement offers a rational solution to the concerns raised by the DMC. By linking reimbursement to actual patient outcomes, this agreement mitigates the potential risks of overly conservative assumptions in the health economic analysis. It ensures that the economic evaluation is based on real-world effectiveness data and addresses the concerns raised by the DMC in their conservative approach. By incorporating real-world data and outcomes, this agreement provides a more accurate assessment of the economic value of Hemgenix compared to Refixia, reducing uncertainties, and enhancing the decision-making process.

IV. CSL Behring does not agree with DMC evaluation of bleeding rate (ABR and AjBR) between Hemgenix and Refixia

We agree that MAIC analyses do not have the power to prove differences between treatments that randomized head-to-head studies have. For this reason, we would like to point out that the MAIC analysis only supplements findings in the phase III HOPE-B study. HOPE-B compared Hemgenix to current standard of care (SOC) (mostly EHL) prophylaxis in developed countries, including patients from Denmark. In the study, following a patient on SOC before treatment was used as comparison for the results after treatment. In the HOPE-B study significantly lower ABR, AsBR and AjBR were found even when including the two non-responders, one who received only 10% of the planned dose and the other who had a very high NAb titer. There is no solid evidence that Refixia is more effective than any other current SOC to reduce ABR. In fact, we consider Refixia treatment as belonging to current SOC, and patients on Refixia prophylaxis were eligible for the HOPE-B study. In conclusion, with the MAIC results in combination with the HOPE-B results CSL Behring claims that Hemgenix has better ABR and AjBR than Refixia.

If demonstrating an improvement in ABR of 3 is seen as not relevant, nothing can ever prove better efficacy than a treatment resulting in an ABR of 3. We suggest aiming higher and find that stance hard to reconcile with the overall goal of haemophilia treatment in Denmark being zero bleeds [H, I].

Further we would like to point out that the comparison regarding number of patients with zero bleeds in HOPE-B and Paradigm 4 for patients with 40 IU/kg weekly dosing underestimates the difference because different observation periods were used. HOPE-B patients with zero bleeds during 18 months are compared to Paradigm 4 patients with varying observation times that could be as short as 3 month. Longer observation time increases the likelihood that patients will have bleeds. For example, about 75% of patients in HOPE-B had zero bleeds during months 19-24 after Hemgenix dosing. Note also that only treated bleeds were counted for Refixia while “zero bleeds” for Hemgenix means no bleeds, treated or not. Finally, there is a bias in recruiting patients from earlier Refixia studies who wished to continue with Refixia for Paradigm 4. Patients with good results are more likely to continue with Refixia.

V. Additional comments

CSL Behring will closely monitor Hemgenix for safety for many years, but it should be noted that also Refixia is currently under additional monitoring from EMA. Further, that Refixia was approved in 2017 and that just as for Hemgenix, there may still be discovered presently unknown long term safety issues.

Regarding the DMCs description on how the discount rate is applied in the health economic model, CSL Behring would like to emphasize that the discount rate is applied from year 0 as described in the submitted dossier. In the preliminary report it is stated that discount rates are applied from year 1, while CSL Behring agrees that discount rates are effectively applied from year 1, technically the function applies also to year 0.

References:

[A] Pipe S, van der Valk P, Verhamme P, et al. Blood 2023;142(Supplement 1):1055-1055.
[B] von Drygalski A, Pipe S, Giermasz A, et al. Haemophilia 2024;30(Supplement 1):53-53.
[C] Miesbach W, Meijer K, Coppens M,et al. Blood 2018;131(9):1022-1031.
[D] Miesbach W, Meijer K, Coppens M, et al. Haemophilia 2024;30(Supplement 1):19-20.
[E] Nathwani AC, Tuddenham EGD, Rangarajan S, et al. N Engl J Med 2011;365(25):2357–65.
[F] Reiss UM, Davidoff AM, Tuddenham EGD, et al. Blood 2023;142(Supplement 1):1056-1056.
[G] Shah J, Kim H, Sivamurthy K, et al. Curr Med Res Opin 2022;39(2):227-237
[H] Nordic haemophilia guidelines. 2024. Available: www.nordichemophilia.org [Accessed May 2024]
[I] Medicinrådet. 2022. Medicinrådets lægemiddelrekommandation og behandlingsvejledning for hæmofili B. 1.1.

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24.05.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	19.06.2024
Leverandør	CSL Behring
Lægemiddel	Hemgenix (etranacogene dezaparvovec)
Ansøgt indikation	Behandling af svær og moderat svær hæmofili B (medfødt faktor IX-mangel) hos voksne patienter uden faktor IX-inhibitorer i anamnesen.
Nyt lægemiddel / indikationsudvidelse	Revurdering, ATMP

Prisinformation

Amgros har forhandlet følgende priser på Hemgenix (etranacogene dezaparvovec). I forhandlingen har Amgros modtaget to pristilbud, som begge er betinget af en anbefaling:

Pristilbud 1: Flad rabat

Tabel 1: Forhandlingsresultat flad rabat

Lægemiddel	Styrke	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Hemgenix	1 behandling	21.500.850	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Hemgenix, indkøbes det til AIP.

Pristilbud 2: [redacted]

[redacted]

[redacted]

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, hvis Medicinrådet anbefaler Hemgenix til den ansøgte indikation. Aftalen er baseret på Amgros' standardaftale for ATMP'er, der rummer forhold for bl.a. logistik flow, persondata og kvalitet. Aftalen vil gælde hurtigst muligt efter Medicinrådets anbefaling, når disse forhold er forhandlet på plads. Amgros forventer, at aftalen kan starte senest den 01.10.2024 og gælde 4 år frem. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Øvrige aftaleforhold for pristilbud 2

[redacted]

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på sammenlignelige lægemidler inkluderet i Medicinrådets vurderingsrapport.

[redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
Sverige	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering

Konklusion

[redacted]

Medicinrådet

Application for the assessment of Hemgenix (etranacogene dezaparvovec) for treatment of haemophilia B

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Hemgenix
Generic name	etranacogene dezaparvovec
Marketing authorization holder in Denmark	CSL Behring AB
ATC code	B02BD16
Pharmacotherapeutic group	Blood coagulation factors
Active substance(s)	Hemgenix (etranacogene dezaparvovec) is a gene therapy medicinal product that employs a non-replicating, recombinant adeno-associated virus-based vector serotype 5 (AAV5) containing a codon-optimized coding DNA sequence for the human coagulation Factor IX (FIX) variant R338L (FIX-Padua) under the control of a liver-specific promoter (LP1).
Pharmaceutical form(s)	Concentrate for solution for infusion (sterile concentrate). For single-dose intravenous (IV) infusion only.
Mechanism of action	Following single IV infusion, Hemgenix preferentially targets liver cells, where the vector DNA will reside almost exclusively in episomal form. Subsequent to transduction, Hemgenix directs long-term liver-specific expression of FIX-Padua protein. As a result, Hemgenix ameliorates the deficiency of circulating FIX procoagulant activity in patients with haemophilia B (PWHB).

Overview of the pharmaceutical	
Dosage regimen	The dose of Hemgenix is a single dose of 2 x 10^{13} gc/kg body weight (bw) or 2 mL/kg bw, administered as an IV infusion after dilution with 0.9% sodium chloride solution (normal saline). The patient`s dose should be calculated as advised below: Hemgenix dose (in mL)=patient's bw (in kg) × 2 Hemgenix can be administered only once.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency [EMA])	Hemgenix is indicated for the treatment of severe and moderately severe haemophilia B (congenital FIX deficiency) in adult patients without a history of FIX inhibitors.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	N/A
Packaging – types, sizes/number of units, and concentrations	Each mL of etranacogene dezaparvovec (Hemgenix) contains 1 x 10^{13} genome copies (gc). Each vial contains an extractable volume of 10 mL of concentrate for solution for infusion, containing a total of 1 x 10^{14} genome copies.
Orphan drug designation	Yes

Abbreviations: bw, Body weight; gc, Genome copies; Kg, Kilograms; NAb, Neutralizing antibody.
Source: CSL Behring (2022c)

2. Abbreviations

Abbreviation	Description of abbreviation
AAV	Adeno-associated virus
AAV5	AAV vector serotype 5
AAV8	AAV vector serotype 8
AB	Annualized bleeding
ABR	Annualized bleeding rate
AE	Adverse event
AFP	Alpha-fetoprotein
AIC	Akaike information criteria
AIR	Annualized infusion rate
AjBR	Annualized joint bleeding rate
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ASAT	Aspartate aminotransferase
AsBR	Annualized spontaneous bleeding rate
AST	Aspartate aminotransferase
AT	Anti-thrombin

Abbreviation	Description of abbreviation
ATC	Anatomical therapeutic chemical
AUP	Pharmacy retail price
BIC	Bayesian information criteria
BIM	Budget impact model
BMI	Body mass index
BNF	British National Formulary
BPI	Brief pain inventory
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Controlled Attenuation Parameter
CCC	Comprehensive care center
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CFB	Change from baseline
CGT	Cell and gene therapy
CHESS	Cost of haemophilia across Europe – a Socioeconomic Survey
CI	Confidence interval
COVID	Coronavirus disease 2019
CRD	Chronic respiratory disease
CRD	Centre for Rare Disorders
CRP	C-reactive protein
CSF	Case report form
CSR	Clinical study report
CT	Clinical trial
CVD	Cardiovascular disease
DKK	Danish kroner
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
DRG	Diagnosis-related group
EAHAD	European Association for Haemophilia And Allied Disorders
ED	Emergency department
EHC	European Haemophilia Consortium
EHCCC	European Haemophilia Comprehensive Care Centre
EHL	European Haemophilia Treatment Centre
EHTC	European Haemophilia Treatment Centre
EMA	European Medicines Agency
EMR	Electronic medical record
EPAR	European public assessment report
EQ-5D	European QolL-5 dimensions
ESS	Effective sample size
EU	European Union
EUHANET	European Haemophilia Network
EUR	Euro
EVF	Erythrocyte volume fraction
FAS	Full analysis set
FIX	Factor IX
FP	Fusion protein
FVI	Factor VI
FVIII	Factor VIII
FXI	Factor XI
gc	Gene copy
HA	Haemophilia A
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia activities list
HAS	Haute Autorité de Santé
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma

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Abbreviation	Description of abbreviation
HCP	Healthcare provider/personnel
HCRU	Health care resource utilization
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HJHS	Haemophilia joint health score
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Health care resource use
HS	Health state
HSUV	Health state utility values
HTA	Heath technology assessment
HTC	Haemophilia treatment center
ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial hemorrhage
ICU	Intensive care unit
IL	Interleukin
IMP	Investigational medicinal product
INN	International non-proprietary names
IPAQ	International physical activity questionnaire
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
IRR	Infusion-related reactions
ISTH	International Society on Thrombosis and Haemostasis
IT	Information technology
ITC	Indirect treatment comparison
ITI	Immune tolerance induction
ITR	Inverted terminal repeat
IU	International units
IV	Intravenous
KOL	Key opinion leader
LAM-PCR	Linear-amplification-mediated polymerase chain reaction
LN	Limit of normal
LOD	Limit of detection
LP	Liver promoter
LS	Least squares
LY	Life year
MAIC	Matching-adjusted indirect comparison
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP	Monocyte chemoattractant protein type 1
MCV	Mean corpuscular volume
MD	Mean difference
MDT	Multi-disciplinary team
MESH	Medical Subject Heading
MIMS	Monthly Index of Medical Specialities
MRI	Magnetic resonance imaging
MSKUS	Musculoskeletal ultrasound
NA	Not applicable/available
NAb	Neutralizing antibody
NCPE	National Centre for Pharmacoeconomics
NCT	National clinical trial
NE	Not evaluable
NHC	Nordic Haemophilia Council
NHP	Non-human primates
NICE	National Institutes for Health and Care Excellence

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Abbreviation	Description of abbreviation
NIS	National inpatient sample
NMA	Network meta-analysis
NR	Not reported
OLE	Open-label extension
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase chain reaction
PD	Plasma derived
pdFIX	Plasma derived Factor IX
PEG	Polyethylene-glycol
PICOS	Population, intervention and comparators, outcomes and study design
PK	Pharmacokinetics
PP	Per-protocol
PPPY	Per person per year
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PROBE	Patient-reported outcomes, burdens and experiences
PRP	Pharmacy retail price
PSA	Probabilistic sensitivity analysis
PSP	Pharmacy selling price
PT	Prothrombin time
PTSD	Posttraumatic stress disorder
PTSS	Posttraumatic stress syndrome
PWH	People/patients with haemophilia
PWHB	People/patients with haemophilia B
QALY	Quality-adjusted life years
QoL	Quality of life
rFIX	Recombinant Factor IX
RNA	Ribonucleic acid
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SHL	Standard half-life
SLD	Study level data
SLD	Study level data
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMD	Standardized mean difference
SmPC	Summary of product characteristics
SOC	Standard of care
SSC	Scientific and Standardization Committee
SUP	Superiority
TEAE	Treatment-emergent adverse event
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TSD	Technical Support Documents
TTO	Time-Trade-Off
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	US dollar
VAS	Visual analogue scale

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Abbreviation	Description of abbreviation
VAT	Value added tax
WFH	World Federation of Haemophilia
WHO	World Health Organisation
WPAI	Work productivity and activity impairment
WT	Wild-type
WTP	Willingness to pay

3. Tables

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4. Figures

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5. Summary

CSL Behring is seeking a positive recommendation in Denmark for the gene therapy candidate Hemgenix (etranacogene dezaparvovec) for the treatment of severe and moderately severe haemophilia B (congenital factor IX [FIX] deficiency) in adult patients without a history of FIX inhibitors. Hemgenix is an adeno-associated virus five (AAV5)-based gene therapy administered as a one-time treatment for haemophilia B patients. This reimbursement dossier is based on results from the pivotal phase III HOPE-B study.

5.1 Population

Haemophilia B is a rare X-chromosome linked congenital bleeding disorder characterized by insufficient activity levels of coagulation FIX (FIX). Lack of functional FIX leads to reduced thrombin generation and thus impaired coagulation and increased bleeding tendency. Haemophilia B generally affects males and the majority (70%) of haemophilia cases are inherited, while approximately 30% result from a spontaneous mutation (Mannucci and Tuddenham, 2001, Srivastava et al., 2020).

Despite the introduction of FIX-replacement therapies and the use of prophylactic treatment, bleeds still occur, sometimes with dire consequences, including bleeding into joints, muscles, and internal organs, resulting in joint diseases and intracranial hemorrhage (ICH) (Srivastava et al., 2020, Nordic Haemophilia Guidelines, 2022). Therefore, a treatment that would eliminate clinical and subclinical bleeding completely by stabilizing FIX activity levels and achieving an annualized bleeding rate (ABR) approaching zero is needed for treatment of haemophilia B (Gringeri et al., 2014).

In Denmark, there are approximately 40 patients with severe or moderate haemophilia B (Nordic Haemophilia Council, 2015). Currently, those with severe or moderately severe haemophilia B are primarily treated prophylactically with FIX concentrates (Nordic Haemophilia Guidelines, 2022). But out of these patients, Hemgenix is only indicated in adults without a history of FIX inhibitors. Furthermore, Hemgenix is not recommended to patients with more pre-existing neutralizing AAV5 antibodies than at a titer of 1:678, and contraindications include hypersensitivity, active infections and known advanced hepatic fibrosis, or cirrhosis (CSL Behring, 2022c). It is also expected that some eligible patients will prefer remaining on factor replacement therapy. [redacted]

5.2 Intervention

Hemgenix is a recombinant AAV5 (rAAV5) vector carrying a gene cassette with the FIX-Padua variant of a codon-optimized human FIX complementary DNA under the control of a liver-specific promoter (Von Drygalski et al., 2019). The clinical development program supporting Hemgenix includes three studies in adult patients (≥18 years) with moderately severe or severe haemophilia B (FIX activity ≤2% of normal).

HOPE-B is an ongoing phase III, open-label, single-dose, multicenter, multinational study evaluating the efficacy of Hemgenix in adult patients (n=54) with severe or moderately severe haemophilia B (ClinicalTrials.gov, 2021a). The primary endpoint of HOPE-B trial is comparison of ABR for all bleeding episodes between Hemgenix and FIX prophylaxis therapy used in the lead-in period. Several secondary endpoints are studied in the HOPE-B trial including FIX activity levels after intervention, use of annual FIX replacement therapies, spontaneous and joint bleeding episodes, number of adverse events (AEs) and patient reported outcome (PRO) measures (ClinicalTrials.gov, 2021a).

5.3 Outcomes

In the pivotal HOPE-B trial, months 7-24 post treatment, Hemgenix provided effective bleed control for study participants, including statistically significant reductions in the ABR (from 4.18 to 1.51, a decrease of 64%; p=0.0002) and in the number of bleeds requiring treatment (from 3.64 to 0.99, a decrease of 73%; p=0.0001) (Pipe et al., 2022b). Furthermore, a significant reduction in mean annualized spontaneous bleeding rate (AsBR) (from 1.52 to 0.38, a decrease of 75%; p=0.0005) and a significant reduction in the annualized joint bleeding rate (AjBR) (from 2.35 to 0.46; p<0.0001, a decrease of 80%) as compared with the lead-in period with FIX prophylaxis therapy (Pipe et al., 2022b).

Of the 54 participants who received Hemgenix, one participant with a markedly higher AAV5 neutralizing antibodies (NAbs) titer (1:3,212) and one participant who received only a partial vector dose (due to an infusion-related reaction [IRR]) did not express FIX-Padua or discontinue FIX prophylaxis. All the other 52 participants (96.3%), discontinued and remained free of continuous FIX prophylaxis from Day 21 to Month 24, including 20 participants with baseline AAV5 NAb titers up to 1:700 (Pipe et al., 2022b). A rapid and sustained significant increase in mean endogenous FIX activity level to 36.66% was observed at 24 months ($p<0.0001$) (Pipe et al., 2022b). According to the latest clinical data from HOPE-B trial, Hemgenix continued to be well tolerated with no treatment-related serious adverse events (TRSAEs) after 24 months follow-up.

5.4 Comparator

Currently, recombinant FIX (rFIX) replacement therapies are the most commonly used treatments for haemophilia B in Denmark (Medicinrådet, 2022). In the [redacted], it was agreed to use Refixia as the main comparator in the current submission. [redacted]

5.5 Durability

A recent update on the durability of Hemgenix and AMT-060 (i.e. a gene therapy product with the same vector and cassette design as Hemgenix but using a wild type FIX transgene) confirms that the therapeutic effect can be projected to have long-term durability by demonstrating stable FIX activity levels without significant decrease after two and three years, respectively, for patients in the phase III and IIb Hemgenix studies and after five years in patients who received AMT-060 (Miesbach, 2022, Von Drygalski et al., 2022, Pipe et al., 2022a). In a recent publication Bayesian and Frequentist linear mixed models were used to predict FIX activity levels for up to 25.5 years. Models predicted that more than 80% of patients would remain free from prophylactic FIX replacement products 25.5 years post-infusion (Shah et al., 2023). The durability analysis has been updated to include data from 36 months of follow up. The addition of the updated analysis provides important confirmation of the initial 24-month analysis and further strengthens the extrapolation of durability.

5.6 Health economic evaluation

The health economic model structure is developed using Microsoft Excel. The economic model follows a Markov model structure and is based on bleeding events. The four Markov states consist of patients experiencing no bleeds, non-joint bleeds, joint bleeds, or death in any cycle. The results of the health economic evaluation shows that Hemgenix is cost-effective compared to FIX prophylaxis treatment with lower costs and higher quality adjusted life years (QALY) gain. FIX prophylaxis is represented by Refixia (nonacog beta pegol) as the comparator. The results are robust over a range of scenario analyses undertaken. Incremental costs are mainly driven by cost offsets for prophylactic treatment for patients treated with the gene therapy. The intervention was found to be cost saving for different FIX level threshold values at which patients would be switched over to prophylactic treatment. In terms of quality of life (QoL), the disutility of infusion associated with administration of Refixia accounts for the largest impact.

6. The patient population, the intervention and choice of comparator(s)

6.1 The medical condition and patient population

6.1.1. Haemophilia B

Haemophilia B is a rare X-chromosome linked congenital bleeding disorder characterized by insufficient activity levels of coagulation FIX. Lack of functional FIX leads to reduced thrombin generation and thus impaired coagulation and increased bleeding tendency. Haemophilia B generally affects males on the maternal side, while females with haemophilia B are rare and often remain asymptomatic. The majority (70%) of haemophilia cases are inherited, while approximately 30% result from a spontaneous mutation (Mannucci and Tuddenham, 2001, Srivastava et al., 2020).

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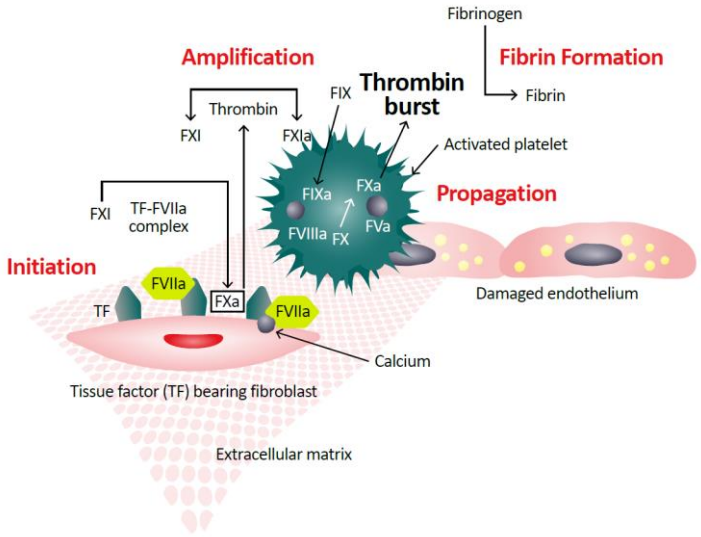
6.1.2. Etiology

Haemophilia B is caused by insufficient activity levels of coagulation FIX, which arises from mutations in the *F9* gene, located on the long arm of the X chromosome at Xq27 (Castaman and Matino, 2019, Srivastava et al., 2020). Disruptions in the *F9* gene that can cause haemophilia B include point mutations, deletions, insertions, duplications and complex changes (Goodeve, 2015). Factor IX is a blood clotting factor, which together with other clotting factors is involved in the activation of a series of steps in the coagulation cascade resulting in the activation of platelets and the formation of a primary blood clot to stop bleeding (Bolton-Maggs and Pasi, 2003). Without FIX, bleeding would ensue because of the insufficient levels of activated factor X (FXa) and thrombin (Figure 1).

Figure 1: The coagulation cascade



Abbreviations: FIX, Factor IX; FVIIa, Active Factor VIIa; FXa, Active Factor Xa; FXI, Factor XI; FXIa, Active Factor XIa; FVa, Active Factor Va; TF, Tissue Factor; TF-FVIIa, Tissue Factor-active coagulation Factor VIIa.
Adapted from Ho and Pavey (2017).

6.1.3. Incidence and prevalence

Based on the 2018 annual global report by the WFH, a total 102 patients were diagnosed with haemophilia B in Denmark (World Federation of Hemophilia, 2018) (Table 1). A 2012 Nordic Haemophilia Council (NHC) survey reported the same number of PWHB (Nordic Haemophilia Council, 2015). Based on the report, 30 patients (29%) had severe form of the disease while nine (8%) and 63 patients (61%) were diagnosed with moderate and mild haemophilia B, respectively (Nordic Haemophilia Council, 2015). According to the Danish Medicines Council (DMC) haemophilia B treatment guideline, in 2016 there were 29 haemophilia B patients treated prophylactically in Denmark (Medicinrådet, 2018). This figure in line with recent Nordic multi-center studies showing that approximately 95% of Nordic patients with severe and 40% of those with moderate haemophilia B are treated prophylactically with FIX concentrates (Kihlberg et al., 2021, Måseide et al., 2020). Hemgenix is indicated for the treatment of severe and moderately severe haemophilia B in adult patients without a history of FIX inhibitors. As shown in Table 2, [redacted]

Table 1: Prevalence in the past five years

Year	2018	2019	2020	2021	2022
Prevalence in Denmark	102	-	-	-	-
Global prevalence	34,289	31,997	33,076	37,998	-

Source: World Federation of Hemophilia (2018), World Federation of Hemophilia (2020), World Federation of Hemophilia (2019), World Federation of Hemophilia (2021).

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Table 2: Estimated number of patients treated

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	X	X	XXX	X	XXX

Source: (CSL Behring, 2022d)

6.1.4. Disease presentation

Severe haemophilia usually manifests in the first few months of life, while mild or moderate haemophilia can present later in childhood or adolescence (Mehta and Reddivari, 2022, Clausen et al., 2014). Classic symptoms of haemophilia are joint bleeds that usually affect knees, ankles, and elbows, with subsequent development of joint disease (haemophilic arthropathy), chronic pain and disability. In addition to joint bleeding, bleeding can occur in other areas, such as muscles, mucous membranes, the gastrointestinal tract, and the central nervous system, which can cause life-threatening and permanent damage (Zimmerman and Valentino, 2013, Srivastava et al., 2020).

In haemophilia patients, joint bleeds (hemarthrosis) account for 70% to 80% of all bleeding episodes (Castaman and Matino, 2019, Srivastava et al., 2020). Joint trauma further increases the likelihood of developing hemarthrosis, especially in patients with severe haemophilia, in which more than 90% of bleeding episodes occur in joints (Simpson and Valentino, 2012).

The risk and severity of bleeding manifestations in haemophilia correlates with the degree of coagulation factor deficiency (Burke et al., 2023, Srivastava et al., 2020). People with severe haemophilia (FIX activity of <1% of normal; 1 international unit [IU]/dL) experience spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge. Moderate haemophilia (FIX activity 1-5% of normal) is associated with prolonged bleeding with minor trauma or surgery and occasional spontaneous bleeding. In mild haemophilia (FIX activity 5-40% of normal), spontaneous bleeding episodes are rare and severe bleeding normally occurs only in connection with trauma or surgery (Srivastava et al., 2020). Haemophilia related morbidity worsen with disease severity, as spontaneous bleeding events are more common with severe than with mild haemophilia.

6.1.5. Diagnosis

Haemophilia B usually presents as bleeding after minor trauma or as spontaneous bleeding. Bleeding symptoms often correlate with the degree of residual factor activity level, which is useful to classify haemophilia severity further (Kloosterman et al., 2022, Konkle et al., 1993, Burke et al., 2023). For a definitive haemophilia B diagnosis, the most commonly used technique is activated partial thromboplastin time (APTT)-based one-stage clotting assays for detecting FIX deficiency and thus, disease severity. The age at diagnosis and the frequency of bleeds are generally related to the FIX activity level (Konkle et al., 1993).

In Denmark, suspected haemophilia patients are examined, and the tests are done at one of the two specialized treatment centers in Copenhagen and Aarhus.

6.1.6. Burden of disease

6.1.6.1 Clinical burden

Mortality

In Europe, the mortality rate of patients with severe haemophilia has been reported as being 2.7 times higher than that of the general population, with a reduction in life expectancy of up to 15 years (Darby et al., 2007). A recent Norwegian study investigated the mean age at the time of death among PWH, who were registered in two independent national registries including the Norwegian Cause of Death Registry (NCoDR), and the patient registry at Centre for Rare Disorders (CRD). The findings showed that despite the improvement in life expectancy between 1986 and 2018, still there was a decreased mean age at the time of death of 56.8 years in the NCoDR and 58.6 years in the CRD data, compared with

73.9 years in the general male population (Skjefstad et al., 2020). A recent study from 2021 assessed the rates of mortality among PWH including patients from Denmark, Sweden, Finland, and Norway. The study reported a higher rate of mortality among PWH when compared to controls in Denmark (14% versus 10%, OR of 1.44, 95% CI: 1.16, 1.78) (Steen Carlsson, 2021).

A serious complication in the treatment of PWHB is the development of NAbs (inhibitors) against FIX, which usually occurs within the first 20 FIX exposure days with a reported historical prevalence of up to 15% in severe patients (Kihlberg et al., 2021). Presence of FIX inhibitors is associated with an increased risk of bleeding, and associated complications, due to loss of function of the infused FIX. Patients with FIX inhibitors have limited evidence-based treatment options, including immune tolerance induction (ITI), FIX desensitization, or initiating a high-dose/high-frequency FIX prophylaxis therapy regimen until tolerance is achieved (Srivastava et al., 2020).

Excluding HIV and viral hepatitis, PWH have higher mortality over time compared with the general population, with the most common causes of death being related to malignancies and hemostatic defects. One Swedish study linked PWH in Sweden who were registered with the national haemophilia centers and/or the Patient Registry, born before 2009, and alive in 1968 with the cause of death, migration-, and medical birth registries (Lövdahl et al., 2013). The hazard ratio (HR) (95% confidence interval [CI]; p-value) for all-cause mortality compared with controls was 1.7 (1.3, 2.2, p<0.001) and 8.2 (3.2, 20.8; p<0.001) for patients with severe haemophilia when patients with HIV and/or viral hepatitis were excluded (Lövdahl et al., 2013).

The leading cause of death related to bleeding is ICH, especially among patients with severe haemophilia and PWH with FIX inhibitors (Konkle et al., 1993, Witmer et al., 2011). PWH are between 20 and 50 times more likely to develop ICH than those without haemophilia, with a reported prevalence of between 2.7-12% (Witmer et al., 2011). Severe disease, the presence of a FIX inhibitor, prior ICH, and young age are some of established risk factors for ICH (Witmer et al., 2011). In a Norwegian study, ICH was found to be the main cause of death in 22.7% of PWH who were registered in two independent Norwegian registries between 1986 to 2018 (Skjefstad et al., 2020).

Joint health

Joint bleeds can lead to swelling, long-term inflammation and acute pain in the affected area. Bleeding in a target joint – defined as a joint that has three or more spontaneous bleeds within a 6-month period – is a major complication in PWH, with deterioration of the joint leading to reduced joint flexion and mobility (Rodriguez-Merchan, 2010). Recurrent and prolonged hemarthrosis causes damage to the joints and increases the risk of chronic synovitis and degenerative arthritis. Patients with repeated bleedings are also susceptible to develop osteoporosis and arthropathies (Knobe and Berntorp, 2011). While on-demand and FIX prophylaxis therapy treatments have helped reduce joint damage, patients with moderate and severe haemophilia continue to be at risk of joint morbidity and bleeds, notably joint bleeds (Davis et al., 2019).

Kihlberg et al. characterized treatment outcomes in persons with severe haemophilia B in the Nordic region, with a focus on joint health. The study, B-NORD, was a multicenter, cross-sectional, observational study conducted in six haemophilia treatment centers (HTCs) in Denmark, Finland, Norway, and Sweden (Kihlberg et al., 2021). Despite the high prophylaxis frequency of 95%, 37% of the PWHB reported at least one joint bleed during the prior 12 months and 44% reported non-joint bleeding episode(s). Moreover, 35% of patients, with median age of 56 (Q1-Q3: 40–66), had undergone joint surgery. Knee arthroplasty was the most common procedure followed by ankle arthrodesis (Kihlberg et al., 2021).

Comorbidities

People/patients with haemophilia B (PWHB) have a higher comorbidity burden than the general population. Patients with haemophilia (PWH) are also at increased risk of hypertension, cardiovascular disease (CVD), and low bone density. Studies in the United States (US) and Netherlands have found that the most common associated diagnoses in discharges of PWH were hypertension (28.1%) and central line infections (15.2%) (Goel and Krishnamurti, 2012, van de Putte et al., 2013). A retrospective study in Portugal found that 98% of PWHB had at least one comorbidity, with the majority having between one and four (Arias, 2021). The most common conditions identified in PWHB were hepatitis C virus (63%),

arthropathy (62%), hypertension (43%), dyslipidemia (38%), HIV (25%), gastrointestinal diseases (20%), obesity (20%), CVD (12%), and cancer (12%) (Arias, 2021).

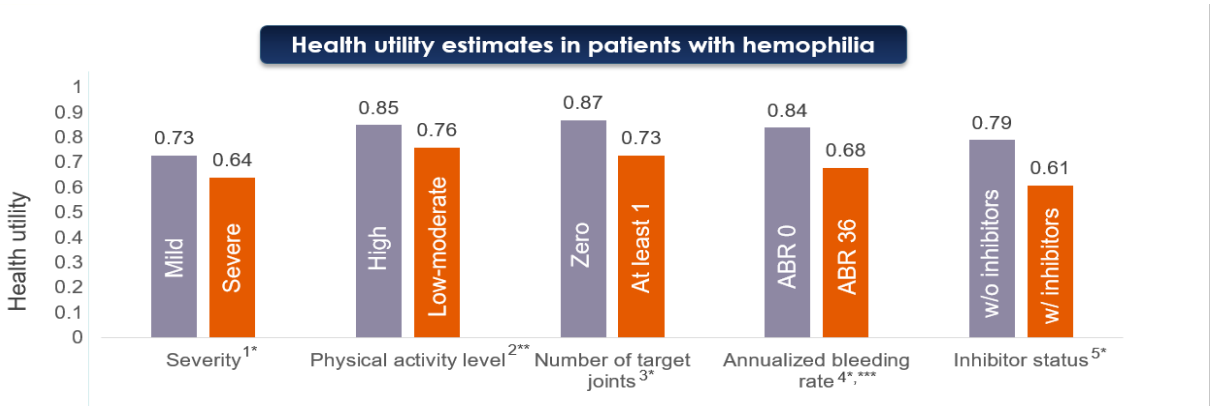
Obesity and overweight status also present a significant disease burden for PWH as a result of reduced mobility due to joint inflammation, muscle dysfunction, and haemophilic arthropathy (Wilding et al., 2018).

6.1.6.2 Humanistic burden

Haemophilia is associated with a reduced QoL due to symptoms including pain, functional impairment, anxiety and depression, while bleeding events and progression of joint disease is associated with a reduction in work productivity and an increase in healthcare resource use (Berntorp et al., 2022, Booth et al., 2018, Steen Carlsson et al., 2022, Burke et al., 2021b, Buckner et al., 2018).

Frequent injections are commonly used to achieve higher trough levels of FIX, yet sufficient and stable hemostatic protection may still not be reached. Despite burdensome and time consuming intravenous (IV) injections, bleeding can lead to increased pain and other injection-related complications (such as problems with venous access including risk of infection and blood clot formation) as well as increased healthcare costs (Valentino et al., 2014, Bauer, 2015, Berntorp, 2009). This can lead to an increased treatment burden for the patient, caregivers, and healthcare providers. In addition, it could have a negative impact on QoL, including limiting the patient's mobility and social interaction, which can be particularly difficult for younger and active patients (Bauer, 2015). Figure 2 demonstrates that the mean health utility score (scale from 0-1) for those with severe disease is lower (0.64 versus 0.73) compared to those with mild disease (Camp et al., 2016, Kritikou et al., 2018, Hoxer et al., 2019, Niu et al., 2014). Similarly, a recently published multinational and observational study (B-Natural study) showed that patients with severe haemophilia B have worse QoL scores when compared to patients with mild and moderate haemophilia B.

Figure 2: Health utility estimates in PWH



Note: Health utilities for 'severity' were derived using the TTO method; for all the other categories, by EQ-5D.
Figure legend: *Patients with both haemophilia A and B; **PWHB; ***ABR was extrapolated based on reported monthly bleed rate
Abbreviations: ABR, Annualized bleeding rate; EQ-5D, EuroQol five-dimension scale; PWHB, Patients with haemophilia B; TTO, Time-Trade-Off.
Source: Niu et al. (2014), Kritikou et al. (2018), Hoxer et al. (2019), Camp et al. (2016).

Beyond the physical burden, the collective experience of living with haemophilia has substantial effects on mental well-being, particularly among young people living with the condition, within whom signs of major depressive disorder are common (Gater et al., 2011, Ghanizadeh and Baligh-Jahromi, 2009, Steen Carlsson et al., 2022). A recent Nordic study analyzed the results of EuroQoL five-dimension 5-level (EQ-5D-5L) questionnaires completed by PWH and treaters from Denmark, Sweden, and Finland. The study demonstrated that pain, depression, and anxiety negatively impacted the health-related quality of life (HRQoL) of PWH (Steen Carlsson et al., 2022). The study reported depression or anxiety due to haemophilia among 35%, 26%, and 16% of patients with severe, moderate, and mild disease, respectively (Steen Carlsson et al., 2022). However, only two out of five haemophilia treatment centers, which were interviewed during the study, agreed that their patients' anxiety/depression is adequately treated (Steen Carlsson et al., 2022). Another study also demonstrated that for PWH, depressive symptoms are associated with more urgent hospital visits due to haemophilia, more bleeding episodes and affected joints, as well as low self-esteem and worse QoL (Kodra et al., 2014).

If recurrent injury occurs in a joint, the joint may need to be replaced, which can be a relatively demanding operation and could also lead to postoperative complications with long-term rehabilitation and chronic pain as a result. Thus, the QoL among individuals with haemophilia is impaired, mainly due to pain and disability associated with haemophilic arthropathy (Srivastava et al., 2020). In the European Chess study (CHESS II), 292 PWH A and B responded to a QoL instrument (EuroQol five-dimension [EQ-5D] questionnaire) (Booth et al., 2018, Burke et al., 2022). The mean HRQoL score for patients with one problem with joint (PJ) and without joint damage was 0.65 and 0.81 ($p<0.001$), respectively, showing that joint injuries have a significant negative impact on the patient's QoL. The study reported even more negative impact on HRQoL score (mean score of EQ-5D: 0.58) in patients experiencing two or more joint problems (≥2PJs) (Burke et al., 2022). Moreover, results from the same study showed that 76% of PWHB experience chronic pain (Burke et al., 2021b).

Long-term impairments in mobility and functional status (as a result of recurrent bleeding episodes) can limit the participation of PWH in daily life activities (Von Mackensen, 2007, Blamey et al., 2019, Goto et al., 2019). Studies also show that adults with haemophilia are less likely to work full-time, and some form of activity limitation is more common among PWH compared to the general population (Plug et al., 2008). Lost productivity influences the financial status of patients and can lead to reduced capacity to work and a reduced ability to participate in society (Burke et al., 2021b). In the CHESS II study, PWH experienced overall work productivity loss which was captured using work productivity and activity impairment questionnaire (WPAI-GH) (Burke et al., 2022).

Frequent IV injections are associated with several complications and reduced QoL (Wells et al., 2019). Patient-reported benefits of reduced infusion frequency and longer duration of the factor level include an increased ability to participate in physical activities and sports, better vein health, less time to schedule and administer the factor concentrate, as well as a reduced impact on daily work and school and improved emotional well-being. Extended dose intervals and reduced bleeding frequency through the maintenance of high factor levels can thus improve QoL in patients and their caregivers (Carcao, 2014, Schwartz et al., 2018).

Although limited data on caregiver burden in the context of haemophilia exist today (Buckner et al., 2018), the available literature suggests that caregiver's burden could be improved as patient outcomes improve and treatment burden decreases (Johnston et al., 2021). An effective treatment for haemophilia would both improve patients' clinical profiles (e.g. the ABR) and reduce caregivers' (perceived) burden (Schwartz et al., 2020).

6.1.6.3 Economic burden

Haemophilia is associated with extensive healthcare resource needs throughout life. Although, haemophilia B is a rare disease, the healthcare resources required are associated with a high aggregated cost, including large direct and indirect costs (Gater et al., 2011).

Direct healthcare resource costs in addition to the cost of current FIX treatment itself, which accounts for approximately >90% of the direct costs, are healthcare visits, medical equipment, laboratory tests, other haemophilia-related medication, support in the home and compensation for care recipients. It has been shown that increasing disease severity is associated with higher annual healthcare costs (Sawyer, 2020, Burke et al., 2021a, Burke et al., 2021c). In addition, the results of several studies have shown that costs of managing severe and moderately severe haemophilia B over a ten-year period amounts to a mean cost of ~€2.4m Euro (EUR) in Europe for patients treated with FIX prophylaxis (Sawyer, 2020, Burke et al., 2021a, Burke et al., 2021c). Joint damage (haemophilic arthropathy) involves a high financial burden and is one of the most cost-driving complications of haemophilia as it entails high costs both for the intervention and rehabilitation (Chen, 2016). Additionally frequent injections of coagulation factors (up to 150 injections per year) cause high financial burden since these could negatively affect adherence to the treatment. If the patient does not follow the treatment recommendations, this could lead to poor bleeding control and an increased number of bleedings as a result, which could lead to increased joint bleeds and eventually higher healthcare costs for society.

Increased indirect costs for the haemophilia B patient population are driven by a higher number of sick leave days, a higher proportion of early retirees, a higher proportion of sickness benefit and activity compensation and a lower

proportion who work full-time compared to the general population (Johnson and Zhou, 2011). Compared to the general population, PWHB miss an additional 3.5-4.5 days from work per year, have higher rates of early retirement and may be unable to enter their career of choice, which not only accounts for negative QoL, but also accounts for €8.97k (EUR) in annual indirect costs per patient (Kloosterman et al., 2020, Burke et al., 2021a, Arya et al., 2022, O'Hara et al., 2017). Moreover, direct medical costs of care for haemophilia B patients including FIX replacement therapies, hospitalizations and treatment of complications amounts to a mean annual cost of ~€235,723 in Europe per patient on FIX prophylaxis therapy per year, which may increase by patient non-adherence, resulting in additional bleeding events and associated costs to treat (Burke et al., 2021a, Berntorp, 2009, Zhou et al., 2015, Witkop et al., 2015, Burke et al., 2021b).

Furthermore, the main direct non-medical costs of haemophilia B are driven by caregiver expenses, both professional and informal, which amount to $2.4k per patient per year (Burke et al., 2021c). Haemophilia B also imposes significant burden on caregivers due to emotional stress and the time required for burdensome IV dosing schedules, which have a negative impact on employment for 84% of caregivers and partners (Witkop et al., 2021, von Mackensen et al., 2019, Cutter et al., 2017).

6.1.7. Patient populations relevant for this application

As discussed in section 6.1.3, there are currently ~100 patients diagnosed with haemophilia B in Denmark, ~40 of whom have a severe or moderate form of the disease. Hemgenix is only indicated for the treatment of severe and moderately severe haemophilia B (congenital FIX deficiency) in adult patients without a history of FIX inhibitors. Furthermore, it is not recommended for patients with very high titers of neutralizing antibodies (NAbs) against AAV5, and as discussed in section 5.1, contraindications include hypersensitivity, active infections and known advanced hepatic fibrosis, or cirrhosis (CSL Behring, 2022c). In conclusion, Hemgenix is suitable [redacted] and subtracted should be [redacted] patients in Denmark already treated with AMT-060 or Hemgenix as part of the clinical study program. It is thus expected that [redacted] in Denmark will formally meet the inclusion criteria to receive Hemgenix; based on discussions in advisory boards and other key opinion leader (KOL) communication, it is estimated that approximately [redacted] are expected to receive Hemgenix over the five consecutive years after introduction in Denmark.

6.2 Current treatment options and choice of comparator(s)

6.2.1. Current treatment options

In Denmark, the standard of care (SOC) for haemophilia B with a severe bleeding phenotype is infusion of replacement FIX concentrate at regular intervals to prevent bleeding events (prophylaxis). Treatment is individualized and optimized based on the patient's bleeding profile, pharmacokinetics (PK) and lifestyle. The Danish treatment practice for PWH is based on the guidelines provided by the NHC working group (Nordic Haemophilia Guidelines, 2022) and the DMC (Medicinrådet, 2022).

The overall goal of haemophilia treatment in Denmark is zero bleeds and healthy joints (Nordic Haemophilia Guidelines, 2022, Medicinrådet, 2022). There is currently no curative treatment for haemophilia B. Current treatment with FIX concentrates aims to preserve functional factor levels, prolong survival and provide a good QoL. Treatment is individualized to maintain sufficiently high factor levels to avoid bleeding and preserve musculoskeletal function.

Despite the availability of plasma derived FIX products, rFIX concentrates are recommended by the NHC and the DMC as the first choice for PWHB in Denmark. Currently, there are four rFIX concentrates reimbursed in the country. Among these, Refixia (nonacog beta pegol), Alprolix (efrenonacog alfa) and Idelvion (albutrepenonacog alfa) are classified as long-acting with extended half-life (EHL).

The Nordic centers have actively conducted and participated in haemophilia studies, including novel therapies (Nordic Haemophilia Guidelines, 2022). Management of joint disease, rehabilitation, and planning for interventions as a multi-expert effort is well coordinated. Also, carrier, obstetric and perinatology issues need predesigned approaches, written plans and consultation chains with multidisciplinary activities and experts involved. A close interaction between the laboratory and clinics establishes the diagnosis, provides opportunities to tailor prophylaxis, treatment of bleeds and

management of major surgery with proper dosing of coagulation factor and appropriate follow-up. Also, the diagnosis of the significant complications of haemophilia, i.e. inhibitors and infections, are based on laboratory medicine.

The FIX treatment of acute bleeds, is called on-demand treatment (Nordic Haemophilia Guidelines, 2022). On-demand treatment is commonly recommended for patients with mild haemophilia.

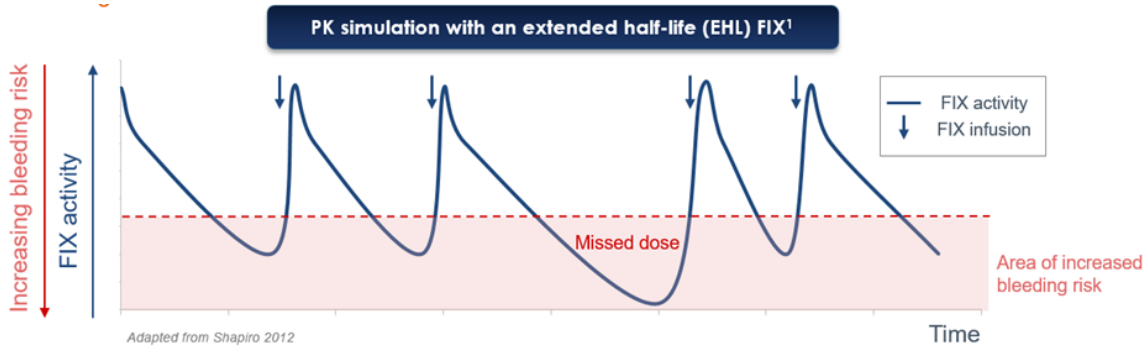
Prophylaxis involves regular IV infusions of the missing coagulation factor, i.e. FIX concentrate for treatment of haemophilia B. The goal of prophylactic treatment is to prevent bleedings, primarily joint bleeds, with subsequent development of arthropathy. Additionally, the treatment goal is to reduce the risk of other serious bleeds such as intracranial bleeds, muscle bleeds and intra-abdominal bleeds (NHC, 2020, Srivastava et al., 2020). According to the B-Nord study which studied patients with severe haemophilia B in the Nordic region, including a haemophilia treatment center (HTCs) in Copenhagen (Denmark), an estimated 95% of patients with severe haemophilia B are treated prophylactically (Kihlberg et al., 2021). Prophylactic treatment is started at one of the two specialized treatment centers in Denmark, i.e. in Copenhagen or Aarhus. The treatment is mainly administered at home by the patient themselves or by caregivers with follow-up at the coagulation center for persons with severe or moderate haemophilia once or twice per year (KOL input, 2022).

According to the Nordic haemophilia guidelines, primary prophylaxis for haemophilia B should be initiated at the age of one year or earlier, before joint bleeds may occur. Patients with moderate haemophilia and a factor level of 1-2% (moderately severe haemophilia) should also be offered primary prophylaxis. The guidelines recommend continued prophylactic treatment during adulthood and in elderly patients (Nordic Haemophilia Guidelines, 2022). Frequency of injections should be planned individually, according to patient activities and need for peak levels, and doses adjusted according to trough and bleeding patterns. At routine check-up, the previous factor infusion should be registered in detail (time point, dose), and a blood sample taken, for PK evaluation. Assessment of individual clinical response includes bleeding rate and joint score assessed by a physiotherapist, while QoL should also be monitored (Nordic Haemophilia Guidelines, 2022).

6.2.1.1 Limitations of current therapies

FIX replacement therapy requires frequent infusions. This high frequency carries a high psychological burden for patients and caregivers and negatively affects patients' QoL (Von Mackensen et al., 2017, Fernández, 2019, Auerswald et al., 2016). With each infusion, patients may experience subsequent pain, bleeds/microbleeds, and local inflammation. Easy and safe venous access is a prerequisite of replacement therapy, especially for performing long-term prophylaxis in the home setting. The requirement for frequent IV administration of FIX replacement therapies may represent an obstacle to treatment adherence. Moreover, SOC treatment results in peaks and troughs of FIX activity levels with an associated suboptimal efficacy (Figure 3). The low trough levels in PWHB are associated with the risk for breakthrough bleeds (Shapiro et al., 2013, Burke et al., 2023). Therefore, novel treatments with long-term duration of effect are needed to stabilize the FIX activity levels to within the normal or near-normal range.

Figure 3: Fluctuation in FIX activity level increases risk of breakthrough bleeding



Abbreviations: EHL, Extended half-life; FIX, Factor IX; PK, Pharmacokinetics.
Adapted from Shapiro et al. (2012).

Adherence to the treatment is vital for PWHB to gain intended benefit from therapy (Remor, 2011). Adherence is defined as the active, voluntary, and collaborative involvement of a patient in a mutually acceptable course of behavior to produce a desired preventative or therapeutic result, and is generally quantified by the number of doses of prophylaxis administered compared with the number of doses prescribed (Thornburg and Duncan, 2017). Patient adherence is a concern, mainly because of the frequency of administration and venous access issues. This lack of adherence to current FIX treatment puts patients at even higher risk of bleeding (Shapiro et al., 2012, Arruda et al., 2018, Thornburg and Duncan, 2017, Shapiro et al., 2013). PWH with better adherence have reported less severe bodily pain scores on QoL measures (Thornburg and Duncan, 2017).

6.2.1.2 Unmet need

As discussed in section 6.1.6 above, despite the introduction of coagulation factor-replacement therapies and the use of prophylaxis, bleeds still occur, sometimes with serious consequences, including bleeding into joints, muscles, and internal organs, resulting in joint diseases (joint arthropathy) and ICH (Hassan et al., 2021). Likewise, while on-demand treatment will temporarily restore hemostasis and stop an ongoing detected/noticed joint bleed (clinical bleed), blood remains in the joint, having harmful long-term effects on the articular cartilage. Unnoticed minimal bleeding can also occur causing damage to joints where patients have not had any symptomatic bleeding, otherwise known as "subclinical" bleeding (Dodd and Watts, 2012, Fischer et al., 2013).

The optimal treatment goal is therefore to completely attenuate or prevent spontaneous bleeding, particularly joint bleeding. Prophylaxis and on-demand treatment regimens cause fluctuations in active FIX plasma levels, which pose the risk of recurrent bleeding episodes (see further details below). Therefore, a treatment that would eliminate clinical and subclinical bleeding completely by stabilizing FIX activity levels and achieving an ABR approaching zero is needed in haemophilia B (Gringeri et al., 2014).

Taken together, even with access to prophylaxis, patients with severe haemophilia B remain at considerable risk of arthropathy and long-term joint damage (Burke et al., 2021c). New treatments are needed to improve clinical outcomes, slow down the progression of the disease, and improve QoL and life expectancy.

6.2.2. Choice of comparator(s)

FIX replacement therapy includes treatment with a standard acting FIX (standard half-life [SHL]), or an EHL product which provides higher circulating plasma levels and/or prolonged protection against bleeding (Nordic Haemophilia Guidelines, 2022). According to Nordic haemophilia guidelines, when using EHL FIX products for prophylaxis treatment of PWHB, the recommended dose is 30-50 IU/kg once weekly meaning lower injection frequency as compared to standard acting FIX. The dose and frequency of injection is tailored according to clinical response. Pharmacokinetic (PK) measurement is recommended upon switching to EHL FIX products, including at peak and trough and one sampling in between doses (Nordic Haemophilia Guidelines, 2022).

EHL rFIX products are the first drug of choice in Denmark and specifically recommended for patients with difficulties performing sufficient prophylaxis with standard acting rFIX, for patients with difficult venous access or with need for high trough levels (Medicinrådet, 2022). [redacted] An overview of all the available FIX products is shown in Table 3 below.

Table 3: Overview of currently available FIX replacement therapies

Product	Date of EMA approval	Active ingredient	Dosing; dosing frequency	Classification
Alprolix (SmPC, 2021a)	12 May 2016	eftrenonacog alfa (rFIX, Fc fusion protein)	50 IU/kg; 1/week 100 IU/kg; every 10 days	EHL
BeneFIX (SmPC, 2022a)	27 Aug 1997	nonacog alfa (rFIX)	40 IU/kg median (not fixed); every 3 to 4 days	Standard acting
Idelvion (SmPC, 2021b)	27 May 2016	albutrepenonacog alfa (rFIX, albumin fusion protein)	35 to 50 IU/kg; 1/week up to 75 IU/kg; every 10 or 14 days; 100 IU/kg; every 21 days	EHL
Refixia (SmPC, 2022b)	02 Jun 2017	nonacog beta pegol (rFIX, pegylated)	40 IU/kg; 1/week	EHL

Abbreviations: EHL, Extended half-life; EMA, European Medicines Agency; IU, International unit; kg, Kilograms; rFIX, Recombinant Factor IX; SmPC, Summary of Product Characteristics.
Source: cited in table.

6.2.3. Description of the comparator(s)

Details of the comparator, Refixia, is presented in Table 4 below.

Table 4: Description of the comparator relevant for this application

Overview of the comparator	
Proprietary name	Refixia
Generic name	Nonacog beta pegol
Marketing authorization holder in Denmark	Novo Nordisk A/S
ATC code	B02BD04
Pharmacotherapeutic group	Antihemorrhagics
Active substance(s)	Refixia (recombinant coagulation FIX)
Pharmaceutical form(s)	Powder and solvent for solution for injection

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Overview of the comparator	
Mechanism of action	Refixia is a purified human rFIX with a 40 kDa polyethylene-glycol (PEG) conjugated to the protein Upon activation of Refixia, the activation peptide including the 40 kDa polyethylene-glycol moiety is cleaved off, leaving the native activated FIX molecule. Factor IX (FIX) is activated by factor XIa and by factor VII/tissue factor complex. Activated FIX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed By replacement therapy the plasma levels of FIX are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies
Dosage regimen	Prophylaxis • 40 IU/kg bw once weekly[a] On-demand treatment • A single dose of 40 IU/kg bw in cases of early hemarthrosis, muscle bleeding or oral bleeding. Same dosage regimen to be used in the cases of more extensive hemarthrosis, muscle bleeding or hematoma • A single dose of 80 IU/kg bw in the cases of severe or life threatening hemorrhages[b] Surgery • A single dose of 40 IU/kg bw in the cases of minor surgery including tooth extraction[b] • A single pre-operative dose of 80 IU/kg bw in the cases of major surgery. After surgery, two repeated doses of 40 IU/kg (in 1–3 day intervals) within the first week are recommended[c] Pediatric population • The dose recommendations in adolescents (12–18 years) are the same as for adults: 40 IU/kg bw • Refixia is not recommended for children below 12 years
Other approved therapeutic indications	N/A
Treatment duration/criteria for end of treatment	Duration of treatment is specified based on the situations described in dosage regimen If symptoms of hypersensitivity or other AEs occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician
Combination therapy and/or co-medication	N/A
Necessary monitoring, both during administration and during the treatment period	Routine monitoring of FIX activity levels for the purpose of dose adjustment is not necessary After repeated treatment with recombinant human coagulation FIX products, patients should be monitored for the development of NAbs (inhibitors) that should be quantified in Bethesda Units using appropriate biological testing

Overview of the comparator	
Packaging – types, sizes/number of units, and concentrations	Refixia 500 IU powder and solvent for solution for injection Each vial contains nominally 500 IU nonacog beta pegol After reconstitution, 1 mL of Refixia contains approximately 125 IU nonacog beta pegol Refixia 1,000 IU powder and solvent for solution for injection Each vial contains nominally 1,000 IU nonacog beta pegol After reconstitution, 1 mL of Refixia contains approximately 250 IU nonacog beta pegol Refixia 2,000 IU powder and solvent for solution for injection Each vial contains nominally 2,000 IU nonacog beta pegol After reconstitution, 1 mL of Refixia contains approximately 500 IU nonacog beta pegol Refixia 3,000 IU powder and solvent for solution for injection Each vial contains nominally 3,000 IU nonacog beta pegol After reconstitution, 1 mL of Refixia contains approximately 750 IU nonacog beta pegol
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Notes:
[a] Adjustments of doses and administration intervals may be considered based on achieved FIX levels and individual bleeding tendency. Patients on prophylaxis who forget a dose are advised to take their dose upon discovery and thereafter continue with the usual once weekly dosing schedule. A double dose should be avoided.
[b] Additional doses of 40 IU/kg can be given, if needed.
[c] The frequency of dosing in the post-surgical period may be extended to once weekly after the first week until bleeding stops and healing is achieved.
Abbreviations: ATC, Anatomical therapeutic chemical; bw, Body weight; FIX, Factor IX; IU, International units; kDa, Kilodalton; kg, Kilograms; mL, Milliliters; N/A, Not applicable; NAb, Neutralizing antibody; PEG, Polyethylene-glycol.
Source: SmPC (2022b).

6.3 The intervention

6.3.1. Mechanism of action

Hemgenix (etranacogene dezaparvovec) is a gene therapy product designed to introduce a copy of the human FIX coding DNA sequence into hepatocytes to address the root cause of the haemophilia B disease (CSL Behring, 2022c). Hemgenix consists of a codon-optimized coding DNA sequence of the gain-of-function Padua variant of the human FIX (hFIXco-Padua), under the control of a liver-specific LP1 promoter, encapsulated in a non-replicating rAAV5 (CSL Behring, 2022c).

Following single IV infusion, Hemgenix attaches to the cell surface and is then internalized, transported to the nucleus and uncoated (see Figure 4). Hemgenix preferentially targets liver cells where the vector DNA will reside almost exclusively in episomal form (CSL Behring, 2022c). After transduction, Hemgenix directs long-term liver-specific expression of FIX-Padua protein (CSL Behring, 2022c). As a result, Hemgenix partially or completely ameliorates the deficiency of circulating FIX procoagulant activity in PWHB, restoring the hemostatic potential (CSL Behring, 2022c).

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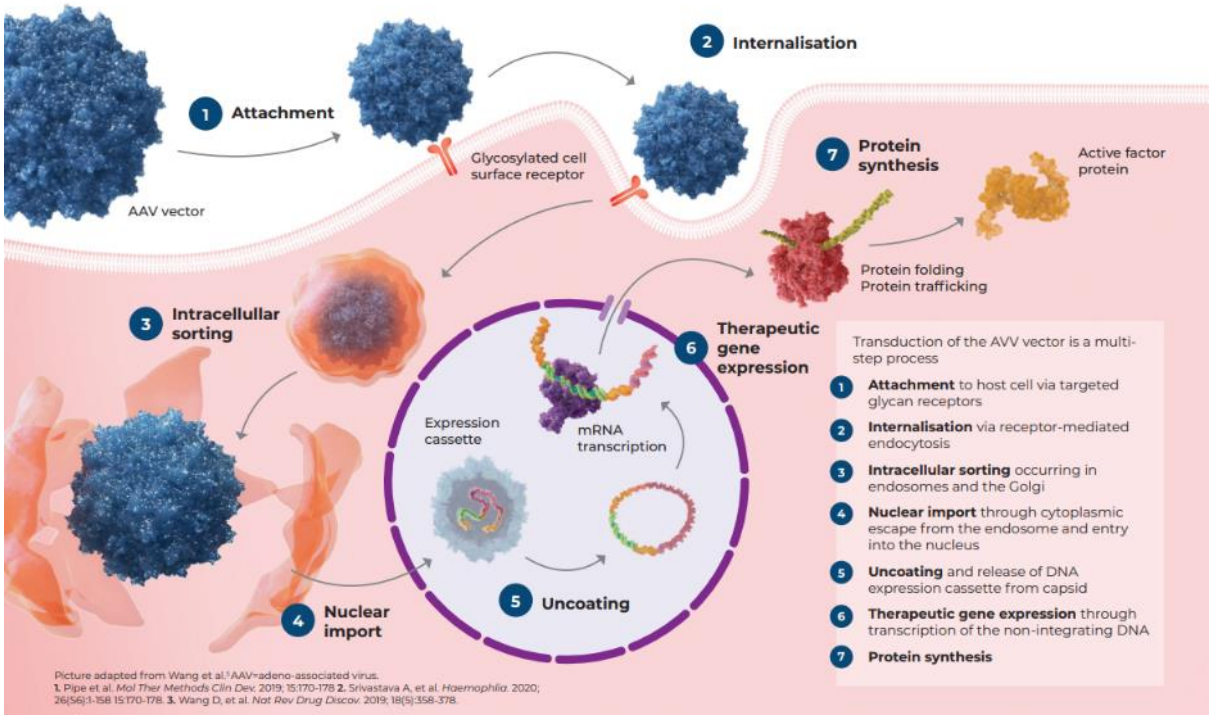
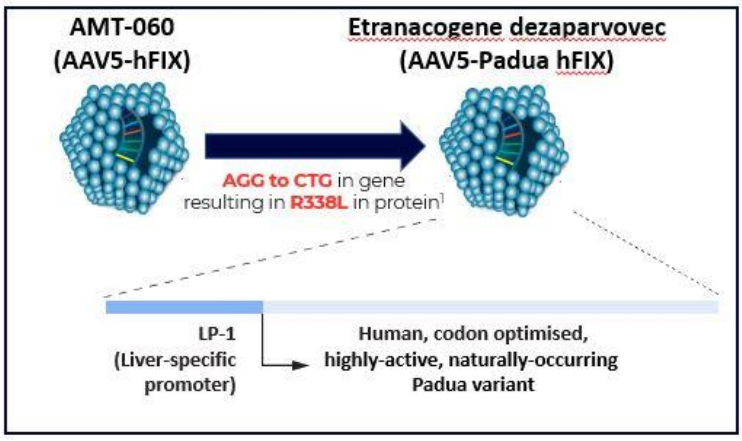
Figure 4: Illustration showing the mechanism of action of Hemgenix



Adapted from Wang et al. (2019).

In summary, the transgene (FIX) expression is targeted to the liver by using a protein capsid that interacts primarily with liver cells, while the transgene is expressed under the control of a liver-specific promoter meaning that the transduced FIX gene is activated specifically in liver cells, and not in any other cells (Butterfield et al., 2020, 2021). The transgene (FIX) selected for Hemgenix encodes a gain-of-function FIX variant known as "Padua" (2021c). Originally, development was started on AMT-060, with the same protein capsid and cassette design as Hemgenix but using a wild-type transgene (FIX), which is different from Padua variant by only one amino acid (see Figure 5).

Figure 5: Hemgenix capsid versus AMT-060



Source: Pipe et al. (2022a).

After the phase I/II trial of AMT-060, the product was updated to AMT-061 (Hemgenix) with the "Padua" variant of the gene (CSL Behring, 2021c). The Padua human coagulation FIX (hFIX) variant is a naturally occurring variation of the FIX gene which differs from the wild type hFIX in only a single amino acid substitution (CSL Behring, 2021c).

The FIX-Padua variant was selected to attain a gain-of-function in FIX activity as compared to the wild-type FIX gene (Kao et al., 2013, Simioni et al., 2009). Expression of this transgene in liver cells yields functional human clotting FIX-Padua, which is secreted into circulation (CSL Behring, 2021c).

Several preclinical studies in haemophilic mice and dogs have demonstrated the potential utility of this variant for haemophilia B gene therapy, as it enables higher FIX activity levels without the need for a higher vector dose to increase transgene expression (Kao et al., 2013, Crudele et al., 2015, Cantore et al., 2012, Monahan, 2015, Finn et al., 2012). A non-human primates (NHP) study (NR-061-17-001) was performed to assess four different doses of a single IV administration of Hemgenix compared with AMT-060 regarding circulating hFIX protein levels, total circulating FIX activity levels, plasma vector DNA, and biodistribution (in more than 25 different organs/tissues). The study also routinely administered a complete safety panel and monitored six different liver enzymes and additional coagulation markers (Spronck et al., 2019).

Key findings:

- Hemgenix demonstrated dose-dependent increases in plasma vector DNA levels, human FIX protein levels, and FIX activity compared with AMT-060.
- No differences between the two products were observed in clinical signs, clinical chemistry, and hematology.
- No effect on plasma D-dimer and thrombin-antithrombin levels, suggesting that the overall clotting cascade is functioning within physiological boundaries.
- At a dose of 5×10^{12} gene copies (gc)/kg, plasma exposure, liver distribution, liver cell transduction, and transgene expression were similar for both AMT-060 and Hemgenix, but transgene activity was approximately six times higher per unit protein (average, 6.10%; range: 5.41–7.47%) for Hemgenix compared with AMT-060.
- The study only included a direct comparison at the 5×10^{12} gc/kg dose level; plasma exposure, liver distribution, liver cell transduction, and transgene expression were similar at that dose. The observed mean FIX protein levels of AMT-060 (average, 4.89%; range: 3.17–7.61%) and Hemgenix (average, 4.85%; range: 2.92–6.17%) were comparable.
- Hemgenix demonstrated an approximately 6.5-fold increase in baseline-corrected FIX activity compared with AMT-060 at a similar dose. On average (from weeks 4–13), an increase in baseline-corrected FIX activity of 9.1% and 58.9% was detected with AMT-060 and Hemgenix, respectively. Increased FIX activity was maintained until the end of study, i.e., six months post-treatment (Spronck et al., 2019).

These results are consistent with the increase/gain-of-function reported for the Padua hFIX protein compared with wild-type hFIX protein in animal models. In this preclinical study of Hemgenix in NHPs, the gene therapy was well tolerated with no significant toxicological findings (Spronck et al., 2019).

Liver tissue samples from mice and NHPs were collected six months after a single IV administration of AMT-060 up to a dose of 2.3×10^{14} gc/kg bw, corresponding to approximately 10 times the clinical dose in humans. The profile of integration of the vector DNA into the host genome was characterized using linear-amplification-mediated polymerase chain reaction (LAM-PCR), non-restrictive LAM-PCR, and deep sequencing. The AAV vector sequences retrieved after LAM-PCR followed by high-throughput sequencing were found to be present almost exclusively as non-integrated episomal forms. The AAV5 vector DNA had a low level of integration into the host genome and did not show evidence of germline transmission. Liver samples from mice administered AAV5-hF9 for six months showed no microscopic abnormalities and no evidence for clonal selection of cells with vector DNA integration into the host genome (an indicator of tumorigenic risk). None of the animals showed any signs of malignant transformation (Spronck et al., 2019).

In conclusion, though the administration of AAV5-hF9 to mice and NHPs is associated with a low level of random integration into the liver, this integration profile does not raise any specific tumorigenic concerns (Spronck et al., 2019). The details on the components of Hemgenix are provided in Table 5.

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Table 5: Features of Hemgenix component expression cassette

Component of Hemgenix expression cassette	Key features
Inverted terminal repeat (ITRs)	Stabilization of the viral genome
Liver promoter 1 (LP1)	To mediate the robust and liver-specific expression of the therapeutic transgene
SV40 intron	To enhance transgene expression
hFIXco coding sequence	Codon-optimized hFIX-Padua sequence enhances protein expression
PolyA signal	Stabilization of messenger RNA

Note: AMT-060 is similar to Hemgenix in all the parameters above, but with a wild-type F9 transgene with two nucleotides difference in the transgene sequence resulting one amino acid difference in the final translated protein sequence.
Abbreviations: hFIX, Human coagulation Factor IX; ITR, Inverted terminal repeat; LP1, Liver promoter 1; RNA, Ribonucleic acid; SV40, Simian virus 40.
Source: Thornburg (2021).

The strength, pack size, and pharmacy selling price per pack for Hemgenix in Denmark is included in Table 6 below.

Table 6: The strength, pack size, and pharmacy purchase price per pack

Treatment	Strength	Pack size	Price per treatment (DKK)
Hemgenix for IV infusion	Single dose	Each mL of etranacogene dezaparvovec (Hemgenix) contains $1x10^{13}$ gc Each vial contains an extractable volume of 10 mL of concentrate for solution for infusion, containing a total of $1x10^{14}$ gc	XXXXXXXXXX

Abbreviations: DKK, Danish kroner; IV, Intravenous; gc, Gene copies; mL, Milliliter; PRP, Pharmacy retail price
*PRP excl. VAT
Source: CSL Behring (2022c).

6.3.1.1 Dose and administration

Hemgenix must be prescribed and administered in a clinical treatment center by a healthcare professional with experience in treating haemophilia B. Individual single-administration doses are calculated based on the patient's bw. Following dilution with 0.9% sodium chloride solution (normal saline), Hemgenix is administered as a single IV infusion of a 2×10^{13} gc/kg bw (or 2 mL/kg bw) dose. See the Hemgenix European Medicines Agency (EMA)-approved label for complete information on its dosing and administration (CSL Behring, 2022c).

6.3.1.2 Contraindications and precautions

Refer to the Hemgenix EMA-approved label for complete information on contraindications and precautions (CSL Behring, 2022c).

Precautions:

- Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded (CSL Behring, 2022c).
- Infusion reactions: Infusion reactions, including hypersensitivity reactions and anaphylaxis, are possible (CSL Behring, 2022c).
- Hepatotoxicity: IV administration of a liver-directed AAV vector may potentially lead to immune-mediated liver transaminase elevations (transaminitis). The transaminitis is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the gene therapy. In clinical studies with Hemgenix, transient, asymptomatic, and predominantly mild liver transaminase elevations were observed, most often in the first three months after Hemgenix administration. These transaminase elevations resolved either spontaneously or with administration of a corticosteroid taper to normal levels after a period of several weeks, pre-steroid levels of FIX were maintained and return to FIX prophylaxis was avoided (Astermark, 2023). To mitigate the risk of potential hepatotoxicity, transaminases should be closely monitored, e.g. once weekly for three months after Hemgenix administration. A course of corticosteroid taper should be considered in the event of alanine aminotransferase (ALT) increase to above the upper limit of normal (ULN)

or to double the patient's baseline levels, along with human FIX activity examinations. Follow-up monitoring of transaminases in all patients who developed liver enzyme elevations is recommended on a regular basis until liver enzymes return to baseline values (CSL Behring, 2022c).

- Immune-mediated inimizeation of the AAV5 vector capsid: In AAV-vector-based gene therapies, the pre-existing neutralizing AAV antibodies may impede transgene expression at desired therapeutic levels. At 18- and 24-months post-treatment, no clinically meaningful correlation between an individual's baseline AAV5 NAb titer and FIX activity levels was identified, up to a NAb titer of <1:700 (24-month Pearson coefficient: -0.29; Spearman coefficient: -0.25; R^2: 0.086). One participant with a markedly high NAb titer of 1:3,212 prior to vector dosing and one participant who only received a partial dose (due to an IRR; NAb titer: 198.9), did not express FIX-Padua and did not discontinue FIX prophylaxis. All other participants (52/54) discontinued FIX prophylaxis (CSL Behring, 2022c, Pipe et al., 2022a)
- Hepatocellular carcinogenicity: Hemgenix is composed of a non-replicating AAV5 vector and an expression cassette that is maintained largely in episomal form with few random DNA integration events. Integration site analysis was performed on liver samples from one patient treated with Hemgenix in clinical studies. Samples were collected one year post-dose. Vector integration into human genomic DNA was observed in all samples. The clinical relevance of individual integration events is not known to date, but it is acknowledged that individual integration into human genome could potentially contribute to a risk of malignancy. No Hemgenix-associated clonal expansion or carcinogenicity was observed in preclinical or clinical studies. It is recommended that patients with pre-existing risk factors for hepatocellular carcinoma (such as hepatic cirrhosis, advanced hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) receive regular abdominal ultrasound screenings and are regularly (e.g. annually) monitored for alpha-fetoprotein elevations in the five years following administration (CSL Behring, 2022c).
- Shedding: Temporary shedding of Hemgenix vector DNA may occur through blood and semen of patients receiving Hemgenix. Due to the non-replicating nature of the shed vector DNA fragments, the risk of an adverse effect to human health upon accidental exposure and the environmental risks are considered negligible. Transient and low-level shedding of vector genomes was observed. Patients treated with Hemgenix should not donate blood, or organs, tissues, and cells for transplantation to minimize the risk of exposure to non-target individuals. Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during Hemgenix use (CSL Behring, 2022c).
- Sodium and potassium content: This medicinal product contains 35.2 mg sodium per vial, equivalent to 1.8% of the World Health Organisation (WHO) recommended maximum daily intake of 2 g sodium for an adult. This medicinal product contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially potassium-free (CSL Behring, 2022c).

6.3.2. Patient eligibility and monitoring

6.3.2.1 Companion diagnostics

A diagnostic test to evaluate a patient's AAV5 NAb titer (CSL Behring, 2021b) should be performed prior to treatment with Hemgenix (CSL Behring, 2022c). [redacted]

6.3.2.2 Patient selection and eligibility

Hemgenix is effective in patients with an AAV5 NAb titer up to 1:678, which includes approximately 98% of patients treated in the pivotal HOPE-B trial. In clinical trials, patients with pre-existing NAbs up to AAV5 1:678 have the same outcomes as patients without Nabs, measured by ABR, mean FIX activity level, and ability to discontinue FIX prophylaxis therapy (CSL Behring, 2022g). Pre-existing neutralizing anti-AAV antibodies above a titer of 1:678 may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of Hemgenix therapy.

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A FIX inhibitor titer test should also be performed. In cases who have a positive test result for human FIX inhibitors, a re-test needs to be performed within approximately two weeks. Hemgenix should not be administered to patients in whom both the initial test and the re-test results are positive.

Contraindications include hypersensitivity, active infections and known advanced hepatic fibrosis, or cirrhosis.

Liver health assessments should be performed, including:

- Enzyme testing (ALT, aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin).
- Hepatic ultrasound and elastography.

In cases of radiological liver abnormalities and/or sustained liver enzyme elevations, a consultation should be considered with a hepatologist to assess eligibility for Hemgenix (CSL Behring, 2022c).

6.3.2.3 Observation of patients

Patients must be monitored for one hour during the IV infusion and for at least three hours after the end of administration. If any symptoms of an infusion reaction occur, consider slowing down or interrupting the infusion. If the infusion is interrupted, it can be restarted at a slower rate when the infusion reaction has resolved.

6.3.3. Supporting treatments

The IV administration of a liver-directed AAV gene therapy vector may potentially lead to immune-mediated liver transaminase elevations (transaminitis). This transaminitis is presumed to occur due to injury of transduced hepatocytes and may reduce the efficacy of the gene therapy (CSL Behring, 2022c).

In clinical studies of Hemgenix, transient, asymptomatic, and predominantly mild liver transaminase elevations have been observed, most often within the first three months after administration of Hemgenix. These transaminase elevations resolved either spontaneously or with administration of a corticosteroid taper to normal levels after a period of several weeks (CSL Behring, 2022c).

Transaminases should be monitored weekly for a period of three months after administration of Hemgenix. A tapered course of oral corticosteroids should be considered in the event of ALT increases to above the ULN or to double the patient's baseline levels.

Medications equivalent to prednisolone may also be used. A combined immunosuppressant regimen or the use of other products can also be considered in cases of prednisolone treatment failure or contraindication (CSL Behring, 2022c).

6.3.4. Proposed positioning

Hemgenix can represent a step-change in the management of patients with moderately severe or severe haemophilia B, as a single-infusion is capable of inducing stable FIX expression, potentially eliminating regular FIX IV injections as well as reducing long-term complications. Figure 6 shows the current treatment pathway in Denmark and the proposed positioning of Hemgenix, also considering patient choice.

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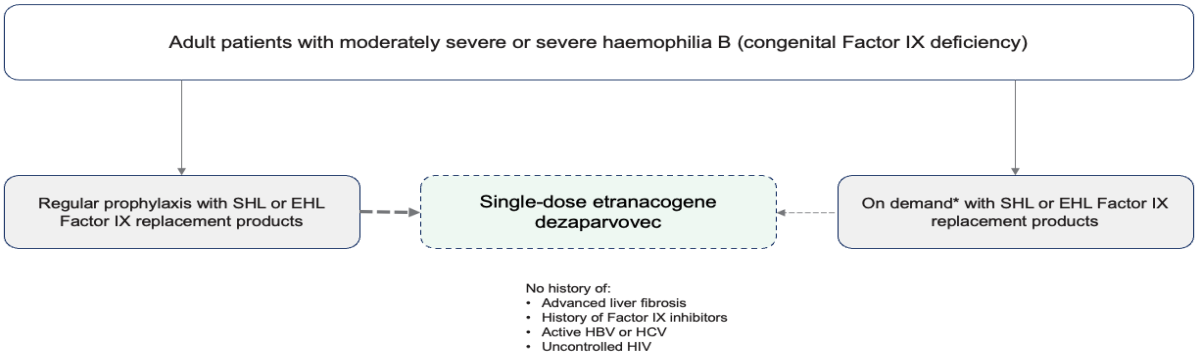
Figure 6: Current treatment pathway in Denmark and the proposed positioning of Hemgenix, also considering patient choice



Note: Dotted line denotes intended positioning of Hemgenix, mainly displacing prophylaxis as demonstrated by the thicker, dotted line.
*Unlike prophylaxis, on-demand treatments are administered at the time of a bleed and aim to stop hemorrhages rapidly. A small number of patients opt to receive on-demand treatment despite being eligible for prophylaxis due to personal choice or clinical challenges and, in this group, Hemgenix could displace on-demand treatment.
Abbreviations: EHL, Extended half-life; FIX, Factor IX; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; SHL, Standard half-life.

6.3.5. Role of gene therapy in improving QoL

By further reducing bleeding episodes, as well as the treatment burden associated with current therapies, it is expected that haemophilia-directed gene therapy will improve the overall QoL for PWH (Leebeek and Miesbach, 2021). Gene therapy trials in haemophilia B have shown sufficient expression of FIX to significantly decrease the number of bleeding events and eliminate the need for FIX prophylaxis therapy, resulting in a clinical benefit that can change the lives of patients with severe haemophilia (Leebeek and Miesbach, 2021).

Very little data are currently available with respect to PROs and QoL among PWHB (Leebeek and Miesbach, 2021). A survey of PWH in the United Kingdom (UK) who received gene therapy reported that, overall, gene therapy was a positive experience for them, with most of them describing gene therapy as life changing because of being liberated from concern about bleeds, the ability to participate in sport and freedom from rigorous treatment regimens (Fletcher et al., 2022). This study has highlighted the importance and benefits of treating haemophilia with gene therapy, as well as concerns surrounding immunosuppression due to transaminitis. In HOPE-B, all instances of elevated transaminases were non-serious and resolved via reactive corticosteroid treatment, with the patients who received steroids (n=9/54) being able to discontinue steroid use within six months post-treatment (mean duration: 79.8 days, standard deviation [SD]: 26.6 days; range: 51–130 days) (CSL Behring, 2022i, Pipe et al., 2023). Moreover, despite the transaminase elevations, FIX activity was preserved in the mild or non-haemophilic range (Astermark, 2023). The substantial patient burden associated with the use of corticosteroids to treat transaminase elevation in patients receiving gene therapy for haemophilia, as highlighted by the qualitative interview study and patient testimonials, indicates that the ability to limit corticosteroid use while maintaining FIX activity is key in improving patient QoL (Fletcher et al., 2022). Despite the challenges associated with corticosteroid treatment, the majority of those interviewed in the qualitative study (patients, n=12/16; family members, n=3/10) described gene therapy as life changing (Fletcher et al., 2022).

7. Literature search and identification of efficacy and safety studies

7.1 Identification and selection of relevant studies

The clinical evidence base for Hemgenix was established using a systematic literature review (SLR) of publications (abstracts, manuscripts) in literature databases (e.g., PubMed, EMBASE), trial registries, and major scientific/medical congresses. Searches were run on 18 August 2021 for the time period of 22 March 2013 to 18 August 2021. An 'update review' was then run on 17 October 2022 (full search strategies are provided in Appendices A & H). Publications prior

to these SLRs were identified from two published SLRs that identified clinical, economic and HRQoL evidence in haemophilia B have been conducted (Berger et al., 2015, Thorat et al., 2018).

Appendices A and H further describe the process and methods used to identify and select clinical evidence relevant to the technology being appraised.

7.2 Population

The patient population of interest in the review comprises males aged 12 and over and/or aged 18 and over with congenital haemophilia B.

7.3 Eligibility criteria

The selection criteria specified in Appendix A was used to inform the inclusion of studies at first and second pass stages of the reviews. Studies published as abstracts, conference presentations or press releases were eligible if adequate data were provided in line with the inclusion criteria. Eligibility criteria were specified in terms of population, intervention and comparators, outcomes and study design (PICOS).

7.4 Data sources

Searches to identify evidence for all six review questions were conducted in the following databases(databases updated daily):

- Embase (covers biomedical literature from 1974 to present).
- MEDLINE (covers journals from 1966 to present).

In addition to the databases listed above, searches to identify clinical studies were conducted in:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library).
- Cochrane Clinical Answers.

Supplementary searches of grey literature were performed in Google Scholar and through the National Institutes of Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Clinical and Economic Review and Scottish Medicines Consortium (SMC) websites. Further grey literature searches included clinicaltrials.gov, searches of the manufacturer's repository of evidence, websites of manufacturers of comparator products, bibliographic searching of any SLRs identified during screening, and the following relevant congresses over the last two years:

- British Society for Haematology.
- European Haematology Association.
- American Society of Haematology.
- European Haemophilia Consortium.
- European Association for Haemophilia and Allied Disorders.

Appendix H presents the search strategies for Embase, MEDLINE and Embase Classic, CENTRAL and Cochrane Clinical Answers, CRD HTA Database, CRD NHS EED, ScHARRHUD and EuroQol database. These strategies included terms for free text and keywords (Medical Subject Heading [MESH] and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review questions. Publication dates were restricted to start from 22nd March 2013 to 18th August 2021.

7.5 Study selection

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the review question and

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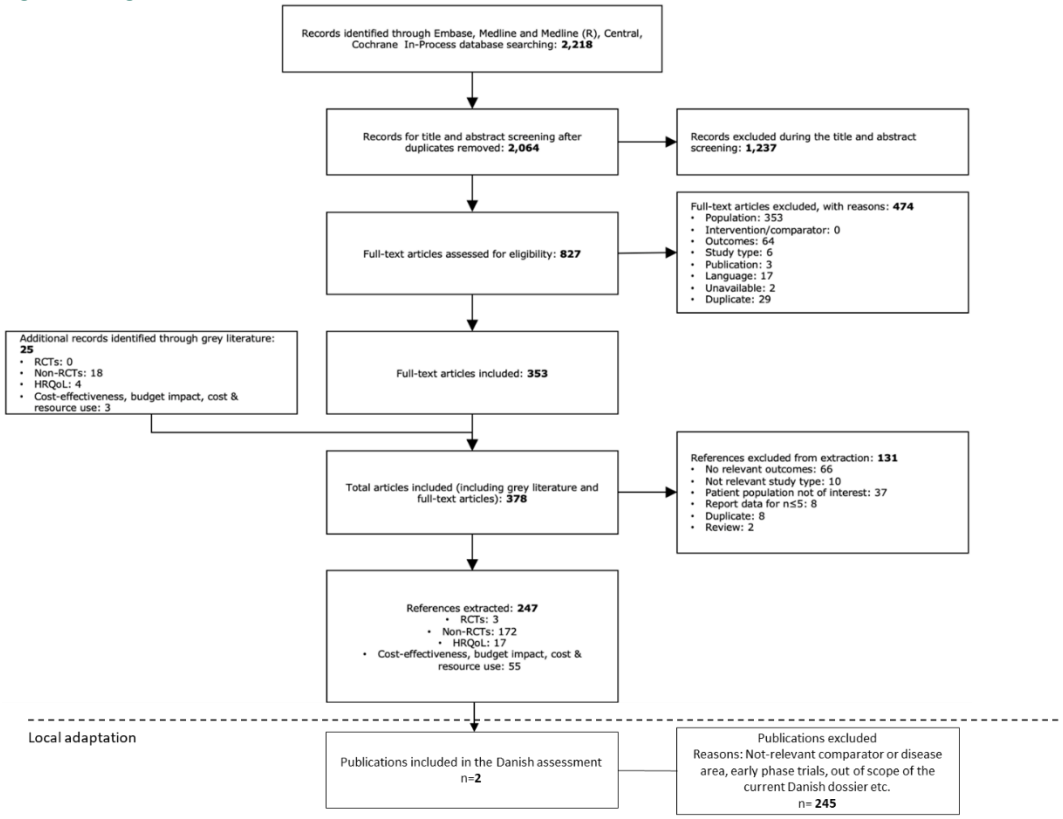
selection criteria. A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required. Following the completion of first pass, full-text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria. Another discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required. A reason for exclusion was provided for studies excluded following the full-text review during the second pass. A full list of excluded articles and the reasons for exclusion is presented in Appendix A (Table 65).

Following the completion of first pass, full-text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria.

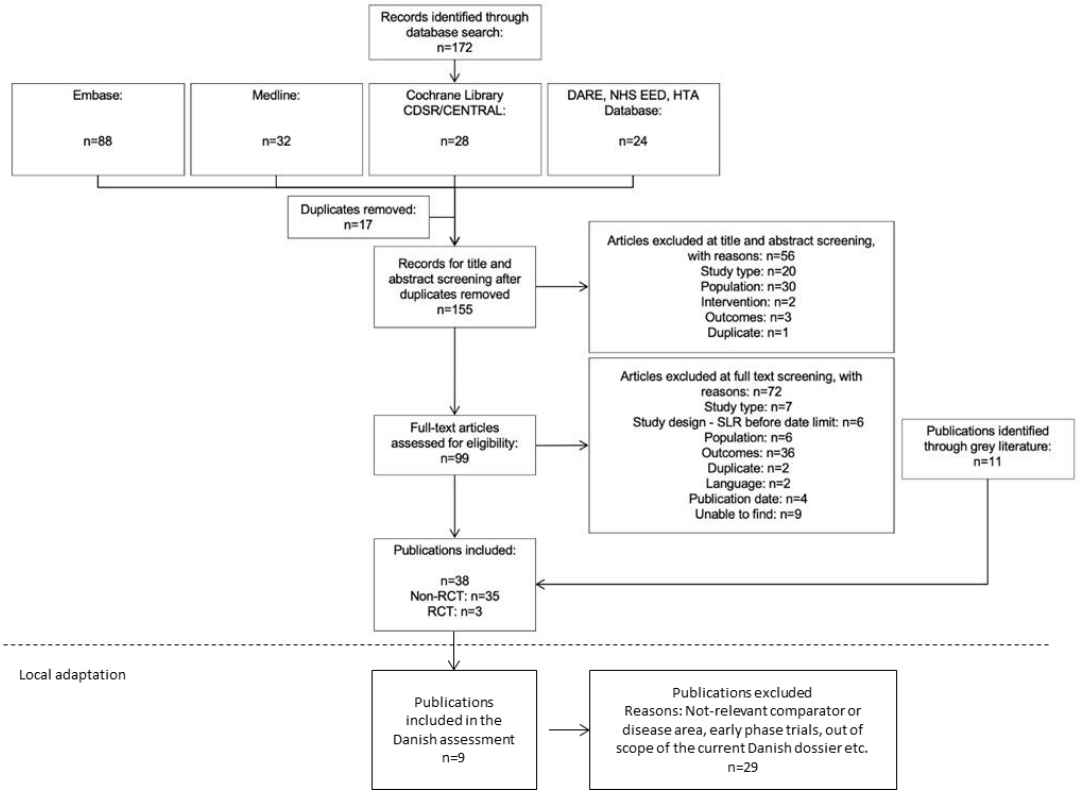
The study PRISMA flow diagram is provided in Figure 7 and Figure 8 below. A local adaptation box has been added in line with the DMC guidelines to present the number of studies that have been found relevant to the current application in Denmark. Additionally, the local adaptation box presents the number of studies that were found not relevant to the current dossier and were excluded. The detailed information of the relevant studies is presented in the Table 8 in Section 7.7.

Figure 7: Original review PRISMA



Abbreviations: HRQoL, Health-related quality of life; RCT, Randomized controlled trial.

Figure 8: Update review clinical PRISMA diagram



Abbreviations: RCT, Randomized controlled trial; SLR, Systematic literature review.

7.6 Strengths and limitations of SLR

Systematic reviews involve explicit, transparent methods which are clearly stated and reproducible (minimize bias by using objective, pre-defined inclusion criteria). The robustness of the review is primarily determined by (i) the quality of and (ii) the data reported in the eligible studies. Limitations concerning the systematic review and evidence synthesis include the limitations of using published data. The robustness of the evaluation may be compromised by the internal validity of the identified studies. However, to assess this, studies are critically appraised for potential bias using appropriate methodology.

7.7 List of relevant studies

The clinical development program of Hemgenix includes two prospective, open-label, single-dose, single-arm studies: a Phase IIb study performed in the US (CT-AMT-061-01, NCT03489291) (Von Drygalski et al., 2022, CSL Behring, 2022i) and a pivotal Phase III multinational study performed in the US and Europe (HOPE-B, CT-AMT-061-02, NCT03569891). Two sites in the Nordics included patients in the pivotal Phase III HOPE-B study: Rigshospitalet in Copenhagen, Denmark, and Skåne University Hospital in Malmö, Sweden. Thus, the HOPE-B trial is the main relevant study for the presentation of efficacy and safety data of Hemgenix compared to prior therapy with prophylactic FIX replacement products (lead-in period) for PWHB.

Prior to the final development of Hemgenix, initial development of the gene therapy resulted in AMT-060, a gene therapy product with the same vector and cassette design as Hemgenix but using a wild-type FIX transgene (as explained in Section 6.3) (Miesbach et al., 2018). One site in the Nordics included patients in the Phase I/II trial of AMT 060 (CT AMT 060 01, NCT02396342): Rigshospitalet in Copenhagen, Denmark. After the Phase I/II trial, the vector's FIX transgene was replaced with the gain-of-function hFIXco-Padua variant of the gene, and that product was designated AMT-061 (Hemgenix) (Von Drygalski et al., 2019). Table 7 provides a summary of the Phase III HOPE-B, Phase I/II, and

Phase IIb open-label, multicenter studies designed to assess the efficacy and safety of AMT-060 and Hemgenix (AMT-061).

Table 7: Clinical trial program of AMT-060 and Hemgenix

	AMT-060		Hemgenix	Hemgenix
Name/code	CT-AMT-060-01 NCT02396342		CT-AMT-061-01 NCT03489291	**HOPE-B,** CT-AMT-061-02 NCT03569891
Phase	Phase I/II	Extension	Phase IIb	Phase III
Design	Open label	Extension	Open label	Open label with observational lead-in period
Dose (gc/kg)	Cohort 1: 5×10^{12} Cohort 2: 2×10^{13}	–	2×10^{13}	2×10^{13}
Number of subjects	Cohort 1: 5 Cohort 2: 5	Transfer from Phase I/II	3	75 screened 67 lead-in period 54 dosed*
Planned follow-up	5 years after dosing	10 years after dosing	5 years after dosing	5 years after dosing
Follow-up to date	6 years†		3 years	2 years
Primary objective	AEs over 5 years	Long-term safety over 6–10 years post-treatment	To confirm that a single dose of 2×10^{13} gc/kg AMT-061 resulted in FIX activity levels of ≥5% at 6 weeks after dosing	To demonstrate the non-inferiority of AMT-061 during the 52 weeks following establishment of stable FIX expression (months 6 to 18) post-treatment (AMT-061) follow-up compared to SOC continuous routine FIX prophylaxis during the lead-in phase, as measured by the ABR

Note:
*Partial dose (~10%) administered to one patient with hypersensitivity reaction.
†Follow-up of 6 years completed for 8 patients, with 1 patient dying of causes not related to the study treatment and 1 not consenting to follow-up (CSL Behring, 2022g).
Abbreviations: AE, Adverse event; ABR, Annualized bleeding rate; FIX, Factor IX; gc, Gene copies; SOC, Standard of care.
Source: ClinicalTrials.gov. Identifier NCT02396342;(ClinicalTrials.gov Identifier) ClinicalTrials.gov. Identifier NCT03489291;(ClinicalTrials.gov) ClinicalTrials.gov. Identifier NCT03569891(ClinicalTrials.gov Identifier); CT-AMT-060-01 CSR, CSL Behring; (CSL Behring, 2022d) CT-AMT-061-01 CSR, CSL Behring;(CSL Behring, 2022h) HOPEB CSR, CSL Behring (CSL Behring, 2022i).

The data from the Phase I/II and Phase IIb trials were not used to populate the economic model as per rationales below:

- CT-AMT-060-01 (NCT02396342): the 5-year data of this study can support the validation of the durability of the effect of Hemgenix. This study was not included in the economic model, as the expression cassette within AMT-060 was a predecessor to Hemgenix. AMT-060 contains the coding DNA sequence of wild-type human FIX, whilst Hemgenix has a codon-optimized coding DNA sequence of the gain-of-function Padua variant of the human FIX (containing a single amino acid change).
- CT-AMT-061-01 (NCT03489291): This study was not included in the economic model because it only included three patients.

The Phase III HOPE-B clinical trial, captured by the SLR through several abstracts (Miesbach, 2022, Leebeek FW, 2021a, Leebeek FW, 2021b, Pipe et al., 2021b, Pipe et al., 2021c, Recht, 2021, Schmidt, 2021, Pipe et al., 2020a), investigates the safety and efficacy of Hemgenix for PWHB.

For the comparator, Refixia, one pivotal Phase III study publication (Paradigm 2) that was captured by the SLR was found relevant to the current application and was used as a source of the clinical efficacy and safety data for the comparator, Refixia (Collins et al., 2014). This study was also used as the primary source of data for the indirect treatment comparison (ITC) between Hemgenix and Refixia. In parallel, the study was used in the indirect treatment comparison (ITC) of Hemgenix versus Refixia.

Details of the studies included in the assessment of the present reimbursement application are presented in Table 8. There are several studies associated with HOPE-B trial, with many presenting earlier follow-up data cuts from the trial (e.g, 6 months follow-up). One additional study for the HOPE-B trial that was included in the current application was published after the SLR was conducted and is included in the table (Pipe et al., 2023). For this application, the latest available data cut from the HOPE-B trials (i.e. 23 month follow up) has been used. It is noted however that this data has not yet been published by CSL Behring (2022g).

For detailed information about the included trials of HOPE-B and Paradigm™ 2, refer to Appendix B.

Table 8: Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study	Literature review
Recombinant long-acting glycoPEGylated factor IX in hemophilia B: A multinational randomized phase 3 trial. Collins et al. (2014)	Paradigm™ 2	NCT01333111	Completed (March 31, 2013)	Original SLR (August 2021)
Clinical outcomes in adults with hemophilia b with and without pre-existing NAbs to AAV5: 6 month data from the phase 3 etranacogene dezaparvovec hope-b gene therapy trial. (Leebeek FW, 2021a)	HOPE-B	NCT03569891	Ongoing	Updated SLR (October 2022)
Clinical outcomes in adults with hemophilia B with and without pre-existing NAbs to AAV5: 6 month data from the phase 3 etranacogene dezaparvovec HOPE-B gene therapy trial. (Leebeek FW, 2021b)				Updated SLR (October 2022)
Final analysis from the pivotal phase 3 Hope-B gene therapy trial: stable steady-state efficacy and safety of etranacogene dezaparvovec in adults with severe or moderately severe hemophilia B. Miesbach (2022)				Updated SLR (October 2022)
First data from the phase 3 HOPE-B gene therapy trial: Efficacy and safety of etranacogene dezaparvovec (AAV5-padua hFIX variant; AMT-061) in adults with severe or moderate-severe hemophilia b treated irrespective of pre-existing anti-capsid NAbs. Pipe et al. (2020b)				Original SLR (August 2021)
26 Week efficacy and safety of etranacogene dezaparvovec (AAV5-PADUA HFIX VARIANT; AMT-061) in adults with severe or moderate-severe hemophilia B treated in the phase 3 hope-B clinical trial. Pipe et al. (2021a)				Updated SLR (October 2022)
Efficacy and safety of etranacogene dezaparvovec in adults with severe or moderate-severe hemophilia B: First data from the phase 3 HOPE-B gene therapy trial. Pipe et al. (2021d)				Updated SLR (October 2022)

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Reference	Trial name	NCT number	Dates of study	Literature review
52 Week Efficacy and Safety of Etranacogene Dezaparvovec in Adults with Severe or Moderate-severe Hemophilia B: Data from the Phase 3 HOPE-B Gene Therapy Trial. Pipe et al. (2021e)				Updated SLR (October 2022)
Management of Infusion Reactions: Lessons from the Phase 3 HOPE-B Gene Therapy Trial of Etranacogene Dezaparvovec in Adults with Hemophilia B. (Recht, 2021)				Updated SLR (October 2022)
Liver safety case report from the phase 3 hope-B gene therapy trial in adults with hemophilia B. (Schmidt, 2021)				Updated SLR (October 2022)
Shah J, Kim H, Sivamurthy K, Monahan PE, Fries M. Comprehensive analysis and prediction of long-term durability of factor IX activity following etranacogene dezaparvovec gene therapy in the treatment of hemophilia B. Current Medical Research and Opinion. 2022 Oct 25;1:1.				Updated SLR (October 2022)
Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B (Pipe et al., 2023)				Desktop research (February 2023)

Abbreviation: NCT, National Clinical Trial

8. Efficacy and safety

8.1 Relevant studies

8.1.1. Overview of HOPE-B trial

An overview of the HOPE-B trial is shown in Table 9. The main study characteristics for the HOPE-B trial are summarized in Appendix B.

Table 9: Clinical effectiveness evidence

Study	HOPE-B, CT-AMT-061-02, NCT03569891
Study design	Phase III, open-label, single-dose, single-arm, multicenter (including two Nordic centers)
Population	Adult patients with moderately severe or severe haemophilia B with FIX level ≤2% of normal
Intervention(s)	Hemgenix (previously AMT-061)
Comparator(s)	Lead-in period (minimum of 26 weeks) during which patients received FIX prophylaxis
Indicate if study supports application for marketing authorization	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable

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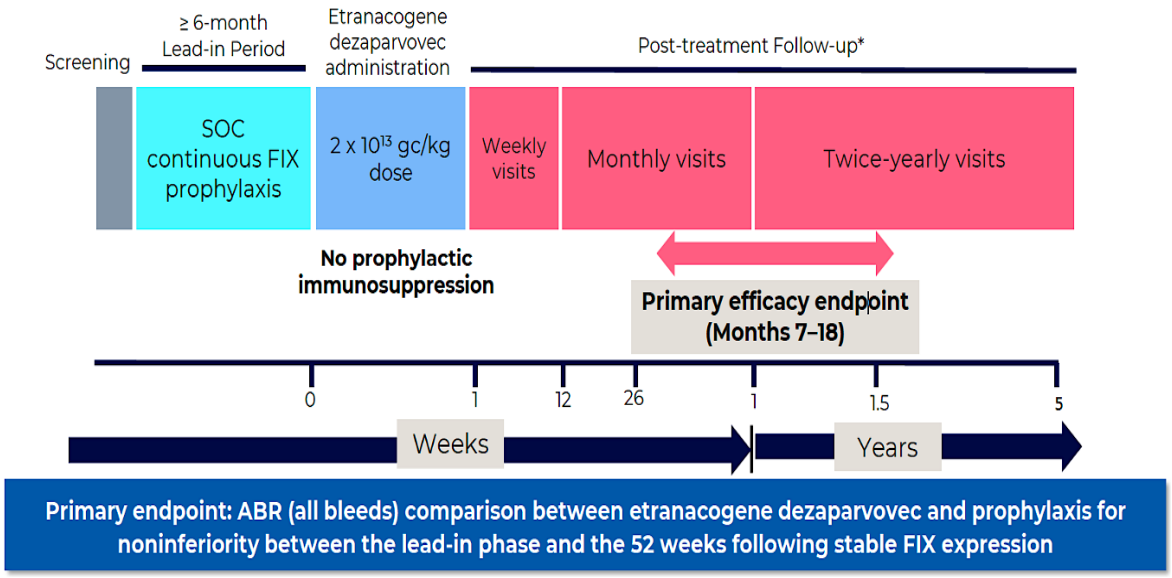
Study	HOPE-B, CT-AMT-061-02, NCT03569891
Reported outcomes specified in the decision problem*	**ABR at 7–24 months post-treatment and comparison of ABR between FIX prophylaxis therapy used in the lead-in and after administration of Hemgenix** **AjBR at 7-24 months post-treatment and comparison of AjBR between FIX prophylaxis therapy used in the lead-in and after administration Hemgenix** Secondary endpoints: FIX activity levels at 6, 12, 18 and 24 months after Hemgenix dosing
All other reported outcomes*	Use of FIX prophylaxis therapy, **AsBR, AjBR**, FIX activity levels correlated to pre-existing AAV5 NAb titers, PROs (**EQ-5D,** iPAQ, BPI, HAL, Haem-A-QoL, WPAI, PROBE), **treatment-related adverse events**.

Notes: *Outcomes marked in bold are incorporated into the economic model.
Abbreviations: AAV5, Adeno-associated virus vector serotype 5; ABR, Annualized bleeding rate; AjBR, Annualized joint bleeding rate; AsBR, Annualized spontaneous bleeding rate; BPI, Brief Pain Inventory; EQ-5D, EuroQol-5 dimensions; FIX, Factor IX; HAL, Haemophilia Activities List; HOPE-B, Health Outcomes with Padua Gene, Evaluation in Haemophilia B; iPAQ, International Physical Activity Questionnaire; NAb, Neutralizing antibody; PROBE, Patient Reported Outcome Burdens and Experiences; PROs, Patient-reported outcomes; UK, United Kingdom; WPAI, Work Productivity and Activity Impairment Questionnaire.
Source: ClinicalTrials.gov. Identifier NCT03569891 (ClinicalTrials.gov Identifier).

The HOPE-B study is an ongoing phase III, open-label, single-dose, multicenter, multinational study which investigates the efficacy and safety of Hemgenix in adult patients with severe or moderately severe haemophilia B (Figure 9) (CSL Behring, 2021c, Pipe et al., 2023). A more detailed description of the trial can be found in Appendix B.

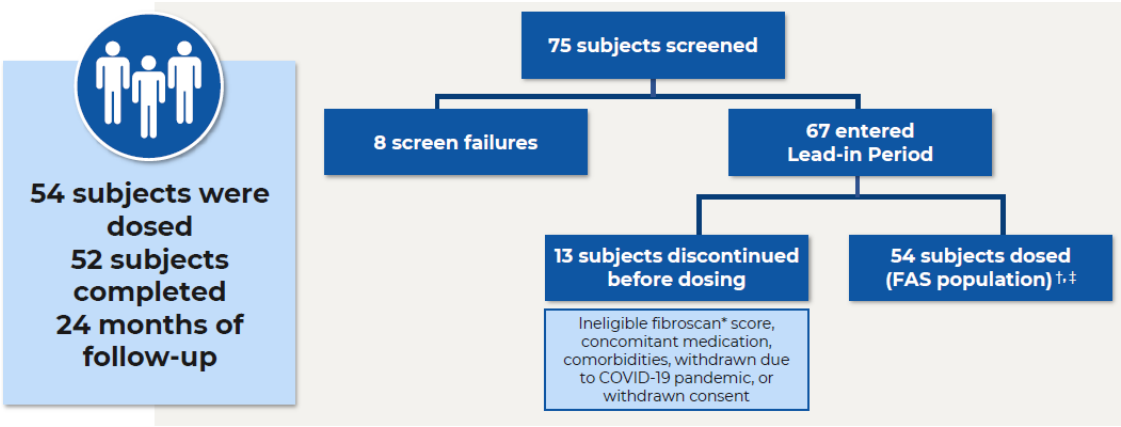
Figure 9: HOPE-B study design



Note: *At least quarterly contact (±2 weeks) between site staff and subjects to monitor occurrence of AEs. Last subject visit planned Q1 2025.
Abbreviations: ABR, Annualized bleeding rate; AE, Adverse event; FIX, Factor IX; gc, Gene copies; SOC, Standard of care.
Source: ClinicalTrials.gov. NCT03569891(ClinicalTrials.gov Identifier).

A total of 75 patients were screened, of whom 67 entered the lead-in phase. Of these 67 patients, 13 discontinued the study prior to dosing due to an ineligible FibroScan® score, concomitant medication, comorbidities, the COVID-19 pandemic, or withdrawal of consent. The remaining 54 patients constitute the full analysis set (FAS) population (Figure 10) (CSL Behring, 2021c). One patient in the FAS received only a partial vector dose (estimated ~10%) due to a suspected IRR, this patient did not express FIX-Padua or discontinue FIX prophylaxis (CSL Behring, 2022g). A total of 53 patients received the full dose of Hemgenix, whereof 52 completed six, 12, 18, and 24 months of follow-up and one patient completed six, 12 and 18 months of follow-up (CSL Behring, 2022g). One of the 53 patients who received a full dose of Hemgenix died of urosepsis and cardiogenic shock at 65 weeks post-treatment, an event confirmed as not treatment-related (CSL Behring, 2022g). The baseline characteristics of the FAS population who were recruited to HOPE-B trial are summarized in Appendix C.

Figure 10: Overview of selected patients in the HOPE-B trial



Note:
*Or equivalent scan (magnetic resonance elastography, shear wave elastography).
†FAS included subjects who enrolled, entered the lead-in period, were dosed with Hemgenix and provided ≥1 efficacy endpoint assessment.
‡PP population (N=53) included all subjects from the FAS who adhered to stable and adequate prophylaxis use during the lead-in period, completed ≥18 months of efficacy assessments, and had no major protocol deviations that impacted the interpretation of efficacy.
Abbreviations: FAS, Full analysis set; PP, Per protocol.
Source: (CSL Behring, 2022g, Pipe et al., 2023)

8.1.2. Overview of Paradigm™ 2 trial

An overview of the Paradigm™ 2 trial is shown in Table 10. The main study characteristics for the Paradigm™ 2 trial are summarized in Appendix B.

Table 10: Clinical effectiveness evidence

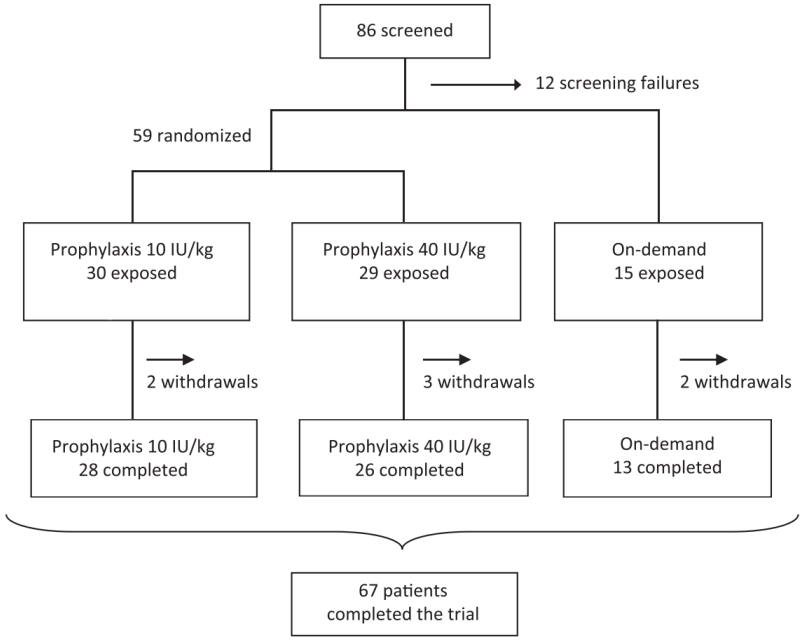
Study	Paradigm™ 2, NCT01333111
Study design	A prospective, randomized, single-blind, multicenter, phase III
Population	Male patients aged 13 to 70 years with haemophilia B (FIX activity ≤ 2 IU/dl), with no history of inhibitors to FIX, and with at least 150 exposure days to any FIX product
Intervention(s)	Refixia (Nonacog beta pegol)
Arms	• Refixia prophylaxis group 10 IU/kg once weekly • Refixia prophylaxis group 40 IU/kg once weekly • On-demand group
Indicate if study supports application for marketing authorization	Yes (ITC, see section 8.2.2)
Indicate if study used in the economic model	Yes (ITC, see section 8.2.2)
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	• Incidence of inhibitory antibodies against FIX defined as titer equal to or above 0.6 BU • Incidence of inhibitory antibodies against FIX defined as titer equal to or above 0.6 BU
All other reported outcomes	• Hemostatic effect of Refixia when used for prophylaxis of bleeding episodes, assessed as success/failure based on a four-point scale for hemostatic response (28 and 52 weeks) • Number of bleeding episodes per patient during routine prophylaxis • FIX trough levels

Study	Paradigm™ 2, NCT01333111
	• Incidence of AEs

Abbreviations: ABR, Annualized bleeding rate; AE, Adverse events, BU, Bethesda units; FIX, Factor IX; ITC, Indirect treatment comparison; IU, International unit.
Source: Collins et al. (2014).

Paradigm™ 2 is a prospective, randomized, single-blind, phase III clinical trial with the aim of evaluating the safety, efficacy and PK of Refixia (nonacog beta pegol) in previously treated PWHB (Collins et al., 2014). A total of 86 patients were screened, of whom 12 were screening failures, leaving 74 patients who were exposed to Refixia (see Figure 11). At the screening visit, 15 patients were assigned to the on-demand group while the remaining 59 patients were randomly assigned to one of two prophylaxis groups: once-weekly dosing of either 10 or 40 IU/kg. A total of seven patients were withdrawn during the trial (none due to AEs), while 67 completed the trial. The baseline characteristics of population recruited to the Paradigm™ 2 trial are summarized in Appendix C).

Figure 11: Overview of selected patients in the Paradigm™ 2



Abbreviations: IU, International units, kg, Kilograms.
Source: Collins et al. (2014).

8.2 Efficacy and safety – results per study

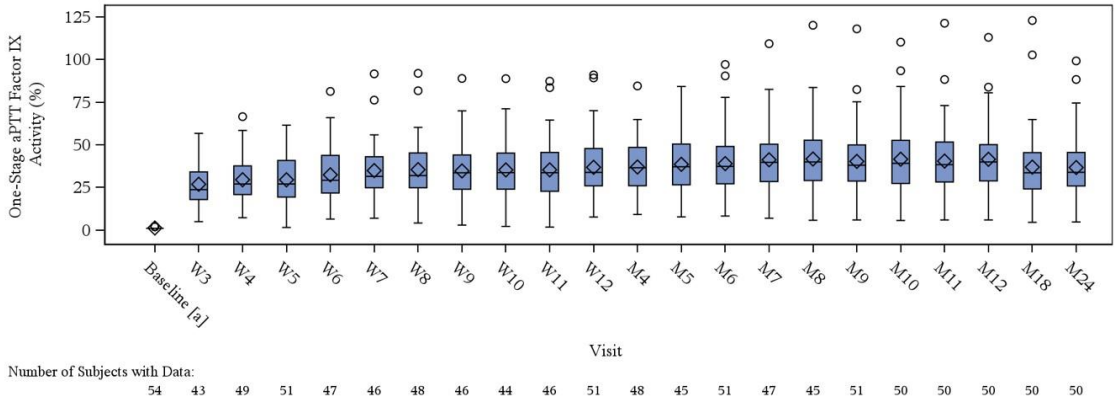
8.2.1. HOPE-B trial

8.2.1.1 FIX activity levels at 24 months after Hemgenix dosing

At 24 months, participants continued to demonstrate durable, sustained endogenous FIX activity levels with a mean endogenous FIX activity of 36.7 IU/dL (SD; min, max= ±19.0; 4.7, 99.2), as measured by a one-stage APTT-based clotting assay (Figure 12) (Pipe et al., 2022b). At 24 months, the increase in endogenous FIX activity level from baseline was 34.13 IU/dL ($p<0.001$). The cumulative proportion of subjects with an increase in average endogenous FIX activity level at Month 24 post-treatment was significantly higher ($p<0.0001$) compared with the lead-in period. By the end of the lead-in period, 43/54 (79.6%) subjects had endogenous FIX activity levels <12% of normal, and at Month 24, only 5/50 (10.0%) subjects had endogenous FIX activity levels <12% of normal. The results in Appendix D show the endogenous FIX activity levels in the post-treatment period for subjects with and without pre-existing NAbs to AAV5. As shown in Table 72 (Appendix D), both groups showed a significant increase in endogenous FIX activity level ($p<0.0001$) at 24 months compared with the lead-in period. At 18 and 24-months post-treatment, no clinically meaningful correlation

between an individual's baseline AAV5 NAb titer and FIX activity levels was identified, up to a NAb titer of <1:700 (24-month Pearson coefficient: -0.29; Spearman coefficient: -0.25; R^2: 0.086)(Pipe et al., 2022b).

Figure 12: Endogenous FIX activity level at 24 months post-treatment



Note: [a] Baseline FIX was imputed based on the historical severity of subjects' haemophilia B as documented in the case report form. For subjects who had documented severe FIX deficiency (FIX plasma level <1%), the baseline FIX activity level was imputed as 1%. For subjects who had documented moderately severe FIX deficiency (FIX plasma level ≥1% and ≤2%), the baseline FIX activity level was imputed as 2%. The standard error was not provided at baseline.
Abbreviations: aPTT, Activated partial thromboplastin time; FIX, Factor IX; M, Month; W, Week.
Source: Pipe et al. (2022b).

8.2.1.2 ABR at 24 months post-treatment

Participants recorded bleeding episodes and FIX replacement therapy use in a dedicated electronic diary from screening until 12 months post-treatment and used a paper diary from month 13 post-treatment (Pipe et al, 2023), thus any occurrence of what was believed by the patient to be a bleed was recorded and included in the calculation of ABR.
In the HOPE-B trial, the mean ABR for all types of bleeds decreased in the FAS (N=54) (Table 11), from 4.18 for the lead-in period with FIX prophylaxis to 1.51 at both 18 months and 24 months post-treatment, a reduction of 64% (95% CI: 37%, 79%; p=0.0002). Mean AsBR decreased by 75% (from 1.52 to 0.38; p=0.0005) at 24 months compared with FIX prophylaxis in the lead-in period (Pipe et al., 2022b). The mean AjBR decreased by 80% (from 2.35 to 0.46; p<0.0001) at 24 months compared with FIX prophylaxis in the lead-in period (Pipe et al., 2022b).

At 24 months post-treatment, Hemgenix demonstrated a 73% reduction in the number of bleeds that required treatment, compared with FIX prophylaxis in the lead-in period (from 3.64 to 0.99; p=0.0001) (Figure 13). Hemgenix also demonstrated a reduction of 87% in traumatic bleeds at 24 months compared with FIX prophylaxis in the lead-in period (from 1.74 to 0.23; p<0.0001) (Pipe et al., 2022b). Figure 14 shows the ABR during lead-in and post-treatment period by sub-group for FAS with baseline NAb titer <1:700.

[redacted]

8.2.1.3 Zero bleeds

The number of subjects with zero bleeds increased from [redacted] subjects at 24 months post-treatment. No clinically relevant correlation was found between baseline AAV5 NAb titer and rate of subjects with zero bleeds. For subjects with a negative baseline AAV5 NAb titer, the number of subjects with zero bleeding episodes increased from [redacted] For subjects with a positive baseline AAV5 NAb titer, the number of subjects with zero bleeds increased from [redacted]

Table 11: ABR by bleeding type during the lead-in and post-treatment periods

	≥6 month lead-in period		Months 7–24 post-treatment period				
Endpoint	**Unadjusted ABR[a] (mean no. of bleeds)**	**Adjusted ABR (95% CI)[b]**	**Unadjusted ABR[a]**	**Adjusted ABR (95% CI)[b]**	**Rate ratio (post-treatment/ lead-in)[b]**	**Two-sided 95% Wald CI**	**p-value[c]**
All bleeding episodes (N=54)	4.11	4.18 (3.22, 5.45)	0.99	1.51 (0.83, 2.76)	0.36	0.21, 0.63[d]	0.0002
All bleeding episodes (baseline AAV5 NAb negative) (N=33)							
All bleeding episodes (baseline AAV5 NAb positive) (N=21)							
All bleeding episodes (baseline AAV5 NAb titer <1:700) (N=53)	4.17	3.89 (2.93, 5.16)	0.93	1.09 (0.67, 1.79)	0.28	0.17, 0.46[d]	<0.0001
All bleeding episodes (baseline AAV5 NAb titer >1:700) (N=1)							
Spontaneous bleeding episodes (N=54)	1.51	1.52 (1.01, 2.30)	0.24	0.38 (0.16, 0.89)	0.25	0.11, 0.57[d]	0.0005
Spontaneous FIX replacement therapy-treated bleeding episodes (N=54)	1.33	1.34 (0.87, 2.06)	0.20	0.42 (0.15, 1.19)	0.31	0.11, 0.87 [d]	0.0127
Bleeding episodes, FIX replacement therapy-treated (N=54)	3.56	3.65 (2.82, 4.74)	0.58	0.99 (0.48, 2.03)	0.27	0.14, 0.54[d]	<0.0001
Joint bleeding episodes (N=54)	2.33	2.35 (1.74, 3.16)	0.35	0.46 (0.24, 0.89)	0.20	0.10, 0.37[d]	<0.0001
Joint bleeding episodes, FIX replacement therapy-treated (N=54)	2.11	2.13 (1.58, 2.88)	0.30	0.40 (0.20, 0.83)	0.19	0.09, 0.38[d]	<0.0001
Traumatic bleeding episodes (N=54)							
Traumatic bleeding episodes, FIX replacement therapy-treated (N=54)							

	≥6 month lead-in period		Months 7–24 post-treatment period				
Endpoint	**Unadjusted ABR[a] (mean no. of bleeds)**	**Adjusted ABR (95% CI)[b]**	**Unadjusted ABR[a]**	**Adjusted ABR (95% CI)[b]**	**Rate ratio (post-treatment/ lead-in)[b]**	**Two-sided 95% Wald CI**	**p-value[c]**
New and true bleeding episodes (N=54)	XXX XXX	XXX XXX XXX	XXX	XXX XXX XXX	XXX	XXX XXX	XXX XXX
New and true bleeding episodes, FIX replacement therapy-treated (N=54)	XXX XXX	XXX XXX XXX	XXX	XXX XXX XXX	XXX	XXX XXX	XXX XXX

Notes:
[a] Unadjusted ABR was calculated as the ratio of the number of bleeding episodes to the time at risk (in years).
[b] Adjusted ABR and comparison of ABR between the lead-in and post-treatment periods was estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.
[c] One-sided p-value ≤0.025 for post-treatment/lead-in <1 was regarded as statistically significant.
[d] The upper limit of the CI of the rate ratio was compared with the non-inferiority margin of 1.8. If the upper limit was <1.8, then non-inferiority was declared (NI met).
[e] This subject did not respond to the treatment with Hemgenix, and was switched to prophylactic treatment. The subject's last visit was 18 months after receiving Hemgenix. The time within five half-lives of a FIX injection was removed from the time at risk, which resulted in approximately 1 day (1.09 days) at risk during Months 7 to 12, 7 to 18, and 7 to 24 after receiving the intervention. During this time, the subject had four spontaneous and one unknown bleeding event, giving an ABR of 1673.97.
[f] p-value not adjusted for multiplicity.
Abbreviations: AAV5, Adeno-associated virus vector serotype 5; ABR, Annualized bleeding rate; CI, Confidence interval; FAS, Full analysis set; FIX, Factor IX; NAb, Neutralizing antibody; N/A, Not applicable; NI, Non-inferiority; SUP, Superiority.
Source: HOPE-B study results overview: 24-month data (CSL Behring, 2022i, EMA, 2023)

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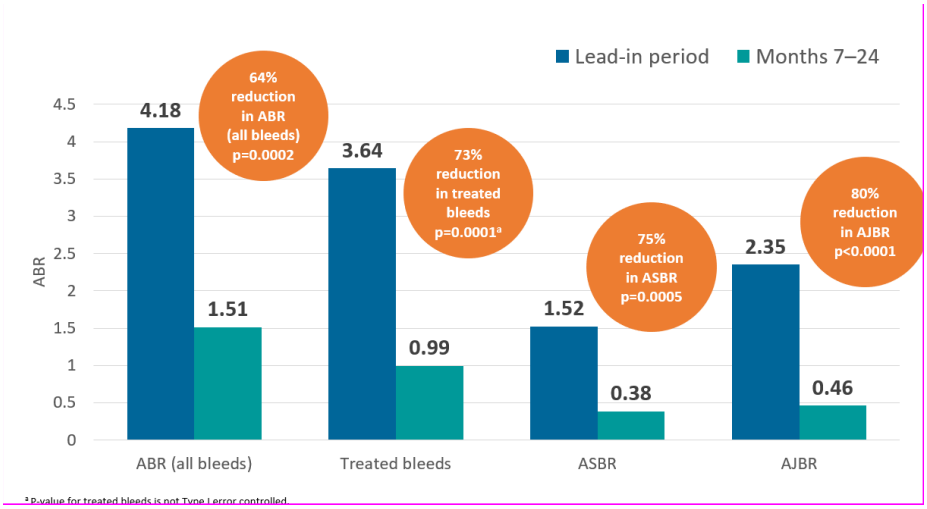
Figure 13: ABR comparison of the lead-in phase with the post-treatment period (7–24-month post-treatment of Hemgenix)a



Abbreviations: ABR, Annualized bleeding rate; AsBR, Annualized spontaneous bleeding rate; AjBR, Annualized joint bleeding rate.
Source: (Pipe et al., 2022b).

Figure 14: ABR during lead-in and post-treatment period by sub-group (FAS baseline NAb titer <1:700)

Note:
[a] Ratio is the ABR ratio of post-treatment Months 7–24 versus lead-in-adjusted ABR; a comparison of ABR between the lead-in and post-treatment periods is estimated from a repeated measures generalized estimating equations, negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. The treatment period is included as a categorical covariate.
[b] Two-sided 95% Wald CI is compared with the non-inferiority margin of 1.8. If the upper limit was <1.8, then non-inferiority was declared.
[c] One-sided p-value ≤0.025 for post-treatment/lead-in <1 was regarded as statistically significant.
Abbreviations: ABR, Annualized bleeding rate; CI, Confidence interval; FAS, Full analysis set; HIV, Human immunodeficiency virus; NAb, Neutralizing antibody; S2, Moderate steatosis.
Source: HOPE-B study results overview: 24-month data [data on file] (CSL Behring, 2022i).

8.2.1.4 Annualized consumption of FIX replacement therapy at 24 months

In the HOPE-B trial, Hemgenix demonstrated a significant reduction in consumption of FIX replacement therapy at 24 months compared with the lead-in period on FIX prophylaxis therapy, with a mean (SD) difference in consumption of FIX replacement therapy being [redacted] Table 73, Appendix D). In subjects with a baseline NAb titer <1:700, the adjusted mean consumption of FIX replacement therapy decreased by [redacted] At month 24, compared with the lead-in period on FIX prophylaxis therapy, the number of subjects (N=54) using FIX replacement therapy decreased from 100% to 24.5% (N=13) Table 73, Appendix D). The mean number of infusions/year of FIX replacement therapy per subject decreased from 44.1 to 0.8 (CSL Behring, 2022h).

8.2.1.5 Bleed rate sensitivity analysis

In the HOPE-B trial, sensitivity analysis was conducted to assess the ABR, AjBR and AsBRs for patients using different definitions for bleeds. Six definitions for bleeds and time at risk were used in the primary and sensitivity analysis. These definitions are

summarized in Table 12 and form the Primary Endpoint, Sensitivity 2, Sensitivity 3, Sensitivity 5, Sensitivity 6, and Sensitivity 7 analyses of HOPE-B and are described more fully in the HOPE-B SAP (CSL Behring, 2021c).

Table 12: ABR definitions available in the HOPE-B trial

Endpoint defined in HOPE-B SAP	Definition for Bleed count	Definition for Time at risk
Primary Endpoint[a]	Any bleeding events between stable FIX expression and study completion or early withdrawal	Time between stable FIX expression and study completion or early withdrawal, excluding time within 5 half-lives subsequent to exogenous FIX use
Sensitivity Analysis 2	Same as primary endpoint	Time between stable FIX expression and study completion or early withdrawal, but not excluding (including) time within 5 half-lives subsequent to exogenous FIX use
Sensitivity Analysis 3	Any bleeding events between stable FIX expression and study completion or early withdrawal that were treated with exogenous FIX	Same as primary endpoint
Sensitivity Analysis 5	Any bleeding events between stable FIX expression and study completion or early withdrawal that were determined to be new and true[b]	Same as primary endpoint
Sensitivity Analysis 6	Any bleeding events between stable FIX expression and study completion or early withdrawal that were both treated with exogenous FIX and determined to be new and true[b]	Same as primary endpoint
Sensitivity Analysis 7	Same as primary endpoint	Time between stable FIX expression and study completion or early withdrawal, excluding time within 5 half-lives subsequent to exogenous FIX use and periods contaminated by systemic corticosteroid exposure

Note:
[a]The primary endpoint definition is accompanied by several details in the HOPE-B Protocol and Statistical analysis plan (SAP) and those details apply to all sensitivity analyses unless the modification introduced by the sensitivity analysis overrides the element defined in the primary endpoint. Details include: "The post-AMT-061 administration time at risk of (having) a bleeding event is the subject's time on the study between stable FIX expression … and the time that is 52 weeks following stable FIX expression …, the time of study completion, or the time of early withdrawal from the study, whichever is earlier. Any bleeds prior to stable FIX expression … of the post-treatment period are not considered in the analysis. …In the analysis, any person-time during the post-treatment period within 5 half-lives subsequent to exogenous FIX use will not be counted in the time at risk of (having) a bleeding event. Nevertheless, any bleeds occurring on or after stable FIX expression … should still be counted as events, even if they occurred during a time interval of "contamination"." (Source: HOPE-B SAP Version 4.0, p. 49) (CSL Behring, 2021a, CSL Behring, 2021c).
[b]New and true bleeds were determined as follows: "Investigators will review and assess reported bleeds as a means of verifying that patient-reported events meet the clinical criteria required to be characterized as new, true bleeds. … The Principal Investigator or designee evaluates the signs and symptoms reported in the diary and/or during discussions with the patient and assesses whether the reported event was a true bleed and whether the reported event was a new bleed. …based on such sign and symptom evaluation, the investigator in some cases may need to distinguish whether there is a new bleed or whether the patient is experiencing pain (due e.g. to previous chronic joint bleeds and damage) that is not really a new bleed. … When patients are next at the study site, the physician may elect to use a diagnostic scan (X-ray, ultrasound, MRI, CT scan, etc.) to confirm the presence of blood or signs of acute inflammation. Blood or signs of acute inflammation observed using one or more of these confirmatory methods coupled with the physician's assessment will serve as sufficient confirmation to identify an event as a true bleed." (CSL Behring, 2021c).
Abbreviations: ABR, Annualized bleeding rate; FIX, Factor IX; SAP, Statistical analysis plan.
Source: (CSL Behring, 2021b, CSL Behring, 2021c)

In the health economic model, the ABR and AjBR results from Sensitivity analysis 6 are used to inform the efficacy parameters. The results from sensitivity analysis 6 are therefore presented in Table 13. For the economic model, the Sensitivity Analysis 6 results are used because the definition for a bleed allows an assessment of the effectiveness of the Hemgenix compared to the Refixia to reduce bleeds post-administration, independent of a patient's previous bleed or health history.

Table 13: Bleeding outcomes (ABR, AsBR, AjBR) for HOPE-B sensitivity analysis 6

Outcome	HOPE-B (N=51)[a]	95% CI
ABR, per Sensitivity Analysis 6 from HOPE-B	[redacted]	[redacted]
ABR, per Primary Analysis from HOPE-B	[redacted]	[redacted]
AsBR, per Sensitivity Analysis 6 from HOPE-B[b]	[redacted]	[redacted]
AsBR, per Primary Analysis from HOPE-B	[redacted]	[redacted]
AjBR, per Sensitivity Analysis 6 from HOPE-B[b]	[redacted]	[redacted]
AjBR, per Primary Analysis from HOPE-B	[redacted]	[redacted]

Note:
[a] Rates calculated from Month 7 – 24 post-treatment follow-up period of HOPE-B.
[b] AjBR and AsBR per sensitivity analysis 6 of HOPE-B were derived in HOPE-B for this analysis and values are not present in the clinical study report.
Abbreviations: ABR, Annualized bleeding rate; AsBR, Annualized spontaneous bleeding rate; AjBR, Annualized joint bleeding rate.
Source: CSL Behring (2022g)(CSL Behring, 2022d, CSL Behring, 2022c)

8.2.1.6 Results of patient reported quality of life outcomes at month 24

In the pivotal HOPE-B trial, PWHB treated with Hemgenix (N= 54) demonstrated significant improvements (i.e. lower Haem-A-QoL scores indicating better QoL) at 24 months in total score and across four sub-domains (feelings, treatment, work/school and future) of the Haem-A-QoL PRO measure [redacted] and in mean EQ-5D-5L VAS [redacted] and EQ-5D-5L index score [redacted] as shown in Table 14 (CSL Behring, 2022h, CSL Behring, 2022i). As could be expected with the limited number of patients, the HOPE-B study failed to prove significance for improvement in many QoL parameters where the difference is more subtle; this is the case for the other Haem-A-QoL domains (e.g. physical health, family planning, dealing with haemophilia, sport and leisure, view of yourself, partnerships and sexuality) and for non-haemophilia-specific measures (iPAQ, PROBE, WPAI) (CSL Behring, 2022h).

Improvements in QoL suggest that Hemgenix can reduce the treatment burden of regular infusions associated with FIX prophylaxis therapy. This may contribute to the observed improvement in work and school performance and may provide PWHB with a sense of optimism for the future (CSL Behring, 2022h).

Table 14: PROs Haem-A-QoL treatment domain score comparison between treatment periods, 24 months data (FAS population; N=54)

Domain (overall lead-in period versus post-treatment period, first year)	Lead-in period, LS mean[a]	Post-treatment period, LS mean[a]	Difference between treatment period, mean (SE)[a]	One-sided p-value[b]
Haem-A-QoL, total	[redacted]	[redacted]	[redacted]	[redacted]
Work/school	[redacted]	[redacted]	[redacted]	[redacted]
Feelings	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Future	[redacted]	[redacted]	[redacted]	[redacted]
Physical health	[redacted]	[redacted]	[redacted]	[redacted]
Family planning	[redacted]	[redacted]	[redacted]	[redacted]
Dealing with haemophilia	[redacted]	[redacted]	[redacted]	[redacted]
Sport and leisure	[redacted]	[redacted]	[redacted]	[redacted]
View of yourself	[redacted]	[redacted]	[redacted]	[redacted]
Partnerships and sexuality	[redacted]	[redacted]	[redacted]	[redacted]
WPAI				
Absenteeism	[redacted]	[redacted]	[redacted]	[redacted]
Presenteeism	[redacted]	[redacted]	[redacted]	[redacted]
Work productivity loss	[redacted]	[redacted]	[redacted]	[redacted]
Activity impairment	[redacted]	[redacted]	[redacted]	[redacted]
BPI, FAS				

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Domain (overall lead-in period versus post-treatment period, first year)	Lead-in period, LS mean[a]	Post-treatment period, LS mean[a]	Difference between treatment period, mean (SE)[a]	One-sided p-value[b]
Pain intensity	[redacted]	[redacted]	[redacted]	[redacted]
Pain interference	[redacted]	[redacted]	[redacted]	[redacted]

Note: Questionnaires completed within 2 weeks of a bleed were not included in the analysis or descriptive summaries. A higher score indicated a lower QoL. Score ranged from 0 to 100.
[a] LS mean from a repeated measures linear mixed model with period (lead-in or post-treatment), Visit (A or B), and period-by-visit interaction as categorical covariates. Subject was modelled as a random effect.
[b] The overall p-value for the lead-in period versus post-treatment first year was based on a contrast across Visits A and B, with equal weight. A one-sided p-value ≤0.025 for post-treatment lead-in of <0 was regarded as statistically significant.
Abbreviations: BPI, Brief Pain Inventory; FAS, Full analysis set; Haem-A-QoL, Haemophilia-Specific Quality of Life Index; LS, Least squares; SE, Standard error; WPAI, Work Productivity and Activity Impairment questionnaire.
Source: CSL Behring. EMAT PRO Results Part II [data on file], 2022 CSL Behring (2022h).

Table 15: PROs EQ-5D-5L score comparison between treatment periods, 24 months data (FAS population; N=54)

EQ-5D-5L measure	Lead-in period, LS mean[a]	Post-treatment period, LS mean[a]	Difference between treatment period, mean (SE)[a]	One-sided p-value[b]
EQ-5D-5L index score	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS	[redacted]	[redacted]	[redacted]	[redacted]

Note:
[a] LS mean from repeated measures linear mixed model with period (lead-in or post-treatment), Visit (A or B), and period-by-visit interaction as categorical covariates. Subject was modelled as a random effect.
[b] The overall p-value for the lead-in period versus post-treatment first year was based on a contrast across visits A and B, with equal weight. A one-sided p-value ≤0.025 for post-treatment lead-in of <0 was regarded as statistically significant.
Abbreviations: EQ-5D-5L, EuroQol five-dimension 5-level; FAS, Full analysis set; LS, Least squares; PROs, Patient-reported outcomes; SE, Standard error; VAS, Visual analogue scale.
Source: CSL Behring (2022h), CSL Behring (2021b)

8.2.1.7 AEs

During the 24 months post-dose, all participants experienced at least one treatment-emergent AE (TEAE); of the 557 events, 424 (76%) were mild, 115 (21%) were moderate, and 18 (3%) were severe. A total of 38 participants (70.4%) experienced 93 treatment-related TEAEs, with only one occurring during Months 18–24. There were no serious AEs (SAEs) related to treatment; a SAE of hepatocellular carcinoma was determined by independent molecular genomic and integration analysis to be unrelated to treatment (Pipe et al., 2022b). TRAEs with an incidence of >5% are reported in Table 75 in Appendix E.

8.2.1.8 Safety of Hemgenix versus SOC

The EMA concluded in their public assessment report that the short- to medium-term magnitude and durability of the demonstrated clinical benefits (i.e. clinically relevant levels of endogenous FIX activity, improvement of bleeding frequency over SOC, minimal need for external factor replacement) of treatment with Hemgenix are considered to outweigh the observed short-to medium-term safety concerns (i.e. infusion reactions, influenza-like illness, headache, transaminitis).

However, in their assessment, the EMA considered diligent post-marketing surveillance of utmost importance to detect potential rare AEs and to investigate the potential risk of malignancy (due to vector integration) on the longer term. As detailed in section 6.3.1.2, patients must be well-informed about this to receive Hemgenix. In this regard, a warning has been added to the Summary of Product Characteristics (SmPC) and package leaflet to inform on the potential risk of malignancy as a result of vector integration in liver cells and in other body cells (see section 6.3.1.2). These aspects are covered in the SmPC and Package leaflet and in the educational materials in the risk management plan.

8.2.2. Paradigm™ 2

8.2.2.1 Efficacy

For information on the efficacy results of the Paradigm™ 2 trial and how are they used as part of an ITC, please refer to Section 8.3 below.

8.2.2.2 Safety

In the Paradigm 2 trial, it was reported that no patients developed FIX inhibitors, and no deaths, thromboembolic events, or allergic reactions related to Refixia (Collins et al., 2014).

A total of 215 AEs (seven severe, 25 moderate, and 183 mild) in 60 (81%) patients were reported, corresponding to 3.33 AEs per patient year of exposure. The most commonly reported AEs were nasopharyngitis (13 events in 10 patients [13.5%]), influenza (10 events in eight patients [10.8%]), and upper respiratory tract infection (10 events in eight patients [10.8%]). There were four SAEs (hip fracture, worsening of skin ulcer, retroperitoneal hematoma, and abdominal pain) in four patients (5.4%). These SAEs were reported by the investigator as unlikely to be related to Refixia. No safety concerns were identified from physical examinations or clinical laboratory tests (Collins et al., 2014).

In the European public assessment report (EPAR) on Refixia, the EMA reported that the adverse events identified in the six assessed trials for Refixia did not give rise to concern and did not reveal unexpected safety concerns (EMA, 2017). Of the 645 adverse events reported across a pooled trial population of 98 patients, the majority of the adverse events were of mild severity and considered unrelated to treatment. Only 37 adverse events in 23 patients were considered possible or probably related to Refixia, with an exposure rate of 0.2 events per patient year of exposure. The EMA assessed that of these 37 adverse events, a causal relationship with Refixia could not be excluded for the following adverse events; fatigue, hot flush, nausea and palpitations. Subsequently, these adverse events were added to the list of adverse reactions in the Refixia SmPC (SmPC, 2022b).

A summary of the possibly or probably related adverse events assessed by the EMA is provided in Appendix E.

8.3 Comparative analyses of efficacy and safety

In the absence of head-to-head evidence, an ITC has been conducted to determine the comparative efficacy of Hemgenix to Refixia (CSL Behring, 2022e). It should be noted that the Paradigm™ 2 trial started in 2011, while HOPE-B started seven years later in 2018. The introduction of Refixia and other EHL FIX products, as evidenced by the Paradigm™ 2 trial, was an important step forward and improved outcome for Hemophilia B patients. While no EHL FIX products were available in 2011, most patients entering the HOPE-B study in fact had EHL FIX prophylaxis before entering the study. This is also reflected in that 15/29 patients in the Refixia 40IU/kg group of the Paradigm™ 2 trial had identified target joints, while at the time for Hemgenix dosing only 2/54 HOPE-B patients had target joints (, both resolved after Hemgenix treatment,) identified during the lead-in period(Collins et al., 2014, EMA, 2023). Though the definition for a target joint was slightly more strict in the HOPE-B trial, counting only *spontaneous* bleeds(EMA, 2023, Collins et al., 2014), it reflects a pre-trial population that had benefitted from progress made in clinical haemophilia B treatment, since the Paradigm™ 2 trial. Differences in study population make it important to match-adjust the comparison to compensate. However, it is not possible to match all known and unknown parameters that may affect outcome in two different trials; for that reason, it is important to see an ITC as a complement to the more robust results obtained from the HOPE-B study itself, comparing lead-in to post treatment phase in the same patient population(Pipe et al., 2023).

8.3.1. Method of synthesis

The ITC included results from HOPE-B and other data sources identified in a SLR by Davis et al. 2019 (Davis et al., 2019) which has been updated for this submission (see Appendix D). The SLRs identified a pivotal Phase III comparator trial, namely Paradigm™ 2, as a key source of efficacy data for Refixia (Table 16)(Collins et al., 2014).

Table 16: Summary of the single-arm trials used to carry out the ITCs

Trial name	Treatment	Data cut-off	Post-treatment follow-up (months)	Analysis dataset	N
HOPE-B	Hemgenix	24-month data cut	Approximately 18 months[b] (months 7 to 24)	[redacted]	[redacted]
Paradigm™ 2	Refixia	Final data as reported by (Collins et al., 2014)	Approximately 12 months[f]	[redacted]	[redacted]

Note:
[a]Data cut-offs with the most complete data availability were included.
[b]The median follow-up time in HOPE-B 24-month data-cut is approximately 1.485 years.
[f]The follow-up time in Paradigm™ 2 was reported as 52 (±2) weeks of treatment (Collins et al., 2014).
Abbreviations: ITC, Indirect treatment comparison; FAS, Full analysis set, IU, International unit.

Source: Eversana ITC report 2022 CSL Behring (2022e).

8.3.2. Overall approach and summary of feasibility assessments

An ITC feasibility assessment determined the best sources of data to support an ITC of Hemgenix and Paradigm™ 2 for Refixia (CSL Behring, 2022e). Because the Phase III trial provides only single-arm data with no common comparators, a network meta-analysis (NMA) was not feasible. The indirect comparison of Hemgenix and recombinant FIX products therefore depended on pairwise, unanchored ITC methods using the best available data (i.e. individual patient-level data [IPD] versus summary-level data [SLD]) per comparison (Figure 15).

Figure 15: Summary of feasibility of ITC analyses

Comparison	ABR	AsBR	AjBR	% 0 ABR	% 0 AsBR	% 0 AjBR	Fix consumption	EQ-5D	Haem-A-QoL
EntranaDez (IPD) Vs Refixia (SLD)	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	Not possible due to lack of comparator data	Not possible due to lack of comparator data	Not possible due to lack of comparator data	MAIC adjusting for key factors	MAIC adjusting for key factors

Abbreviations: ABR, Annualized bleeding rate; AjBR, Annualized joint bleeding rate; AsBR, Annualized spontaneous bleeding rate; EQ-5D, EuroQol-5 dimensions-5 levels; EtranaDez, Hemgenix; FIX, Factor IX; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; IPD, Individual patient-level data; IPTW, Inverse probability of treatment weighting; SLD, Summary-level data.
Source: Adapted from ITC report 2022 (CSL Behring, 2022e).

Differences in trial designs and patient populations between HOPE-B and the pivotal Phase III Paradigm™ 2 trial were identified, suggesting that population-adjustment ITC methods leveraging IPD from HOPE-B would be a feasible and robust approach to mitigating bias while comparing Hemgenix with Refixia. Given the limited sample sizes between the two trails to the number of potentially prognostic or effect-modifying factors, it is expected that only a small number of factors may be included in adjustments. Nevertheless, an improvement upon unmatched and unadjusted (naïve) comparisons can and should be made.

8.3.3. Methodology of the ITCs

A panel of two methodological experts was assembled to provide expertise and guidance regarding ITC methodology and analytical approaches comparing HOPE-B using IPD to the Paradigm™ 2 trial using IPD or SLD. Given that HOPE-B is a single-arm trial and comparator trials provide single-arm data, a NMA between treatments of interest is not possible. Thus, the ITC methods deemed appropriate to consider for this analysis were population-adjustment methods. The indirect comparisons of Hemgenix (HOPE-B) with Refixia (Paradigm™ 2) was performed using unanchored matching-adjusted indirect comparison (MAIC) (Signorovitch et al., 2012).

Propensity-score based methods were favored over outcome regression-based approaches due to more severe limitations encountered with the latter, related to modelling rare event count outcomes with small sample sizes (e.g., lack of model convergence). Importantly, simulated treatment comparisons (STCs) of count type outcomes would require simulation-based approaches to overcome aggregation bias in the relative treatment effects (Ishak et al., 2015, Daniel et al., 2021). This approach would require very strong assumptions regarding the multivariate correlation between baseline covariates and time at risk (e.g., through a copula) (Phillippo et al., 2020) to adequately simulate the data and estimate relative treatment effects.

The statistical methods behind the chosen propensity-score based population-adjustment approaches and specifications of primary and sensitivity analyses follow the NICE guidance and Technical Support Documents (TSD) approach (Faria R, 2015, Phillippo DM, 2016).

8.3.4. MAIC for Hemgenix (HOPE-B) versus Refixia (Paradigm™ 2)

8.3.4.1 Target population

Ideally, the target population for the comparison between Hemgenix and Refixia would have been that defined by the eligibility criteria of HOPE-B, being adult patients with severe haemophilia B who received prior prophylaxis with FIX products (see Section 8.2.2). However, given the restrictions of MAIC due to only having IPD from HOPE-B, the target population was that of the 40 IU/kg group of Paradigm™ 2. As described previously, data was scarcely reported for the prior prophylaxis subpopulation from Paradigm™ 2. Therefore, to provide the best estimates of relative treatment effect possible per outcome, ITCs were conducted using both the prior prophylaxis subpopulation (the “primary population” or “primary analysis” in this Hemgenix versus Refixia analysis) and the full 40 IU/kg population (the “secondary population” or “secondary analysis” in this Hemgenix versus Refixia analysis) from Paradigm™ 2, which consists of subjects who had received either prophylaxis or on-demand FIX products prior to study entry.

8.3.4.2 Matching on eligibility criteria

Eligibility criteria that were broader for HOPE-B compared to Paradigm™ 2 included age (HOPE-B allowed patients aged ≥70 while Paradigm™ 2 did not) and BMI (HOPE-B had no restriction on BMI while Paradigm™ 2 required ≤35). However, matching on these factors were not performed to retain sample size for analysis. The HOPE-B population was narrower in the remainder of key eligibility criteria that differed, thus matching on eligibility criteria was not performed for the comparison of Hemgenix and Refixia. However, the availability of outcome data for the prior prophylaxis population from Paradigm™ 2 enabled an analysis restricted to that population (i.e., matched on prior FIX replacement type [prophylaxis or on-demand]). Despite the lack of baseline characteristics reported by Paradigm™ 2 for this prior prophylaxis population, this was deemed such a crucial moderator of baseline characteristics and outcomes, and overall alignment between trial populations, that it was considered as the primary population and primary analysis to use in ITCs.

8.3.4.3 Calculating patient weights and choice of estimand

The adjustment step of MAIC involves estimating patient weights through the method of moments estimator for the propensity score (Phillippo, 2018, Signorovitch et al., 2012, Phillippo DM, 2016). Method-of-moments is typically chosen both out of necessity, due to only having SLD for comparator trials, and because it guarantees an exact balancing on the first and second moments (mean and variance) of clinical factors between trials. Specifically, the first and second moments (mean and variance) of clinical factors from HOPE-B will become almost exactly equal to those reported for Paradigm™ 2 (Signorovitch et al., 2010, Phillippo DM, 2016). The estimand can be perceived as the average treatment effect in the comparator (ATC); a mapping of the outcome for patients taking Hemgenix to the Paradigm™ 2 population. Implementation of the approach was performed following code from NICE TSD 18 (Phillippo DM, 2016) in R version 3.6.1 (R Core Team, 2019).

8.3.4.4 Estimating indirect relative treatment effects

Estimates of the relative efficacy of Hemgenix versus Refixia were derived as the difference between (a) an estimate of the outcome of interest (ABR, AjBR, AsBR, % 0 ABR, EQ-5D, Haem-A-QoL) for Hemgenix based on weighted IPD from HOPE-B, and (b) the reported outcome for Refixia from SLD from Paradigm™ 2, respectively. The weighted estimate from HOPE-B was derived using a weighted, intercept-only generalized linear model with an appropriate distribution and link function to ensure a suitable scale was used for estimation per outcome, applying the patient weights derived. A Poisson distribution with log link function was used for rate outcomes ABR, AjBR and AsBR to match the model used and reported by Paradigm™ 2; estimated naïve rates for HOPE-B in Hemgenix versus Refixia comparisons will therefore differ to those estimated versus other comparators for which a negative binomial model was used. The intercept represents an estimate of the outcome of interest on the linear predictor scale (i.e., log-rate) had patients from Paradigm™ 2 received Hemgenix. A binomial distribution with logit link function (i.e., logistic regression) was used for binary outcome % 0 ABR, where the intercept represents the log odds of the outcome of interest had patients from Paradigm™ 2 received Hemgenix. A Gaussian (normal) distribution with identity link function (i.e., linear regression) was used for the continuous outcomes EQ-5D and Haem-A-QoL, where the intercept represents the mean of the outcome of interest had patients from Paradigm™ 2 received Hemgenix.

Robust standard error (SEs) were estimated using the sandwich estimator to account for weights being estimated rather than known (Austin and Stuart, 2015, Joffe et al., 2004). The SEs were used to construct two-sided 95% Wald CIs with corresponding P values. Test-wise P values are presented, and multiplicity of testing was not considered.

8.3.4.5 Deriving quantities from reported Paradigm™ 2 data

The relative treatment effects estimated from MAIC for rate outcomes rely on the comparator study (Paradigm™ 2) adequately reporting log rates and their variances per outcome. Derivation or imputation with assumptions was required for certain quantities from Paradigm™ 2 to enable estimation of relative treatment effects via MAIC for rate outcomes. The approaches are described here. Notably, additional efficacy outcomes for the Hemgenix versus Refixia comparison (% 0 ABR, EQ-5D, and Haem-A-QoL) did not require derivation or imputation, and quantities from Paradigm™ 2 used to estimate relative treatment effects from MAIC for binary and continuous outcomes were directly reported by Paradigm™ 2.

For ABR and AsBR in the full population, Paradigm™ 2 reported the estimated rate and 95% CI from a Poisson model. The reported rate was log-transformed and directly used in the estimation of the relative treatment effect via MAIC. The variance of the log rate was derived from log-transformed lower and upper bounds of the reported 95% CI, assuming the CI had been constructed using the Wald approach (the approach was not reported).

For ABR in the prior prophylaxis population, Paradigm™ 2 only reported the estimated rate without a CI. The estimated rate was log-transformed and directly used, while the variance was imputed to be equal to the variance of the log rate derived for the full population. This same variance was also used to impute the standard deviation estimate for the prior ABR baseline characteristic. The validity of this assumption depends on there being similar distribution in ABR across the prior prophylaxis group and full group in Paradigm™ 2.

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8.3.4.6 Performance assessment and model selection

For a given set of ranked factors included in the estimation of MAIC patient weights, the performance and suitability of each model was assessed based on the following criteria:

- Effective sample size (ESS): Calculated by $ESS = (\sum w_i)^2/(\sum w_i^2)$, where $w_i, i = 1, \dots N$, are the patient weights estimated by the propensity score model. A low ESS relative to the original sample size N indicates large variability in patient weights due to large imbalances in patient populations prior to reweighting. The ESS is interpreted as the number of independent, non-weighted individuals needed to obtain an equally precise estimate compared to that calculated from the weighted sample (Phillippo, 2018). That is, it may be interpreted as the number of patients in a sample after weighting in the context of the current MAIC. Given the use of an ATC estimand, the ESS for HOPE-B varied based on the set of ranked factors included, while the ESS of Paradigm™ 2 was equal to the N behind reported outcome data. Patients from HOPE-B with missing data in any of the outcome or set of ranked factors involved in the analysis were removed, resulting in a complete-case analysis and assumption that missingness was at random.
- Distribution of patient weights: The distribution of patient weights was evaluated, and five-point summaries involving the minimum, Q1, median, Q3, and maximum of the distribution were presented. Extreme patient weights can indicate uncertainty in the resulting relative treatment effect. For example, a large maximum patient weight relative to the ESS could indicate that the relative treatment effect is predominantly determined by a single patient.
- Balance of baseline characteristics: Summary statistics (e.g., means, SDs, proportions) for each ranked and available factor before and after matching and adjusting steps were assessed to evaluate the improvement in balance between trial populations. Balance was assessed using the absolute value of the SMD for each ranked factor, as calculated by Yang and Dalton (2012) (Yang and Dalton, 2012). An SMD ≥0.2 is considered indicative of potentially important imbalances between comparisons (Austin, 2009). For a given ranked factor, a reduction in the SMD after matching and adjusting signifies a reduction in imbalance between studies.

Naïve comparisons were first conducted to establish a benchmark for the relative treatment effect. Then, univariable (one-at-a-time) MAIC estimates were derived for each ranked factor to determine the impact on the diagnostics described above. Separate MAICs were then conducted sequentially, adjusting for one additional factor at a time in order of ranked importance. If a particular ranked factor dramatically reduced ESS for marginal gains in baseline characteristic balance and at the expense of including additional factors, then the sequential process was re-initiated skipping that factor. This process was repeated until a reasonable number of highly ranked factors were included considering the trade-off of ESS, distribution of patient weights, and improvement in baseline characteristic balance (e.g., through SMDs). The final model selected from this sequential process was declared the base case relative treatment effect from which to draw conclusions regarding the relative efficacy of Hemgenix to Refixia for each outcome.

8.3.4.7 Efficacy outcomes for base-case analysis

A total of nine efficacy outcomes were assessed in this analysis, ABR, AsBR, AjBR, % 0 ABR, % 0 AsBR, % 0 AjBR, annualized FIX consumption, EQ-5D, and Haem-A-QoL, with the full results and summaries available in the ITC report (CSL Behring, 2022e). In this submission, we have reported on the efficacy outcomes used to inform the model, namely ABR, AjBR and the PROs EQ-5D and Haem-A-QoL, where available. AsBR was reported where available for completeness.

Due to reporting limitations from the comparator trials, a change from baseline analysis was not possible for most bleeding outcomes. Therefore, absolute comparisons of bleeding outcomes were pursued, adjusting for prior ABR where possible. In contrast, a change-from-baseline analysis was favored for the PRO endpoints over using an absolute measure and adjusting for baseline. This was because the comparator trials did not report post-treatment adjusted values for these endpoints.

8.3.5. Results from the comparative analysis

The MAICs for Hemgenix versus Refixia were split by Paradigm™ 2 trial population. The primary analysis compared HOPE-B to the subgroup of patients from the 40 IU/kg weekly prophylaxis group of Paradigm™ 2 who received pre-study prophylaxis and assessed ABR. The secondary analysis compared HOPE-B to the full population from the 40 IU/kg weekly prophylaxis group of Paradigm™ 2 and assessed ABR, AsBR, % 0 ABR, EQ-5D utility score change from baseline, and Haem-A-QoL total score change from baseline. As the secondary analysis informed the economic model, its ABR, AjBR, AsBR, EQ-5D and Haem-A-QoL outcomes are described here.

ABR

Overall, the results of the MAIC showed statistically significantly lower ABR for Hemgenix versus Refixia. The unmatched and unadjusted (naïve) ABR was lower for Hemgenix [redacted] than for Refixia [redacted] (Table 17). This corresponded to

a statistically significant RR in favor of Hemgenix [redacted] Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Table 17, Hemgenix continued to have a favorable ABR in comparison to Refixia. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A favorable ABR for Hemgenix [redacted] in comparison to Refixia [redacted] was also reported [redacted] (Table 18).

Table 17: Hemgenix vs Refixia – ABR naïve and univariable MAICs results

Analysis	Paradigm™ 2		HOPE-B		HOPE-B Weights (min; q25; q50; q75; max)	SMD Mean	HOPE-B Rate[a]	Paradigm™ 2 Rate	MAIC Estimate (RR) & 95% CI	MAIC Estimate P value
	N	ESS (%)	N	ESS (%)						
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										

[a] Definition of ABR aligns with the definition used in sensitivity analysis 6 of the HOPE-B trial. This definition includes any new-and-true and treated bleeds.
[b] Data for covariate were taken at screening for HOPE-B and the comparator trial.
[c] Data for covariate were taken during the lead-in period for HOPE-B and were taken at screening for the comparator trial.
[d] Data for covariate were taken after the lead-in period for HOPE-B and were taken at screening for the comparator trial.
Abbreviations: ABR = annualized bleeding rate; BMI = body mass index; CI = confidence interval; EHL = extended half-life; ESS = effective sample size; FIX = factor IX; HIV = human immunodeficiency virus; MAIC = matching-adjusted indirect comparison; RR = rate ratio; SMD = standardized mean difference; SHL = standard half-life.

Source: CSL Behring (2022e)

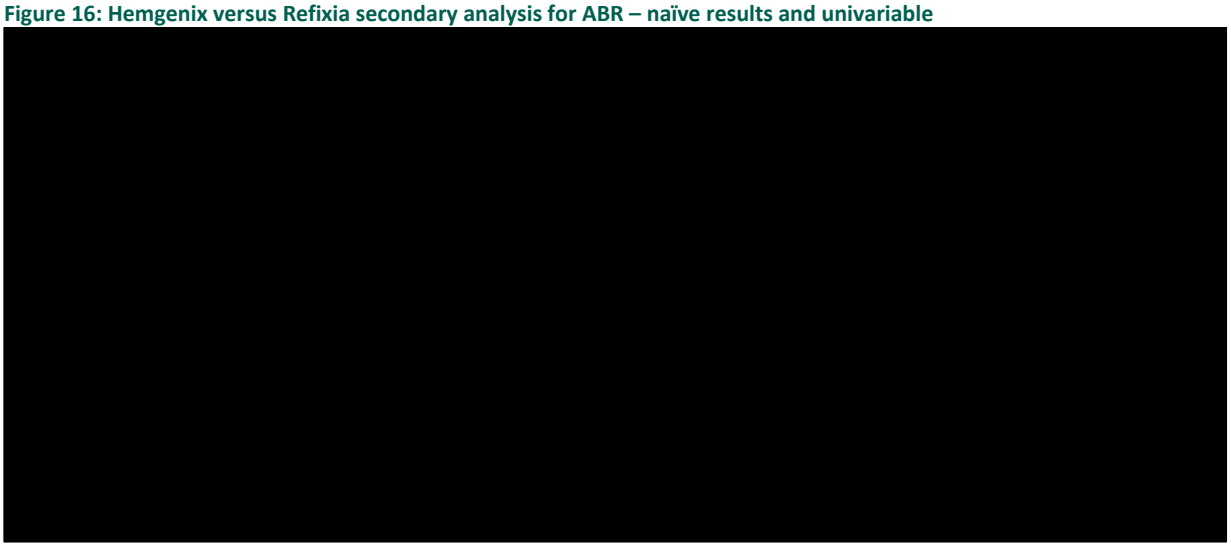
Table 18: Hemgenix vs Refixia – ABR sequential and multivariable MAICs results

Analysis	Paradigm™ 2		HOPE-B		HOPE-B Weights (min; q25; q50; q75; max)	SMD Mean	HOPE-B Rate[a]	Paradigm™ 2 Rate	MAIC Estimate (RR) & 95% CI	MAIC Estimate P value
	N	ESS (%)	N	ESS (%)						
[redacted]										
[redacted]										
[redacted]										

[a] Definition of ABR aligns with the definition used in sensitivity analysis 6 of the HOPE-B trial. This definition includes any new-and-true and treated bleeds.
[b] Data for covariate were taken at screening for HOPE-B and the comparator trial.
[c] Data for covariate were taken after the lead-in period for HOPE-B and were taken at screening for the comparator trial.
Abbreviations: ABR = annualized bleeding rate; BMI = body mass index; CI = confidence interval; ESS = effective sample size; MAIC = matching-adjusted indirect comparison; RR = rate ratio; SMD = standardized mean difference.

Source: CSL Behring (2022e)

Figure 16: Hemgenix versus Refixia secondary analysis for ABR – naïve results and univariable



Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents RR=1.
Abbreviations: ABR, Annualized bleeding rate; BMI, Body mass index; CI, Confidence interval; EHL, Extended half-life; ESS, Effective sample size; FIX, Factor IX; HIV, Human immunodeficiency virus; MAIC, Matching-adjusted indirect comparison; RR, Rate ratio; SMD, Standardized mean difference; SHL, Standard half-life.
Source: CSL Behring (2022e).

Figure 17: Hemgenix versus Refixia secondary analysis for ABR – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: ABR, Annualized bleeding rate; CI, Confidence interval; ESS, Effective sample size; MAIC, Matching-adjusted indirect comparison; RR, Rate ratio; SMD, Standardized mean difference.
Source: CSL Behring (2022e).

AjBR

Overall, the results of the MAIC showed statistically significantly lower AjBR for Hemgenix versus Refixia. The unmatched and unadjusted (naïve) AjBR was lower for Hemgenix [redacted] than for Refixia [redacted] (Table 19, Table 20). This corresponded to a statistically significant RR in favor of Hemgenix [redacted] Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors, Hemgenix continued to have a favorable AjBR in comparison to Refixia, and all results were statistically significant. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e., adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of hemophilia B and age. A favorable AjBR for Hemgenix [redacted] in comparison to Refixia [redacted] was also reported [redacted] (Table 19, Table 20).

Table 19: Hemgenix vs Refixia – AjBR naïve results and univariable MAICs results

Analysis	Paradigm™ 2		HOPE-B		HOPE-B Weights (min; q25; q50; q75; max)	SMD Mean	HOPE-B Rate[a]	Paradigm™ 2 Rate	MAIC Estimate (RR) & 95% CI	MAIC Estimate P value
	N	ESS (%)	N	ESS (%)						
[redacted]										
[redacted]										
[redacted]										
[redacted]										

[redacted]										

[a] Definition of AjBR aligns with the definition used in sensitivity analysis 6 of the HOPE-B trial. This definition includes any new-and-true and treated bleeds.

[b] Data for covariate were taken at screening for HOPE-B and the comparator trial.

[c] Data for covariate were taken during the lead-in period for HOPE-B and were taken at screening for the comparator trial.

[d] Data for covariate were taken after the lead-in period for HOPE-B and were taken at screening for the comparator trial.

Source: CSL Behring (2022e)

Abbreviations: ABR = annualized bleeding rate; BMI = body mass index; CI = confidence interval; EHL = extended half-life; ESS = effective sample size; FIX = factor IX; HIV = human immunodeficiency virus; MAIC = matching-adjusted indirect comparison; RR = rate ratio; SMD = standardized mean difference; SHL = standard half-life.

Table 20: Hemgenix vs Refixia – AjBR sequential and multivariable MAICs results

Analysis	Paradigm™ 2		HOPE-B		HOPE-B Weights (min; q25; q50; q75; max)	SMD Mean	HOPE-B Rate[a]	Paradigm™ 2 Rate	MAIC Estimate (RR) & 95% CI	MAIC Estimate P value
	N	ESS (%)	N	ESS (%)						
[redacted]										

[a] Definition of AjBR aligns with the definition used in sensitivity analysis 6 of the HOPE-B trial. This definition includes any new-and-true and treated bleeds.

[b] Data for covariate were taken at screening for HOPE-B and the comparator trial.

[c] Data for covariate were taken after the lead-in period for HOPE-B and were taken at screening for the comparator trial.

Source: CSL Behring (2022e)

Figure 18: Hemgenix versus Refixia secondary analysis for AjBR SA6 – naïve results and univariable MAICs

Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents RR = 1.

Abbreviations: AjBR = annualized joint bleeding rate; BMI = body mass index; CI = confidence interval; EHL = extended half-life; ESS = effective sample size; FIX = factor IX; HIV = human immunodeficiency virus; MAIC = matching-adjusted indirect comparison; RR = rate ratio; SMD = standardized mean difference; SHL = standard half-life.

Figure 19: Hemgenix versus Refixia secondary analysis for AjBR SA6 – sequential and multivariable MAICs adjusted for severity of hemophilia B and age, in that order

Note: The vertical reference line represents RR = 1.

Abbreviations: AjBR = annualized joint bleeding rate; CI = confidence interval; ESS = effective sample size; MAIC = matching-adjusted indirect comparison; RR = rate ratio; SMD = standardized mean difference.

AsBR

Overall, the results of the MAIC showed statistically significantly lower AsBR for Hemgenix versus Refixia. The unmatched and unadjusted (naïve) AsBR was lower for Hemgenix [redacted] than for Refixia [redacted] (Table 21). This corresponded to a statistically significant RR in favor of Hemgenix [redacted] Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Table 21, Hemgenix continued to have a favorable RR in comparison to Refixia. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A statistically significant and favorable AsBR for Hemgenix [redacted] in comparison to Refixia [redacted] was also reported [redacted]

Table 21: Hemgenix versus Refixia secondary analysis for AsBR – naïve results and univariable MAICs

Note: Prior Factor IX product class refers to EHL versus SHL products; The vertical reference line represents RR=1.

Abbreviations: AsBR, Annualized spontaneous bleeding rate; BMI, Body mass index; CI, Confidence interval; EHL, Extended half-life; ESS, Effective sample size; FIX, Factor IX; HIV, Human immunodeficiency virus; MAIC, Matching-adjusted indirect comparison; RR, Rate ratio; SMD, Standardized mean difference; SHL, Standard half-life.

Source: CSL Behring (2022e).

Table 22: Hemgenix versus Refixia secondary analysis for AsBR – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: AsBR, Annualized spontaneous bleeding rate; CI, Confidence interval; ESS, Effective sample size; MAIC, Matching-adjusted indirect comparison; RR, Rate ratio; SMD, Standardized mean difference.
Source: CSL Behring (2022e).

EQ-5D

Overall, the results of the MAIC showed a higher mean EQ-5D utility score change from baseline for Hemgenix versus Refixia. The unmatched and unadjusted (naïve) mean EQ-5D utility score change from baseline was higher for Hemgenix [redacted] than for Refixia [redacted] (Table 23). This corresponded to a difference in means (MD) in favor of Hemgenix [redacted], however these results were not statistically significant. Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Table 23, Hemgenix continued to have a favorable, yet not statistically significant, higher mean EQ-5D utility score change from baseline change from baseline in comparison to Refixia except when adjusting for prior presence of target joints. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A favorable mean EQ-5D utility score change from baseline for Hemgenix [redacted] in comparison to Refixia [redacted] was estimated [redacted], and again these results were not statistically significant (Table 24).

Table 23: Hemgenix versus Refixia secondary analysis for EQ-5D utility score, change from baseline – naïve results and univariable MAICs

[redacted]

Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents MD=0.
Abbreviations: BMI, Body mass index; CI, Confidence interval; EHL, Extended half-life; ESS, Effective sample size; FIX, Factor IX; HIV, Human immunodeficiency virus; MAIC, Matching-adjusted indirect comparison; OR, Odds ratio; SMD, Standardized mean difference; SHL, Standard half-life.
Source: CSL Behring (2022e).

Table 24: Hemgenix versus Refixia secondary analysis for EQ-5D utility score, change from baseline – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

[redacted]

Note: The vertical reference line represents MD=0.
Abbreviations: CI, Confidence interval; ESS, Effective sample size; MAIC, Matching-adjusted indirect comparison; MD, Mean difference; SMD, Standardized mean difference.
Source: CSL Behring (2022e).

Haem-A-QoL

For the Haem-A-QoL ITC analysis, Paradigm 2 data was used however this data was unavailable in (Collins et al., 2014), therefore data was sourced from the published Novo Nordisk CSR for Paradigm 2 (Nordisk, 2013).

The unmatched and unadjusted (naïve) mean Haem-A-QoL total score change from baseline was slightly less for [redacted] This corresponded to a MD in favor of Refixia [redacted], however these results were not statistically significant. Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 20, still no statistically significant, mean Haem-A-QoL total score change differences from baseline were seen.

In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e., adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A favorable mean Haem-A-QoL total score change from baseline for Hemgenix [redacted] in comparison to Refixia [redacted] was reported (MD: -[redacted], but again these results were not statistically significant.

Figure 20: Hemgenix versus Refixia secondary analysis for Haem-A-QoL total score, change from baseline – naïve results and univariable MAICs

Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents MD=0.
Abbreviations: BMI, Body mass index; CI, Confidence interval; EHL, Extended half-life; ESS, Effective sample size; FIX, Factor IX; HIV, Human immunodeficiency virus; MAIC, Matching-adjusted indirect comparison; OR, Odds ratio; SMD, Standardized mean difference; SHL, Standard half-life.
Source: CSL Behring (2022e).

Figure 21: Hemgenix versus Refixia secondary analysis for Haem-A-QoL total score, change from baseline – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents MD=0.
Abbreviations: CI, Confidence interval; ESS, Effective sample size; MAIC, Matching-adjusted indirect comparison; MD, Mean difference; SMD, Standardized mean difference.
Source: CSL Behring (2022e).

8.3.6. Conclusion of ITCs

Overall, after matching and adjusting for a few important clinical factors and treatment-effect modifiers available, Hemgenix had a statistically significantly lower ABR, AjBR and AsBR compared to Refixia (Paradigm™ 2 trial). No statistically significant differences in Haem-A-QoL total score change from baseline and EQ-5D utility score change from baseline were found between Hemgenix and Refixia based on available data.

Overall, these analyses suggest that patients who receive Hemgenix have fewer bleeds than patients on replacement FIX therapy. Based on these study findings, keeping in mind the limitations of unanchored, non-randomized design with small sample sizes, Hemgenix could confer a large benefit over Refixia for patients with moderately severe or severe haemophilia B.

Unanchored, small-sample size indirect comparisons are broadly considered a weaker form of evidence than direct comparisons involving blinded or randomized trial designs (Phillippo DM, 2016). Comparison of ITC results to those from other study designs is therefore important. The relative treatment effects from these ITCs were aligned with those from the published, 1 year analysis between lead-in and post-treatment designed within HOPE-B (Pipe et al., 2021e). Though patients in the lead-in period for HOPE-B were taking different FIX products for prophylaxis, and the published HOPE-B analysis used the first year of the post-treatment period for Hemgenix (which included the first six months post-treatment), the concordance between results and conclusions from the published pre-post HOPE-B analysis and those from these ITCs strengthens the evidence base comparing Hemgenix to FIX replacement therapies. Please refer to the full ITC report (provided in the reference pack of this submission) for the full discussion of strengths and limitations of the analysis (CSL Behring, 2022e).

8.4 Balance of benefits and risks with Hemgenix vs standard of care

EMA concluded in their public assessment report that the short- to medium-term magnitude and durability of the demonstrated clinical benefits (i.e. clinically relevant levels of endogenous FIX activity, improvement of bleeding frequency over standard of care, minimal need for external factor replacement) of treatment with Hemgenix are considered to outweigh the observed short- to medium-term safety concerns (i.e. infusion reactions, influenza-like illness, headache, transaminitis).

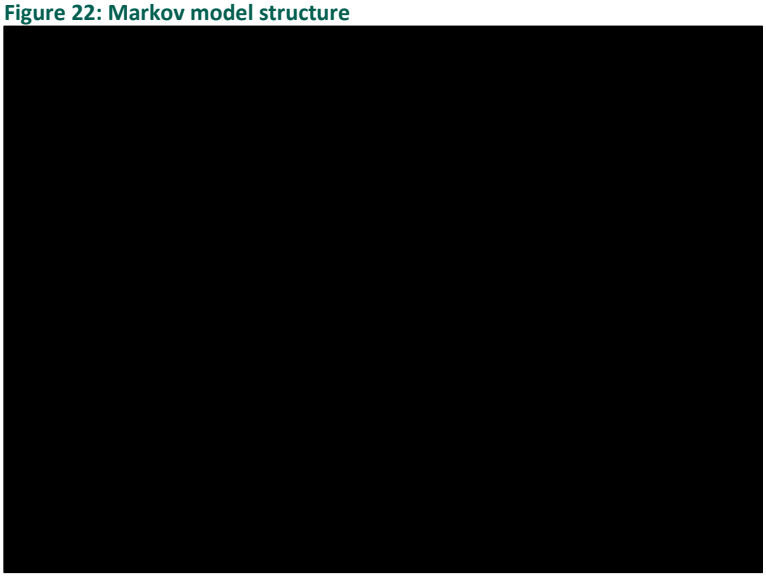
However, EMA in their assessment considered diligent post marketing surveillance of utmost importance to detect potential rare adverse events and to investigate the potential risk of malignancy (due to vector integration) on the longer term. Patients must be well-informed about this to receiving etranacogene dezaparvovec. In this regard, a warning has been added to the SmPC and package leaflet to inform on the potential risk of malignancy as a result of vector integration in liver cells and in other body cells. These aspects are covered in the SmPC and Package leaflet and in the educational materials in the RMP (EMA, 2023).

9. Health economic analysis

9.1 Model

The model structure was developed using Microsoft Excel. The economic model follows a Markov model structure and is based on bleeding events. The four Markov states consist of patients experiencing no bleeds, non-joint bleeds, joint bleeds, or death in any cycle. In the economic model, all patients begin in the no-bleed state and either receive treatment with Hemgenix or FIX prophylaxis. The transition modelled in all cycles are death, non-joint bleed or joint bleed. This process is repeated over the time horizon of 59 years (3,077 weeks), until the cohort of the 1,000 patients reaches an age of 100 years.

Figure 22: Markov model structure



Note: Health states are categorized by treatment response. Arrows represent permissible transitions between states while loops represent no transition. Death is possible from any health state.

The Markov model structure was used because of its proven versatility (Ademi et al., 2013). A Markov model contains Markov states, which encapsulates the aforementioned states that PWHB can reasonably find themselves experiencing at any cycle.

Transitions amongst the Markov states are informed by the ABRs and AjBRs rate ratios from the ITC and then converted into transition probabilities which give the exact probability that transfer patients between the states. The Markov trace offers a mathematical and graphical representation of the progression of the cohort across the cycles which the patients have experienced. The decision problem can be examined through the comparison of the aggregated Markov trace of the intervention against the Markov traces of the comparators. Lastly, the Markov structure offers a framework to capture the durable clinical effects of a gene therapy such as Hemgenix over the patients' lifespan.

9.1.1. Transitions

The transitional probabilities for the intervention and the comparators are outlined in Table 25. The likelihood of a patient entering a Markov state in a cycle is a logical realization of the instantaneous probability over the cycle, calculated using Equation 1. In this formula, P is the transitional probability of interest, e is the Euler's number, r is the rate of the specific bleed events according to

the Markov state of interest, and t is the time horizon of interest relative to the time horizon over which the rates are expressed over (weekly cycles).

Equation 1: Formula for conversion of per-cycle probabilities

$$p = 1 - e^{-\frac{r}{t}}$$

Source: (Jones et al., 2017)

The r value for calculating the probability of a joint bleed is the AjBR for the comparator of interest. The r value for calculating the probability of a non-joint bleed is difference between the ABR and AjBR for the comparator of interest. The probability of entering the no bleed state is unity minus the probability of non-joint bleed and joint bleed states. Values for Hemgenix at a specific cycle are augmented by the mean durability of Hemgenix at that specific cycle. For example, at the median durability of 42 years, half of the make-up of transitional probabilities are subject to r values from Hemgenix bleed rates, and the other half of transitional probabilities are subject to r values from the comparator that the intervention is being compared against.

No deaths attributed to Hemgenix were recorded in the HOPE-B trial over a 24-month period, with haemophilia B patients are expected to live largely normal lives and as such the transition to the death state occurs according to general population statistics provided by Statistikbanken national life tables (Statistics Denmark, 2022), applied appropriately to each cycle according to the age of the cohort at the said cycle.

Table 25: Transitional probabilities matrix of the intervention and comparators per cycle

Comparator	Probability of no-bleed	Probability of non-joint bleed	Probability of joint bleed	Probability of death
Hemgenix *	XXXXX	XXXX	XXXX	XXX
Refixia	XXXXX	XXXX	XXXX	XXX

Note: *Hemgenix values in each cycle are augment by the durability of Hemgenix in that cycle, this table shows initial transitional probabilities with no Hemgenix patients requiring further FIX prophylaxis. Values are accurate to two decimal places.

Abbreviations: GPS, General population statistics.

9.1.2. Cycle length

The cycle length has been chosen to be seven days, in line with the comparators' dose administration of once a week (see section 6.2.2, Table 3), and the fact that patients could ostensibly experience multiple events of a significant importance such as bleeds, in a single cycle if the cycle length were to be extended.

9.1.3. Perspective

As recommended in the guidelines "*Medicinrådets metodevejledning for vurdering af nye lægemidler*" (Medicinrådet, 2022) from DMC a restricted societal perspective is applied where relevant transport costs and time spent in connection with treatment for both patients and relatives are included. Productivity losses due to the disease and any impact that treatment are omitted from the analysis, in line with the DMC guidelines (Medicinrådet, 2022).

9.1.4. Discounting

A time-dependent discount rate is applied in the model as per the discounting guidelines provided by the Danish Ministry of Finance (Finansministeriet, 2021). From year 0 to 35 a discount rate of 3.5% is applied for both costs and health outcomes within the base case analysis. Then from 35 years onwards a 2.5% discount rate is applied for both costs and health outcomes (Medicinrådet, 2022). The user can specify which discount rates should apply independently for costs and QALYs. A scenario analysis is included where no discounting is applied.

9.1.5. Time horizon

A time horizon of 59 years is chosen to reflect a lifetime horizon when considering the patient starting age in the model is 41.5 years which is aligned with the average age of patients in the HOPE-B trial.

9.1.6. Intervention

The intervention considered in the cost-effectiveness analysis is Hemgenix, data from the Phase III HOPE-B trial has been used in this analysis (CSL Behring, 2022f). The model included the recommended single dose of 2×10^{13} gc/kg bw corresponding to 2 ml/kg

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bw, administered as an IV infusion after dilution of the required dose with sodium chloride 9 mg/ml (0.9%) solution for injection (CSL Behring, 2022c).

9.1.7. Comparator

The current treatment options for haemophilia B in Denmark 'on-demand' and 'prophylactic' FIX replacement therapy (Nordic Haemophilia Guidelines, 2022). These treatments include eftrenonacog alfa (Alprolix), nonacog alfa (BeneFIX), nonacog beta pegol (Refixia), and albutrepenonacog alfa (Idelvion) (Medicinrådet, 2022). Patients who receive 'on-demand' therapy only were not included within the cost-effectiveness model (CEM) as the HOPE-B trial enrolled patients that had been on stable FIX prophylaxis therapy for at least two months before screening, and then received at least six months of treatment with prophylaxis (the lead-in period) before Hemgenix administration (CSL Behring, 2021c).

The comparator used in the model is Refixia. [redacted]

9.1.8. Validation

The model structure and its key inputs have been validated by clinical experts (CSL Behring, 2022a, KOL input, 2022). The model has been reviewed by an external pharmaceutical agency and judged as fit for purpose, with minor amendments, which were introduced into the current version.

[redacted]

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[redacted]

[redacted]

9.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

9.2.1. Presentation of input data used in the model and how they were obtained

A full list of the inputs used in the model are included in Table 26.

Table 26: Input data used in the model

Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Treatment efficacy			
[redacted]	HOPE-B trial	[redacted]	Used to inform the number of annual bleeds/joint bleeds in the model which drive the cost and QoL outcomes
[redacted]	HOPE-B trial	[redacted]	
[redacted]	ITC (CSL Behring, 2022e)	[redacted]	
[redacted]		[redacted]	
Treatment cost **(DKK)**			
Treatment costs for Hemgenix (1 course of treatment)	CSL Behring (2022d)	[redacted]	Used to calculate the cost of treatment
Treatment costs for Refixia (500 IU)	Varenummer: 530623. ATC code: B02BD04. Available from: (Medicinpriser)	7,412.15	
Treatment costs for Refixia (1,000 IU)	Varenummer: 179645. ATC code: B02BD04. Available from: (Medicinpriser)	14,792.68	
Treatment costs for Refixia (2,000 IU)	Varenummer: 196150. ATC code: B02BD04. Available from: (Medicinpriser)	29,553.55	
Refixia dosing			
Dose option distribution	(KOL input, 2022)	[redacted]	Used to calculate Refixia dosing
Dose frequency (dose every x days)	(SmPC, 2022b)	[redacted]	
Dose strength (IU/kg)	(SmPC, 2022b)	[redacted]	
Dose per administration (IU)	(SmPC, 2022b)	[redacted]	
Number of administrations per year (n)		[redacted]	
Dose per year (IU)		[redacted]	
Annual cost (DKK)		[redacted]	

Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Administration costs (DKK)			
Administration cost for Hemgenix			
IV infusion cost [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679"Haemofili B" + BWAA60 "Medicingivning ved jections njection") Accessed: January 2023. Available from: (Sundhedsdata, 2023)	[redacted]	Used to inform treatment administration costs
Initial screening (FibroScan) [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + KZXF40A "anvendelse af intraabdominal ultralyd") Accessed: January 2023 Available from: (Sundhedsdata, 2023)	[redacted]	
Blood tests [redacted]	Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC). Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
Wound management (gauze/plaster) [redacted]	ApoPro, Elastomull Gazebind 4cm x 6m Available from: (Apopro.dk)	[redacted]	
Administration cost for Refixia	Self-administered treatment	[redacted]	
Follow-up costs (Year 1) (DKK)			
Hematologist visit [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	Used to inform treatment follow-up costs in year one
Nurse visit [redacted]	Syge- og Sundhedspersonale, basis Reg.. bruttolön OKTOBER 2022 (41974 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Liver function test [redacted]	Test code for NPU19651 (ALAT), NPU19654 (ASAT), NPU27783 (fosfatase), NPU19673 (albumin), NPU01370 (bilirubiner), NPU03278 (protein). Accessed: January 2023. Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
FIX activity levels [redacted]	Test code for NPU29991 Koagulationsfaktor IX. Accessed: January 2023. Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
Follow-up costs (Year 2-5) (DKK)			
Abdominal ultrasound [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + KZXF40 "anvendelse af ultralyd") Accessed: January 2023. Available from: (Sundhedsdata, 2023)	[redacted]	Used to inform treatment follow-up costs in year 2-5

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Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Hematologist visit [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Nurse visit [redacted]	Syge- og Sundhedspersonale, basis Reg.. bruttolön OKTOBER 2022 (41974 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Liver function test [redacted]	Test code for NPU19651 (ALAT), NPU19654 (ASAT), NPU27783 (fosfatase), NPU19673 (albumin), NPU01370 (bilirubiner), NPU03278 (protein). Accessed: January 2023. Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
FIX activity levels [redacted]	Test code for NPU29991 Koagulationsfaktor IX. Accessed: January 2023. Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
Haemophilia B monitoring costs (Unit cost, DKK)			
Joint scans [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + KZXF40 "anvendelse af ultralyd") Accessed: January 2023. Available from: (Sundhedsdata, 2023)	[redacted]	
Hematologist visit [redacted]	Overlæger, lægelige chefer m.v.. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Orthopedist visit [redacted]	Kommunernes og Regionernes Løndatakontor 2022, Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	Used to inform monitoring costs
Psychologist/psychiatrist visit [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Physiotherapist [redacted]	Ergo- Fysio- og Jordemødre, basis Reg. bruttolön OKTOBER 2022 (40564 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	

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Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Hematology Nurse [redacted]	Syge- og Sundhedspersonale, basis Reg.. bruttolön OKTOBER 2022 (41974 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Liver function test [redacted]	Test code for NPU19651 (ALAT), NPU19654 (ASAT), NPU27783 (fosfatase), NPU19673 (albumin), NPU01370 (bilirubiner), NPU03278 (protein). Accessed: January 2023. Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
Telephone call with hematologist [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Bleed-related management costs (DKK)			
Hematologist visit [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Orthopedist visit [redacted]	Overlæger, lægelige chefer m.v.. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Accident and emergency visits [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + BWST2A "Multidisciplinær akutmodtagelse af ikke-traume patient") Accessed: January 2023. Available from: (Sundhedsdata, 2023)	[redacted]	Used to calculate management costs
Hospital stay (inpatient) [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA09 (DD679 "Haemofili B" >=12 timer (lang)) Accessed: January 2023. Available from: (Sundhedsdata, 2023)	[redacted]	
Additional dosage due to bleed event [redacted]	Varenummer: 196150. ATC code: B02BD04. Available from: (Medicinpriser)	[redacted]	
Hemgenix TRAEs with an incidence of ≥5% (Weekly probabilities)			
Headache	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Influenza like illness	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
ALT increased	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Fatigue	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	Used to inform AE costs disutility
Blood creatine phosphokinase increased	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Nausea	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	

Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Dizziness	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
IRR	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Arthralgia	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Infection	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Body pain	Hemgenix: (CSL Behring, 2022i) Refixia: (EMA, 2015)	[redacted]	
Adverse event costs (DKK)			
Headache [redacted]	Overlæger, lægelige chefer m.v.. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. (Kommunernes og Regionernes Løndatakontor, 2023) Laegemiddelstyrelsen. Varenummer: 170773. ATC code: N02BE01, Paracetamol. Available from: (Medicinpriser)	[redacted]	
Influenza like illness [redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + DJ101C "Influenza med pleuraekssudat f.a. anden type influenzavirus") Accessed: January 2023. Available from: (Sundhedsdata, 2023)	[redacted]	
ALT increased [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. (Kommunernes og Regionernes Løndatakontor, 2023) Laegemiddelstyrelsen. Varenummer: 398747. ATC code: H02AB06, Prednisolon. Available from: (Medicinpriser)	[redacted]	
Fatigue [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	Used to inform AE related costs
Blood creatine phosphokinase increased [redacted]	Test code for NPU04998 Kreatinin;P (µmol/L). Accessed: January 2023. Available from: (Rigshospitalets Labportal, 2023)	[redacted]	
Nausea [redacted]	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
Dizziness [redacted]	Overlæger, lægelige chefer m.v.. bruttolön OKTOBER 2022 (99907 DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	[redacted]	
IRRs [redacted]	Varenummer: 188829. ATC code: R06AX27, Desloratidin Available from: (Medicinpriser)	[redacted]	

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Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Arthralgia XXXXXX XXXXXXXXX	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023) Varenummer: 108823. ATC code: N02AJ06, Codein og paracetamol. Available from: (Medicinpriser)	XXXXXX	
Infection XXXXX XXXXXXXXX	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	XXXXXX	
Body pain XXXXXX XXXXXXXX	Overlæger, lægelige chefer m.v. bruttolön OKTOBER 2022 (99907 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. Available from: (Kommunernes og Regionernes Løndatakontor, 2023)	XXXXXX	
Health state utility value			
Hemgenix			Used to inform the QoL outcomes
No bleeds	HOPE-B trial	XXXXX	
Non-joint bleed	HOPE-B trial	XXXXX	
Joint bleed	HOPE-B trial	XXXXX	
Death	HOPE-B trial	X	
Disutility of non-joint bleed per cycle	(Tice et al., 2022)	XXX	
Disutility of joint bleed per cycle	(Tice et al., 2022)	XXX	
Disutility of IV administration	Johnston et al. (2021)	XXXXXX	
Refixia			Used to inform the QoL outcomes
No bleeds	HOPE-B trial	XXXXX	
Non-joint bleed	HOPE-B trial	XXXXX	
Joint bleed	HOPE-B trial	XXXXX	
Death	HOPE-B trial	X	
Adverse reactions			
Disutility of non-joint bleed per cycle	(Tice et al., 2022)	XXX	
Disutility of joint bleed per cycle	(Tice et al., 2022)	XXX	
Disutility of IV administration	Johnston et al. (2021)	XXXXX	
Annual treatment-related resource consumption requiring transportation or patients time			
Hemgenix			
Administration	(KOL input, 2022)	X	

Name of inputs	Source	Value used in the model	How is the value used in the model/comments
Hospital follow-up: first year	(KOL input, 2022)	[redacted]	Used to calculate the time taken for transport and patient time for Hemgenix
Hospital follow-up: subsequent years (2-5)	(KOL input, 2022)	[redacted]	
Refixia			
Administration	(SmPC, 2022b)	[redacted]	Used to calculate the time taken for transport and patient time for Refixia
Hospital follow-up: first year	Assumption	[redacted]	
Hospital follow-up: subsequent years (2-5)	Assumption	[redacted]	
Transport and patient time costs			
Hemgenix			
Transportation unit cost (DKK)	Værdisætning af enhedsomkostninger (2022). Available at: (Medicinrådet, 2022)	[redacted]	Used to calculate transportation and patient time costs for Hemgenix
Patient time unit cost (DKK)	Værdisætning af enhedsomkostninger (2022). Available at: (Medicinrådet, 2022)	[redacted]	
Average patient hospital visit time (hour)	Assumption	[redacted]	
Refixia			
Transportation unit cost (DKK)	Værdisætning af enhedsomkostninger (2022).). Available at: (Medicinrådet, 2022)	[redacted]	Used to calculate transportation and patient time costs for Refixia
Patient time unit cost (DKK)	Værdisætning af enhedsomkostninger (2022). Available at: (Medicinrådet, 2022)	[redacted]	
Average time per administration (hour)	Assumption	[redacted]	

Abbreviations: ABR, Annualized bleeding rate; AjBR, Annual joint bleed rate; ALT, Alanine aminotransferase; DKK, Danish kroner; FIX, Factor IX; HOPE-B, Health Outcomes with Padua Gene; IRR, Infusion-related reaction; IU, International unit; ITC, Indirect treatment comparation, IV, Intravenous; kg, Kilograms; n, Number; RR, Relative risk; TRAE, Treatment-related adverse event.

9.2.2. Relationship between the clinical documentation, data used in the model and Danish clinical practice

9.2.2.1 Patient population

The patient population are subjects with known severe (FIX activity levels <1%) or moderately severe (FIX activity levels 1–2%) congenital haemophilia B for which the subject is on continuous routine FIX prophylaxis. This is the same patient population for both the clinical documentation and the economic analysis.

Table 27: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age	41.5 years (HOPE-B study)	41.5 years (HOPE-B study)	
Gender	HOPE-B study	Male only	Haemophilia B generally affects males and the majority (70%) of haemophilia cases are inherited, while approximately 30% result from a spontaneous mutation (Mannucci and Tuddenham, 2001, Srivastava et al., 2020)
Disease severity	Subjects with known severe (FIX activity levels <1%) or moderately severe (FIX activity levels 1-2%) congenital haemophilia B for which the subject is on continuous routine FIX prophylaxis*	Subjects with known severe (FIX activity levels <1%) or moderately severe (FIX activity levels 1-2%) congenital haemophilia B for which the subject is on continuous routine FIX prophylaxis*	In Denmark, there are approximately 40 patients with severe or moderate haemophilia B (Nordic Haemophilia Council, 2015). Currently, those with severe or moderately severe haemophilia B are primarily treated prophylactically with FIX

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
			concentrates (Nordic Haemophilia Guidelines, 2022, Måseide et al., 2020, Kihlberg et al., 2021)
Treatment history	>150 previous exposure days of treatment with FIX protein Have been on stable FIX prophylaxis for at least 2 months prior to screening	>150 previous exposure days of treatment with FIX protein Have been on stable FIX prophylaxis for at least 2 months prior to screening	rFIX concentrates are recommended as the first choice for PWHB in the Nordics Currently, there are four rFIX concentrates available in Denmark, which are reimbursed by DMC. Among these, Refixia (nonacog beta pegol), Alprolix (efrenonacog alfa), and Idelvion (albutrepenonacog alfa) are long-acting with EHL. Of these, Idelvion and Alprolix are approved for the treatment of children under 12 years of age (Medicinrådet, 2022)

Note: *Continuous routine prophylaxis is defined as the intent of treating with a prior defined frequency of infusions (e.g. twice weekly, once every two weeks, etc.) as documents in the medical records.
Abbreviations: DMC, Danish medicines council; EHL, Extended half-life; HOPE-B, Health Outcomes with Padua Gene; rFIX, Recombinant Factor IX.

9.2.2.2 Intervention

Hemgenix is a gene therapy product designed to introduce a copy of the human FIX coding DNA sequence into hepatocytes to address the root cause of the haemophilia B disease (CSL Behring, 2022c). Hemgenix consists of a codon-optimized coding DNA sequence of the gain-of-function Padua variant of the human FIX (hFIXco-Padua), under the control of a liver-specific LP1 promoter, encapsulated in a non-replicating rAAV5 (CSL Behring, 2022c).

HOPE-B is an ongoing phase III, open-label, single-dose, multicenter, multinational study evaluating the efficacy of Hemgenix in adult patients (n=54) with severe or moderately severe haemophilia B (FIX ≤2%) (ClinicalTrials.gov, 2021a). Hemgenix is a gene therapy product designed to introduce a copy of the human FIX gene into hepatocytes (liver cells) to address the lack of functional FIX protein expression in PWHB (CSL Behring, 2022c). Hemgenix uses the rAAV5 and delivers the gain-of-function Padua-hF9 gene variant (a highly active, naturally occurring variant that generates five to 10 times greater FIX activity levels than the normal wild-type hF9 gene) under the control of a liver-specific promoter (CSL Behring, 2022c) (see section 6.3 for more information) (Table 28).

Table 28: Description of the intervention (Hemgenix) used in the model

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology of Hemgenix	Single IV infusion of a 2×10^{13} gc/kg bw (or 2 mL/kg bw) dose	Single IV infusion of a 2×10^{13} gc/kg bw (or 2 mL/kg bw) dose	Single IV infusion of a 2×10^{13} gc/kg bw (or 2 mL/kg bw) dose

Abbreviations: bw, Body weight; gc, Gene copies; IV, Intravenous; kg, Kilograms; mL, Milliliters.
Source: CSL Behring (2022c).

9.2.2.3 Comparators

The comparator used in the model is Refixia,.[redacted]

Table 29: Description of the comparator (Refixia) used in the model

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology of Refixia	Prophylaxis 40 IU/kg bw once weekly On-demand treatment A single dose of 40 IU/kg bw in cases of early hemarthrosis, muscle bleeding or oral bleeding. Same dosage regimen to be used in the cases of more extensive hemarthrosis, muscle bleeding or hematoma. A single dose of 80 IU/kg bw in the cases of severe or life threatening hemorrhages[b] Surgery A single dose of 40 IU/kg bw in the cases of minor surgery including tooth extraction[b] A single pre-operative dose of 80 IU/kg bw in the cases of major surgery. After surgery, two repeated doses of 40 IU/kg (in 1–3 day intervals) within the first week are recommended[c] Pediatric population The dose recommendations in adolescents (12–18 years) are the same as for adults: 40 IU/kg bw Refixia is not recommended for children below 12 years	40 IU/kg bw once weekly	40 IU/kg bw once weekly
Treatment duration/criteria for end of treatment	Duration of treatment is specified based on the situations described in dosage regimen. If symptoms of hypersensitivity or other adverse events occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician	Patients receive prophylaxis treatment in the comparator arm for the duration of the model	

Notes:
[a] Adjustments of doses and administration intervals may be considered based on achieved FIX levels and individual bleeding tendency. Patients on prophylaxis who forget a dose are advised to take their dose upon discovery and thereafter continue with the usual once weekly dosing schedule. A double dose should be avoided.
[b] Additional doses of 40 IU/kg can be given, if needed.
[c] The frequency of dosing in the post-surgical period may be extended to once weekly after the first week until bleeding stops and healing is achieved.
Abbreviations: bw, Body weight; IU, international units; kg, Kilograms.
Source: SmPC (2022b).

9.2.2.4 Relative efficacy outcomes

In the Nordic countries, SOC for haemophilia B with a severe bleeding phenotype is infusion of replacement FIX concentrate at regular intervals to prevent bleeding events (prophylaxis). Treatment is individualized and optimized based on the patient's bleeding profile, PK and lifestyle. The Danish treatment practice for PWH is based on the recommendations by the guidelines provided by Nordic Haemophilia Council working group (Nordic Haemophilia Guidelines, 2022). The overall goal of haemophilia treatment in Denmark is zero bleeds and healthy joints (Nordic Haemophilia Guidelines, 2022). There is currently no curative treatment for haemophilia B. Current treatment with FIX concentrates aims to preserve functional factor levels, prolong survival and provide a good QoL. Treatment is individualized to maintain sufficiently high factor levels to avoid bleeding and preserve musculoskeletal function.

The Markov model therefore focuses on prevention of bleeds with four Markov states which consists of patients experiencing no bleeds, non-joint bleeds, joint bleeds, or death in any cycle. In the economic model, all patients begin in the no-bleed state and either receive treatment with Hemgenix or FIX prophylaxis. The transitions modelled in all cycles are death, non-joint bleed, or joint bleed. Transitions amongst the Markov states are informed by the ABRs and AjBRs rate ratios from the ITC and the direct ABR and AjBR from the HOPE-B trial. These are then converted into transition probabilities which give the exact probability that transfers patients between the states.

For the intervention (Hemgenix), the ABR and AjBR were informed directly by the results of the HOPE-B trial. However, the direct primary end point values were not used. In the HOPE-B trial, the primary endpoint is defined as *"any bleeding events between*

stable FIX expression and study completion or early withdrawal". As part of the trial analysis, sensitivity analysis was conducted to investigate the ABR and AjBR outcomes according to different bleed rate definitions (see section 8.2.1.5). The definition used to inform the ABR and AjBR in the model is from Sensitivity Analysis 6, which defines a bleed as *"any bleeding events between stable FIX expression and study completion or early withdrawal that were both treated with exogenous FIX and determined to be new and true"*. A bleed is considered to be new and true if an investigator determined that the bleed was not related to previous chronic joint bleeds and damage and was true bleed. This definition is used as it allows an assessment of the effectiveness of the Hemgenix compared to the Refixia in the ITC as the definition for Sensitivity Analysis 6 in HOPE-B is the most closely aligned with the Paradigm 2 trial, which required bleeds to be treated and new to be counted.

Therefore, for Hemgenix the ABR used in the model was [redacted] whilst the AjBR was [redacted] To calculate the relevant efficacy outcomes for the comparator, the relative risk (RR) derived in the ITC (see section 8.2.2) were applied to the Hemgenix ABR and AjBR by dividing each bleed rate by the RR. For the comparator the ABR was calculated as [redacted] and the AjBR [redacted] (Table 30).

Table 30: Summary of text regarding value

Clinical efficacy outcome	Clinical documentation	Used in the model (value)*
Primary endpoint in the study (endpoint's name)	HOPE-B is an ongoing phase III, open-label, single-dose, multicenter, multinational study evaluating the efficacy of Hemgenix in adult patients (n=54) with severe or moderately severe haemophilia B (FIX ≤2%) (ClinicalTrials.gov, 2021a). The primary endpoint of HOPE-B is ABR for all bleeding episodes.	[redacted]
Secondary endpoint (endpoint's name)	Several secondary endpoints are studied in the HOPE-B trial including FIX activity levels after intervention, annual FIX replacement therapies, spontaneous and joint bleeding episodes, number of AEs and PRO measures (ClinicalTrials.gov, 2021a).	

Note: *Model values use the Sensitivity Analysis 6 definition of bleeds to calculate the Hemgenix ABR and AJBR. This definition counts only those bleeds which are considered as new and true bleeds
Abbreviations: ABR, Annualized bleeding rate; AE, Adverse events; AjBR, Annualized joint bleeding rate; FIX, Factor IX; n, Number; PRO, Patient reported outcome.

Table 31: Summary of text regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study (endpoint's name)	ABR	Treatment is individualized to maintain sufficiently high factor levels to avoid bleeding and preserve musculoskeletal function. Therefore comparing treatment effectiveness through the bleed rates is of relevance	Through clinical expert interviews, ABR and AjBR were confirmed as clinically relevant measures in which to measure the impact of bleeds on haemophilia B patients.
Secondary endpoint (endpoint's name)	AjBR		

Abbreviations: ABR, Annualized bleeding rate; AjBR, Annualized joint bleeding rate.

9.2.2.5 Adverse reaction outcomes

From the HOPE-B trial, 54 patients in the phase III HOPE-B study reported a total of 557 AEs, with each patient reported having experienced at least one mild AE (EMA, 2023). However, the majority of TEAEs (464 of 557 events in the post-treatment period) were assessed as not treatment-related to Hemgenix, with a total of 93 TEAEs in 28/54 (70.4%) subjects assessed as treatment-related (EMA, 2023).

The SOCs with the highest incidence of treatment-related TEAEs were general disorders and administration site conditions (35.2% of subjects; 25 TEAEs), investigations (22.2% of subjects; 26 TEAEs), and nervous system disorders (16.7% of subjects; 13 TEAEs) (EMA, 2023). The most commonly reported treatment-related TEAEs were ALT increased (16.7%), headache (14.8%), and influenza-like illness (13.0%) (Table 32) (EMA, 2023). The majority of treatment-related TEAEs (91/93 events) were mild or moderate in severity; two treatment-related TEAEs reported in one subject (ALT increased and AST increased) were severe. The treatment-related TEAE distribution by SOC in the subjects with baseline anti-AAV5 Nab-positive subgroup was similar to the overall post-treatment Safety Population (EMA, 2023). Four (80.0%) of five subjects with elevated transaminases at dosing experienced seven TEAEs that were assessed as treatment-related (EMA, 2023). A total of three events of influenza-like illness were experienced by 2/5 (40.0%) subjects, and infusion related reaction, abdominal discomfort, ALT increased, and night sweats were reported in 1/5 (20.0%) subject each (EMA, 2023).

In the economic model, only treatment-related TEAEs were considered relevant to capture the cost and utility impact of AEs related to patients being treated with Hemgenix. The model also incorporated the 3-week lead-in period for Hemgenix following administration wherein patients could still receive FIX replacement therapy treatment. Therefore, the total weekly probability for each AE was calculated as a sum of both the Hemgenix probability and an average FIX replacement therapy probability, which was weighted by FIX market shares and time to steady state.

For Refixia, there was no reported data on safety from the Paradigm 2 trial (Collins et al., 2014). In the EMA EPAR, there is also limited data on treatment related events for Refixia (section 8.2.2.2), with the only two treatment-related events reported in more than 5% of patients being nausea and fatigue (EMA, 2017). The rates reported in the Refixia EPAR for fatigue (7%) and nausea (6.1%) were taken from pooled study data, with no defined time period of measurement reported (EMA, 2017). The rate of event per person year for both events were reported as <0.1. The absence of a defined time period presents a challenge in calculating the weekly probabilities required for the model and therefore given this fact and the uncertainty over whether these events are treatment related (section 8.2.2.2), a conservative approach was taken to assume no adverse events for Refixia in the model.

As part of scenario analysis, two scenarios were conducted. In the first scenario, AE incident rates were taken from another FIX prophylaxis treatment trial, namely the data on the AEs reported for Benefix in the EMA, BeneFIX assessment report (EMA, 2015). It was assumed that all FIX prophylaxis treatments should offer a similar safety profile and therefore it could be appropriate to apply the same probability of AEs associated with Benefix to Refixia. For use in the scenarios, the AEs were converted from 6-month probabilities to 1-week probabilities i.e. adjusted to the cycle length of the model. For the second scenario, the reported EMA EPAR rates for fatigue and nausea were assumed to be over a year period and converted to weekly probabilities (EMA, 2017).

Table 32: Hemgenix adverse reaction outcomes – incident rate

Adverse reaction outcome	Clinical documentation (%)	Used in the model (weekly probability)
ALT increased	16.70%	XXXX
Headache	14.80%	XXXX
Influenza like illness	13.00%	XXXX
AST increased	9.30%	XXXX
Fatigue	7.40%	XXXX
Blood creatine phosphokinase increased	7.40%	XXXX
Nausea	7.40%	XXXX
Dizziness	7.40%	XXXX
IRRs	5.60%	XXXX
Arthralgia	5.60%	XXXX
Infection	0.00%	XXXX
Body pain*	0.00%	XXXX

Note: *Body pain refers to the acute or chronic joint pain experienced by PWHB.
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; IRR, Infusion-related reaction PWHB, Patients with haemophilia B.
Source: CSL Behring (2022i).

9.3 Extrapolation of relative efficacy

The relative efficacy of Hemgenix has been taken directly from the HOPE-B trial. To estimate the efficacy of the comparator the results of the ITC was used, as described in section 9.2.2.4. For details on the ITC conduction see section 8.2.2.

9.4 Durability of clinical effect

An important component of gene therapy is the duration in which the clinical effectiveness maintains its full effect and at which point, if any the clinical effect will begin to decrease over a period of time, and thus patients 'lose response' to treatment.

To assess the durability, statistical analysis was performed to estimate the long-term durability of FIX activity levels after receiving Hemgenix, using data from the Phase 2b and Phase 3 clinical trials (Shah et al., 2023). Statistical approaches are commonly used to make such prediction and given the limited data set, linear mixed models were considered a good option as they allow for information sharing across subgroups and since not all of the include participants had FIX activity levels recorded at each visit, this approach provides a simple alternative to handle missing data under the missing at random assumption without imputation. The

aim of the model and analysis was to estimate the durability of FIX activity levels in clinical trial participants over an extended period of time after receiving Hemgenix.

Two modelling approaches were initially tested: Bayesian and Frequentist. Since reliable historical data was unavailable on FIX activity levels after receiving gene therapy, the model parameters for the Bayesian modelling approach were assigned non-informative prior distributions. Underlying FIX activity levels for the analysis population (N=55) were then estimated and long-term durability was predicted through extrapolation. The parameters for the Frequentist model were estimated from the 55 participants included in the analysis, and then the long-term FIX activity levels for these 55 participants were predicted using the estimated parameter values. Model selection criteria (AIC, BIC) were used to determine a final model. The results are presented in Appendix G.

Both models, estimate the durability of treatment for two different FIX steady state levels (FIX level <2% and FIX level <5%). The steady state level determines the level of FIX activity whereby if a patients FIX level is above this (i.e. above 2% FIX or 5%) then prophylaxis treatment is assumed to no longer be required. In the context of estimating the durability of Hemgenix, the durability model estimates the time it takes for a patients FIX level to drop below either 2% or 5%, at which time it is assumed they would require prophylaxis treatment once again. In the economic model, a FIX activity level of 2% is considered the cut-off steady state level based on a scale presented by Srivasta et al. 2020 (Srivastava et al., 2020). This scale categorized various levels of haemophilia according to the severity of the associated bleeds. Severe haemophilia involved a FIX level of <1% which leads to spontaneous bleeding or bleeding induced by minimal trauma. Moderate form of haemophilia was classed as a FIX level between 1-5% which could cause the same bleeding pattern as seen in severe haemophilia, but with normally a lower intensity and finally, mild haemophilia was classed as a FIX level between 5-40% where spontaneous bleeding episodes are uncommon and severe bleeding normally occurs in connection with trauma or surgery. Therefore, whilst 1% could be used as the level needed to reach a steady state, to be conservative a 2% FIX activity level was used and therefor the 2% durability data was selected from the durability model.

For use in the economic model, the Bayesian model was selected. The Bayesian model-based predictions indicate that more than 80% of patients will not need FIX prophylaxis treatments at 25.5 years, with the median value reaching 42 years. The inputs for the underlying exponential model, of a 2% durability threshold has been agreed by key opinion leaders as being 'credible and reasonable' because, patients are typically considered for prophylaxis in Denmark if they have baseline FIX levels of 2% or less (Nordic Haemophilia Guidelines, 2022).

The advantage of the Bayesian modelled approach is its ability to predict outcomes for future data conditional on observed data. The model accounts for uncertainty in future observations while considering inherent within-and between-participant variability. That is Bayesian modelling is probabilistic in nature and views the model parameter as random variables while the analysis data is fixed. The Frequentist approach however views the parameters in the model as fixed values and data as a random sample of the population. Given the uncertainty due to a lack of existing durability data on the durability of haemophilia B treatments, the Bayesian model was chosen due to its ability to account for uncertainty in future observations.

The limitations of the 60 years Bayesian predictions include:

- Taking observations from a few years and projecting many years in the future has uncertainty.
- There is a high variability in the FIX activity assay.
- Estimates rely heavily on assumptions – which can only be verified over time with more data.

Updates as of February 2024

The Bayesian analysis has been updated utilizing 36 months of data (CSL Behring, 2024), building on the evidence from the previous analysis that included data from 24 months of follow up. The model is equipped with an option for the user to choose between 24- and 36-month follow up to inform the analysis. CSL Behring strongly suggests that the most updated data source is used to mitigate uncertainty in the analysis.

In the model, durability is modelled such that the modelled cohort of patients who loses response to treatment over time were defined as 'non-responders'. The model applies a reduction in treatment durable clinical effect based on the proportion of patients whose FIX level is expected to drop below 2%. Once FIX activity levels drop below 2% and there is a need for FIX prophylaxis treatment, management of haemophilia B is resumed with FIX replacement prophylaxis; thus, the modelled cohort who are non-responders incur the bleed rates and costs associated with Refixia.

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Table 33: Durability estimates – Bayesian model

Year	FIX level <2%
1	0.0%
2	0.0%
3	0.0%
4	0.0%
5	0.1%
10	0.20%
15	1.3%
20	3.6%
25	7.6%
30	11.0%
35	14.8%
40	19.0%
45	23.2%
50	26.3%
55	29.1%
60	32.1%

Abbreviation: FIX, Factor IX.
Source: (CSL Behring, 2024)

9.5 Documentation of HRQoL

9.5.1. Overview of health state utility values (HSUV)

For health state utilities (Table 34), EQ-5D-5L utilities, from the HOPE-B trial and mapped for the Danish population using the Jensen et al. 2021 Danish EQ-5D-5L value set (Jensen et al., 2021) were used in the economic model. Section 9.5.2 provides more information on the utility values used in the model. Table 35 and Table 36 provide a summary of the other utility values used, which were taken directly from the literature, whilst Appendix H summarizes the literature search for HRQoL data.

Table 34: Overview of HSUV derived from HOPE-B

Health state	Utility values for Hemgenix (SE)	Utility values for comparators (SE)	95% CI Hemgenix	95% CI comparators	Justification
No bleeds	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial data
Non-joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial data
Joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial data
Death	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial data

Abbreviations: CI, Confidence interval; HOPE-B, Health Outcomes with Padua Gene, Evaluation in Haemophilia B; HSUV, Health state utility values; SE, Standard error. Source: CSL Behring (2022i)

An overview of the event-based utilities used from the literature are presented in Table 35.

Table 35: Overview of event-based utilities derived from literature

Health state	Utility values for Hemgenix (SE)	Utility values for comparators (SE)	95% CI Hemgenix	95% CI comparators	Justification
Disutility of non-joint bleed per cycle	[redacted]	[redacted]	[redacted]	[redacted]	Tice JA and Pearson SD (2022)

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Health state	Utility values for Hemgenix (SE)	Utility values for comparators (SE)	95% CI Hemgenix	95% CI comparators	Justification
Disutility of joint bleed per cycle	[redacted]	[redacted]	[redacted]	[redacted]	Tice JA and Pearson SD (2022)
Disutility of administration	[redacted]	[redacted]	[redacted]	[redacted]	Johnston et al. (2021) Abstract and pg 1,412

Abbreviations: CI, Confidence interval; HOPE-B, Health Outcomes with Padua Gene, Evaluation in Haemophilia B; pg, Page; SE, Standard error.
Source: cited in table.

An overview of the AE based utilities used from the literature are presented in Table 36.

Table 36: Overview of AE disutilities derived from literature

Adverse event	Disutility	Source	Additional notes
ALT increased	[redacted]	NICE (2018b)	[redacted]
Headache	[redacted]	Sullivan et al. (2011)	[redacted]
Influenza-like illness	[redacted]	NICE (2018a)	[redacted]
AST increased	[redacted]	NICE (2018b)	[redacted]
Fatigue	[redacted]	Hagiwara et al. (2018)	[redacted]
Blood creatine phosphokinase increased	[redacted]	NICE (2018b)	[redacted]
Nausea	[redacted]	Hagiwara et al. (2018)	[redacted]
Dizziness	[redacted]	Matza et al. (2019)	[redacted]
IRRs	[redacted]	NICE (2018b)	[redacted]
Arthralgia	[redacted]	Hagiwara et al. (2018)	[redacted]
Infection	[redacted]	Matza et al. (2019)	[redacted]
Body pain*	[redacted]	Hagiwara et al. (2018)	[redacted]

Note: *Body pain refers to the acute or chronic joint pain experienced by PWHB.
Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; DAIR, Debridement, antibiotics and implant retention; IRR, Infusion-related reaction NICE, National Institute for Health and Care Excellence; pg, Page; PWHB, Patients with haemophilia B.
Source: cited in table.

9.5.2. HSUV used in the health economic model

For Hemgenix, the data included in the model is the EQ-5D-5L aggregated scores from the 24-month cut-off point in HOPE-B and these were appropriately weighted using the Jensen et al. 2021 Danish EQ-5D-5L value set (Jensen et al., 2021). The utility values associated with the outcomes reported by the patients in HOPE-B (EQ-5D-5L) were appropriately weighted to reflect a Danish population by using the Danish EQ-5D-5L values set published by Jensen et al. 2021 (Jensen et al., 2021).

Given the results of the ITC (section 8.3.5) for EQ-5D did not show any significant difference between Hemgenix and Refixia it was assumed that there was no difference in utilities between the two treatments. Previously, clinical experts have validated a utility difference existing between FIX prophylaxis (CSL Behring, 2022a). They acknowledged that any difference between treatments would reflect FIX treated patients living a precautionary life, as they fear bleeding events and lack of freedom to enjoy usual activities. However, because the ITC showed no statistically significant difference it was decided that a conservative position would be taken where there is no utility difference between treatments. Therefore, the utility for Refixia was equal to the utility for Hemgenix and was taken from the HOPE-B trial.

The HRQoL disutility values for bleed events utilized in the economic model are taken from the US-ICER 2022 gene therapy for haemophilia B evidence report (Tice et al., 2022). The disutility from bleeds is not intrinsically part of the health states themselves. Rather, they are treated like 'adverse' events associated with the relevant health states, for the following reasons. Firstly, the cycle

length is a week whereas [redacted]. Secondly, it allows the disutility of the bleed to be time independent of the FIX prophylaxis treatment.

Table 37 are the scaled disutilities applied in the model in line with the appropriate durations of the bleeds, accurate to two decimal places. Clinical expert has confirmed that [redacted] (CSL Behring, 2022b). The gross utility of a non-joint bleed is [redacted] for a joint bleed (Tice et al., 2022). For FIX administration there was a disutility applied for the administration of FIX treatment which is administered intravenously by the patient. The disutility applied per administration was [redacted] sourced from Johnston et al. 2021 (Johnston et al., 2021).

Decrements in utility for AEs associated with treatment with Hemgenix and Refixia were captured in the model via the application of disutility values and estimated AE duration, where necessary. The disutility associated with AEs were sourced from published literature Table 37.

Table 37: Summary of the HSUV used in the model

Health state	Utility values for Hemgenix (SE)	Utility values for comparators (SE)	95% CI Hemgenix	95% CI comparators	Justification
No bleeds	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial
Non-joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial
Joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial
Death	[redacted]	[redacted]	[redacted]	[redacted]	HOPE-B trial
Adverse reactions	Refer to Table 36				
Disutility of non-joint bleed per cycle	[redacted]	[redacted]	[redacted]	[redacted]	Tice et al. (2022)
Disutility of joint bleed per cycle	[redacted]	[redacted]	[redacted]	[redacted]	Tice et al. (2022)
Disutility of IV administration	[redacted]	[redacted]	[redacted]	[redacted]	Johnston et al. (2021)

Abbreviations: CI, Confidence interval; HSUV, Health state utility value; IV, Intravenous; SE, Standard error.

9.5.3. Age-adjusted utilities

In line with DMC guidelines, treatment-specific utility values were age-adjusted to ensure that the relative level of utility would decline in a rate consistent with the expected decline in HRQoL observed within the general Danish population. The HRQoL from the general Danish population published in Wittrup-Jensen et al. 2009 (Wittrup-Jensen et al., 2009) as used to derive an adjustment index (multiplier) which subsequently was used to perform the age-adjustment, as recommended by the DMC in the *"Appendiks: Aldersjustering for sundheds-relateret livskvalitet"* (Medicinrådet, 2022). The adjustment index was calculated dividing the age-specific utility values presented in Table 38 with the utility value corresponding to the group including the mean age of the HOPE-B trail of 41.5 years, used in the health economics model as the starting cohort age. The adjustment index thus takes value one for the age-group 40-49, and declines post this age category, displayed the rightmost column in Table 38.

Table 38: Danish general population health utility by age group

Age group	Health utility value	Adjustment index (multiplier)
18-29	[redacted]	[redacted]
30-39	[redacted]	[redacted]
40-49	[redacted]	[redacted]
50-69	[redacted]	[redacted]
70-79	[redacted]	[redacted]
80+	[redacted]	[redacted]

Source: Jensen et al. (2021).

9.6 Resource use and costs

The model included direct healthcare costs applicable to limited societal perspective. The model was built to include the cost categories as outlined in the sections below.

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9.6.1. Treatment costs

The cost of Hemgenix used in the model was [redacted] Danish kroner (DKK) per pack (pharmacy retail price [PRP] excl. VAT). This cost is applied when the drug is administered.

Treatment costs for Refixia was sourced from Medicinpriser.dk with multiple cost and pack sizes available, as shown in Table 39 (Medicinpriser). The dosing frequency for Refixia was based on SmPC dosing schedules and dosages. These dosing frequencies were then validated with Danish KOLs (KOL input, 2022). In the base case drug wastage is not applied. To calculate the annual cost of Refixia, the total dose required per cycle was calculated (using the SmPC dosing schedules) (SmPC, 2022b). The cost of fulfilling this dosing was then calculated for each individual pack size. Finally, the minimum cost to meet the dosing requirements was selected.

Table 39: Treatment costs for Hemgenix and Refixia

Drug	Pack size	Cost per pack (DKK)*	Reference/source for costs
Hemgenix	1 course of treatment	[redacted]	CSL Behring
Refixia	500 IU	7,412.15	Varenummer: 530623. ATC code: B02BD04.Available from: (Medicinpriser)
	1,000 IU	14,792.68	Varenummer: 179645. ATC code: B02BD04. Available from: (Medicinpriser)
	2,000 IU	29,553.55	Varenummer: 196150. ATC code: B02BD04. Available from: (Medicinpriser)

Note: *PRP excl. VAT.
Abbreviations: DKK, Danish kroner; IU, International unit; PRP, Pharmacy retail price; VAT, Value-added tax.
Source: cited in table.

Table 40: Refixia dosing

Drug	Dose option distribution	Dose frequency (dose every x days)	Dose strength (IU/kg)	Dose per administration (IU)	Number of administrations per year	Dose per year	Annual cost (DKK)	Reference
Refixia	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Drug costs: ATC code: B02BD04. (Medicinpriser) Dosage: (SmPC, 2022b)

Abbreviations: DKK, Danish kroner; IU, International unit; kg, kilograms.
Source: cited in table.

All patients in the FIX prophylaxis arm, including those whose FIX activity level dropped below 2% after treatment with Hemgenix, received prophylaxis treatment for their whole lifetime until death or they developed inhibitors. The treatment of inhibitors is complex and can include high-dose clotting factor concentrates, bypassing agents, and ITI therapy (Ljung et al., 2019). Inhibitors typically develop during childhood in the first 50 days of treatment (Ljung et al., 2019). In all durable clinical effect scenarios included within the model, 0% of patients were assumed to develop inhibitors, since patients taking part in HOPE-B trial had been on stable FIX prophylaxis for at least two months prior to screening.

9.6.2. Administration costs

Administration of Hemgenix was applied as a one-off cost in cycle 1. The included administration costs were (Table 41):

If patients developed inhibitors while on FIX replacement prophylaxis, they received treatment including high-dose clotting factor concentrates, bypassing agents, and ITI therapy. However in the base case, no patients develop inhibitors, as per the HOPE-B trial results (CSL Behring, 2022i). There is no administration cost associated with the administration of Refixia which is self-infused by the patient (Table 41).

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Table 41: Administration costs for Hemgenix and Refixia

Intervention	Administration resources	Administration costs (DKK)	Frequency	Source
Hemgenix	IV infusion cost	[redacted]	[redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + BWAA60 "Medicingivning ved renchatio renchat") Accessed: January 2023. Available from: (Sundhedsdata, 2023)
	Initial screening (FibroScan)	[redacted]	[redacted]	Sundhedsdata DRG Grouper, 2023. DRG group: 16MA98 (DD679 "Haemofili B" + KZXF40A "anvendelse af intraabdominal ultralyd") Accessed: January 2023. Available from: (Sundhedsdata, 2023)
	Blood tests	[redacted]	[redacted]	Rigshospitalets Labportal (2023). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC). Available from: (Rigshospitalets Labportal, 2023)
Wound management (gauze/plaster)		[redacted]	[redacted]	ApoPro, Elastomull Gazebind 4 cm x 6 m Available from: (Apopro.dk)
Refixia		[redacted]		Self-administered treatment

Abbreviations: DKK, Danish kroner; Erc-MCV, Erythrocytes-mean corpuscular volume; IV, Intravenous.
Source: cited in table

9.6.3. Follow-up costs

Follow-up costs for Hemgenix, as described in Table 42, were applied with a varied rate in first year of treatment versus subsequent years:

In cycle 1:

- Weekly follow-up sessions from week 1 to 12 – [redacted]
- Monthly follow-up sessions from month 4 to 12 – [redacted]

In cycles 2-5:

- Long-term follow-up for five years [redacted]

There were no treatment follow-up costs associated with Refixia due to the self-administration of treatment.

Table 42: Follow-up costs

Intervention	Resource	Unit costs (DKK)	Resource use per cycle	Source
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Resource	Unit costs (DKK)	Resource use per cycle	Source
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Year 2-5	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner; FIX, Factor IX.
Source: cited in table.

9.6.4. Subsequent treatment costs

Subsequent treatment costs are included for patients who did not respond to Hemgenix (non-responders). [redacted]. The treatment and administration costs for Refixia were the same as use of Refixia in first-line treatment.

9.6.5. Disease management

Health state costs were driven by events (all bleeds and joint bleeds) experienced by patients in the CEM. Each event was associated with resource use and management costs. Published literature sourced from a targeted review was used where possible.

Event costs for Hemgenix were based on the ABRs observed within HOPE-B (CSL Behring, 2022i). For Refixia, event costs were based on the bleed rates overserved in the HOPE-B ITC (see section 8.3.5) (CSL Behring, 2022e). The cost per cycle for disease management and events were calculated using unit costs sourced from the Kommunernes og Regionernes Løndatakontor and Sundhedsdata DRG Grouper (Sundhedsdata, 2023, Kommunernes og Regionernes Løndatakontor, 2023). The costs for disease management were then multiplied by the annual ABR rates to calculate total disease management costs.

The following monitoring costs were included in the model once every cycle, as presented in XXXXXXXX XXXXXXXXXXXXXX

- [redacted]

Table 43, with the number of visits per year being informed by a Danish KOL (KOL input, 2022):

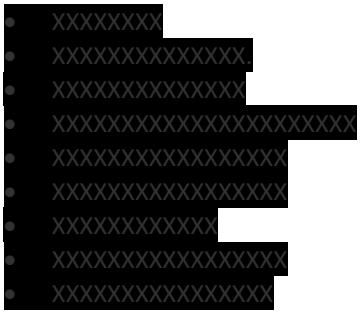

Table 43: Haemophilia B monitoring costs

Resource	Unit Cost (DKK)	Resource use per cycle	Total cost per cycle (DKK)	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner.
Source: cited in table.

9.6.5.1 Bleed-related/event management costs

Bleed-related/event management costs, as described in Table 44, were applied based on likelihoods of events per cycle and included:

Resource use for AE visits and hospital stays were taken from the CHESS US study, resource use for all other monitoring costs were taken from O'Hara et al. 2018 and Nissen et al. 2022 (O'Hara et al., 2018, Nissen, 2022). The hospital stays resource use was calculated as the average of mean inpatient days [redacted] and mean intensive care unit days [redacted] per year from the CHESS US study (Nissen, 2022). These resource use frequencies were also validated with Danish KOLs (KOL input, 2022).

Table 44: Bleed-related management costs

Resource	Unit Cost (DKK)	Resource use per event	Total cost per event (DKK)	Source
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]

Abbreviations: DKK, Danish kroner; DRG, Diagnosis related group; IU, International unit.
Source: cited in table.

Treatment of bleeds was assumed to be with FIX therapies. Market shares from subsequent treatments (see section 9.6.4) were applied to the subsequent treatment acquisition costs to calculate a weighted average cost of treatment a bleed event. For treatment of bleeds, patients were assumed to have a single dose of FIX treatment (see section 9.6.4).

9.6.6. AE costs

Grade 3 and above AEs that occur in ≥5% of patients were incorporated into the model because they incur substantial costs to the healthcare system. In the Hemgenix arm, the AEs were included based on the probabilities per year reported within the population in the post-treatment period of the HOPE-B trial and are summarized in section 9.2.2.5. The duration of AEs is assumed to be seven days following treatment with Hemgenix. This assumption is made due to a lack of data on AE duration. The costs associated with these AEs are presented in Table 45.

Table 45: AE costs

Adverse Event	Hemgenix	Cost	Source
Headache	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]

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Adverse Event	Hemgenix	Cost	Source
			[redacted]
ALT increased	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
IRRs	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Infection	[redacted]	[redacted]	[redacted]
Body pain	[redacted]	[redacted]	[redacted]

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; DKK, Danish kroner; IRR, Infusion-related reaction; SOC, Standard of care.
Source: cited in table.

9.6.7. Patient costs

Costs incurred by patients as a consequence of the pharmaceutical treatment in terms of in terms of transport costs and patient time were be included in line with guideline recommendations (Medicinrådet, 2022). Treatment-related resource consumption requiring transportation to a hospital or patients time is presented in XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Table 46. No direct estimate for transportation costs could be obtained, for this reason, transportation costs were obtained by multiplying the estimated frequency of transport for medical services with the unit cost of the average transportation. The unit cost for the average transportation including return trip was calculated [redacted] in line with guidance from the DMC (Medicinrådet, 2022). The cost of patients' time was valued to [redacted] This results in a total unit cost per event of DKK (Medicinrådet, 2022). Patient time consumption related to administration of Refixia was estimated to [redacted] amounting to a patient time cost per administration of [redacted] (Medicinrådet, 2022). Patient time consumption related to administration of Refixia was estimated [redacted] (KOL input, 2022), amounting to a patient time cost per administration of [redacted]

Table 46: Annual treatment-related resource consumption requiring transportation or patients time

Treatment	Hemgenix	Refixia
Administration	[redacted]	[redacted]
Hospital follow-up: first year	[redacted]	[redacted]
Hospital follow-up: subsequent years (2-5)	[redacted]	[redacted]

Note: *Administration of Hemgenix is included as one-time hospital visit during year one.

Table 47: Transport and patient time costs

Treatment	Hemgenix	Refixia	Source
Transportation unit cost	[redacted]	[redacted]	(Medicinrådet, 2022)
Patient time unit cost	[redacted]	[redacted]	(Medicinrådet, 2022)
Average patient hospital visit time (hour)	[redacted]	[redacted]	Assumption
Average time per administration	[redacted]	[redacted]	(KOL input, 2022)

Source: cited in table.

9.7 Results

9.7.1. Base case overview

The model settings used in the base case analysis for evaluating Hemgenix are presented in Table 48.

Table 48: Summary of settings used for the base case analysis

Input	Base case	Justification
Time horizon	59 years	This provides a lifetime horizon based on the starting cohort age
Perspective	Restricted societal perspective (see 9.1.3).	As per the DMC guidelines
Discounting	3.5% for both costs and QALYs for years 0-35	As per the DMC guidelines
Starting cohort age	41.5 years	This is the mean age of patients in the HOPE-B trial
Body weight (kg)	85.1	This is the mean body weight of patients from the HOPE-B trial
Proportion male	100 %	This is the population in the HOPE-B trial
Comparator	Refixia	As per the pre-meeting with DMC on 21 December 2022. See section 9.1.7

Abbreviations: QALY, Quality of life adjusted years.

9.7.2. Base case results

The results of the base case analysis are presented in Table 49. Incremental life years gained and QALYs are [redacted] The lower number of bleeds and the disutility of administrating Refixia with infusion account for the difference in QoL. Incremental total costs are about [redacted] with treatment costs accounting for the majority of costs. The impact of the remaining cost items is very low. This amounts to a dominating incremental cost effectiveness ratio (ICER) per QALY.

Table 49: Base case results

	Hemgenix	Refixia	Incremental*
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Costs			
Treatment costs	[redacted]	[redacted]	[redacted]
Follow-up costs	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Transportation cost (DKK)	[redacted]	[redacted]	[redacted]
Patient time cost (DKK)	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
ICER			Dominating

Note: *Incremental calculations may not be exact due to rounding of figures.
Abbreviations: ICER, Incremental cost effectiveness ratio; QALY, Quality adjusted life years.

9.8 Sensitivity analyses

9.8.1. Probabilistic sensitivity analyses (PSA)

The results of the PSA (for 1,000 iterations) are presented in Table 50 which also presents results from the deterministic analysis for comparison. This analysis supports the conclusions from the deterministic analysis.

Table 50: Result summary from probabilistic sensitivity analysis

Hemgenix versus	Analysis	Inc. costs, DKK	Inc. QALYs	Incremental cost per QALY, DKK
Refixia	Deterministic	[redacted]	[redacted]	Dominating
	Probabilistic	[redacted]	[redacted]	Dominating

Abbreviations: DKK, Danish kroner; LY, Life years, QALY, Quality adjusted life year; WTP, Willingness-to-pay.

The result of the cost-effectiveness analyses is presented in a cost-effectiveness plane in Figure 23. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 23. As indicated in
Figure 24, the probability that Hemgenix is a cost-effective intervention is just above 99% across the WTP thresholds up to one million DKK.

Figure 23: Cost-effectiveness plane

Abbreviations: PSA, Probabilistic sensitivity analysis; QALY, Quality adjusted life year.

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Figure 24 Cost-effectiveness acceptability curve

[redacted]

Abbreviations: DKK, Danish kroner.

10. Scenario analyses

Scenario analyses were undertaken to investigate the effect of structural assumptions and evaluate the model's sensitivity towards the settings chosen for the base case. Table 51 presents a list of scenario analyses and the outcomes.

Table 51: Scenario analyses

Input	Base case	Scenario analysis
Bleed duration	[redacted]	[redacted]
Joint bleed duration	[redacted]	[redacted]
Administration disutility	[redacted]	[redacted]
Starting cohort age	[redacted]	[redacted]
FIX threshold for switching to prophylactic treatment	[redacted]	[redacted]
Relative risk of bleeding	[redacted]	[redacted]
Discounting	[redacted]	[redacted]
Transport costs excluded	[redacted]	[redacted]
Patient costs excluded	[redacted]	[redacted]
Price discount	[redacted]	[redacted]
Adverse events – Benefix rates	[redacted]	[redacted]
Adverse events – EPAR adverse event rates	[redacted]	[redacted]

Abbreviations: FIX, Factor IX; QALYs, Quality adjusted life years.

The scenario results varying the base case setting are presented in Table 52. [redacted]

[redacted]

Table 52: Results from scenario analyses – varying base case settings

Scenario	Total Cost Hemgenix	Total Cost Refixia	Total QALYs Hemgenix	Total QALYs Refixia	Incremental Costs	Incremental QALYs	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Bleed duration: 1 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Bleed duration: 5 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Joint bleed duration: 5 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Joint bleed duration: 7 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Administration disutility: 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Age: 47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Age: 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
FIX duration threshold: 5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Relative risk of bleeding: 0.24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Discounting: 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Discounting: 5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Exclude transport and patient costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Price discount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Adverse events – Benefix rates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Adverse events – Refixia EPAR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: FIX, Factor IX; ICER, Incremental cost effectiveness ratio; QALYs, Quality adjusted life-years.

11.Budget impact analysis

As mentioned in Section 6.1.7 discussions in advisory boards estimate that approximately [redacted] will receive gene therapy over the next five years (Table 53 and Table 54). The total 5-year budget impact if [redacted] patients are treated with Hemgenix is then estimated to be [redacted] (Table 57). The total incremental cost per patient is [redacted] It is noted that whilst the upfront of cost of Hemgenix provides the largest budget impact, the results may not correspond to the expected budget impact when accounting for payment models, where treatment costs can be paid in increments. [redacted]

Number of patients

Table 53: Max number of patients expected to be treated over the next five-year period – if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration – Hemgenix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Competitive pharmaceutical – Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 54: Max number of patients expected to be treated over the next five-year period – if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration – Hemgenix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Competitive pharmaceutical – Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Expenditure per patient

Table 55: Costs per patient per year – if the pharmaceutical is recommended (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Competitive pharmaceutical – Refixia	-	-	-	-	-

Abbreviations: DKK, Danish kroner.

Table 56: Costs per patient per year – if the pharmaceutical is NOT recommended (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient	-	-	-	-	-
Competitive pharmaceutical – Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner.

Table 57: Expected budget impact of recommending the pharmaceutical for the current indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Follow-up costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Disease monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Follow-up costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Disease monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cumulative budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, Adverse event; DKK, Danish kroner.

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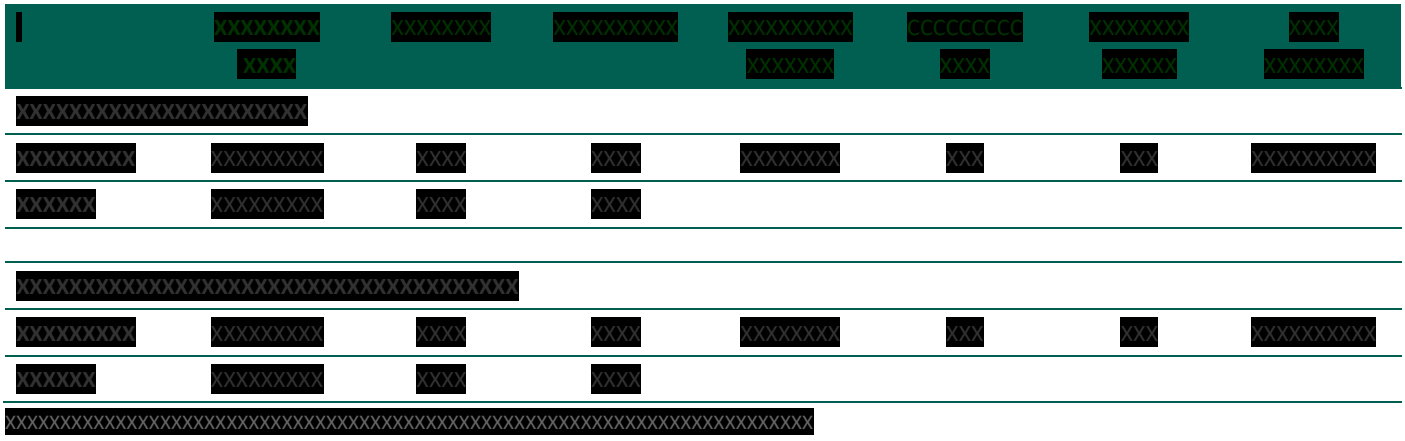
[redacted]

[redacted]



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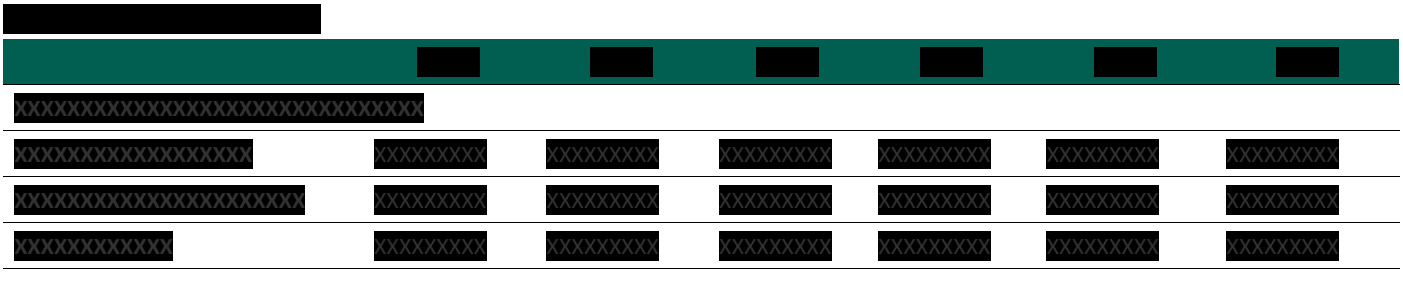

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[redacted]

13. Discussion on the submitted documentation

The objective of this analysis was to assess the cost-effectiveness of Hemgenix versus FIX replacement prophylaxis for PWHB in the Danish setting. The results of the cost-effectiveness analysis showed that over a lifetime time horizon, Hemgenix dominated the most common prophylactic treatment in Denmark, Refixia, with lower total costs and the higher QALY gain. Similar results were observed in all sensitivity and scenario analyses conducted within the model.

Patients with haemophilia B are faced with frequent invasive administration of coagulation therapy, and reduced QoL. Despite the availability of rFIX concentrates, patients still experience bleed events which can be serious or life threatening and, in the case of joint bleeds, can lead to chronic health issues. Therefore, a strong need exists for an effective therapy that eliminates bleedings for this patient population.

Bleed rate data from HOPE-B 24 months post treatment follow up shows that Hemgenix provides effective bleed control for PWHB, including statistically significant reductions in the ABR and in the number of bleeds requiring treatment. Mean AsBR and AjBR were also significantly reduced at 7-24 months compared with the lead-in period with FIX prophylaxis therapy. Hemgenix demonstrated a rapid and sustained significant increase in mean endogenous FIX activity levels and eliminated the need for routine FIX prophylaxis therapy in nearly all (96%) PWHB at 24 months (need for FIX prophylaxis eliminated in all patients treated according to current label). Fifty percent of PWHB treated with Hemgenix experienced zero bleeds at 24 months compared with the lead-in period on FIX prophylaxis therapy (Pipe et al., 2023, CSL Behring, 2022i).

Hemgenix is expected to have a sustained therapeutic effect over many years, as indicated by data from the clinical study program; a recently published statistical durability model based on study data predicts that the majority of treated patients will have no need for prophylaxis treatment for more than 25 years (Shah et al., 2023, Miesbach et al., 2022)

The results of the health economic evaluation, taking a limited societal payer perspective, showed that use of Hemgenix is cost-effective compared to Refixia, the most common prophylactic FIX treatment in Denmark, with lower costs and higher QALY gain. The results are robust over a range of scenario analyses undertaken where Hemgenix dominates FIX replacement prophylaxis. The cost-effectiveness results are mainly driven by the elimination of costs for FIX prophylactic treatment for patients dosed with Hemgenix. For patients on prophylaxis (FIX activity levels ≤2% of normal), treatment with Hemgenix offers cost offsets as long as patients maintain FIX activity levels over 2% threshold. Uncertainty around the durability of clinical effect was explored in a scenario analysis exploring the conservative assumption that patients would switch over to prophylactic treatment at a FIX activity level of 5%. Results from this scenario analyses indicated significant cost savings and a dominating ICER for patients switching to FIX prophylaxis even at a FIX activity level of 5%. Varying the duration of the disutility associated with bleeding events only has a minor impact of QoL.

Probabilistic sensitivity analyses estimated that Hemgenix is above 99 % likely to be cost-effective versus Refixia at a WTP threshold of up to 1,000,000 DKK per QALY. No one-way sensitivity analysis was performed, as the magnitude of the ICER does not have a meaningful interpretation with a dominating ICER.

[redacted]

One limitation is the absence of a head-to-head trial for Hemgenix versus Refixia. The use of the ITC has limitations including potential residual bias in the relative treatment effects (due to the use of single-arm, non-randomized trial data) and potential bias due to differing bleed rate outcome definitions between HOPE-B and Paradigm 2™ trials. However, this bias when assessed was deemed to be minimal. The ITC feasibility assessment did show however that an ITC assessment was suitable to conduct between the HOPE-B and Paradigm trials (CSL Behring, 2022e) (see Appendix C for more information).

Despite the aforementioned limitations, a number of strengths of the model and analysis should be recognized. A strength of the current analysis is that it reflects the haemophilia B natural disease course and treatment pathway. Drug therapy, co-medication, AE management, healthcare resource use, and disease monitoring costs were populated to reflect recent Danish-specific values, having been sourced from Danish clinical guidelines, the Danish Diagnosis-related group (DRG) (Sundhedsdata, 2023), laboratory price list (Kommunernes og Regionernes Løndatakontor, 2023), or the Danish drugs costs database (Medicinpriser). Another strength of this analysis was the use of clinical evidence for a haemophilia B population from the HOPE-B clinical trial as the best available source. The model was informed with as much trial data as possible in order to have consistency with the trial findings.

Taken together, this economic analysis predicted that compared to the current SOC in Denmark (Refixia), Hemgenix is less costly and more effective i.e., cost-saving. Given the need for an effective therapy to eliminate bleedings in this patient population, one-time treatment with Hemgenix should become a treatment option for adult patients with moderately severe or severe haemophilia B in Denmark as it will reduce both the clinical and economic burden for the patient as well as for the society.

14.List of experts

[redacted]

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Version log

Version	Date	Change
1.0		-
1.2	24 May, 2023	Updates to sections based on DMC validation questions. Please see the attached response document for detailed references.
1.3	29 July, 2023	Updates to sections based on DMC validation questions. Please see the attached response document for detailed references.
1.4	25 August, 2023	Updates to sections based on DMC validation questions. Please see the attached response document for detailed references.
2.0	21 February, 2024	Cost effectiveness model updated with 36-month data

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16. Appendix A Literature search for efficacy and safety of intervention and comparator(s)

A SLR of clinical trials, economic evidence and HRQoL studies was conducted to identify published clinical, cost-effectiveness, budget impact, HRQoL, cost and resource use studies conducted in haemophilia B. Appendix A describes the results from a single integrated SLR was conducted to answer the following research questions, which follow the PICOS (population, interventions, comparators, outcomes and study type) principle:

1. What randomized controlled trials (RCTs) have measured the efficacy and safety of treatment in adult male PWHB, and how were these measured?
2. What non-RCTs have measured the efficacy and safety of treatment in adult male PWHB, and how were these measured?

The following tables show the selection criteria used for each of the review questions.

Table 58: Selection criteria to be used for research question 1 (RCTs)

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Males aged 12 and over and/or aged 18 and over with congenital haemophilia B	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	Any intervention or procedure for the treatment of haemophilia B	No intervention or procedures of interest
Outcomes	AEs Discontinuation Discontinuation due to AEs Changes in: ABR FIX activity levels Number of target joints Spontaneous bleeds Traumatic bleeds Joint replacements Mortality rates	No reported outcomes of interest, i.e., only reporting pharmacodynamics, genetic, cellular, or molecular outcomes
Study type	RCTs	Prospective non-RCTs OLE studies Single arm studies Placebo-controlled studies Crossover studies Observational studies Retrospective studies Cross-sectional studies Economic analyses Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports Case reports or case series of fewer than 10 patients In-vitro, animal, or fetal studies
Publication type	Primary publications Secondary publications Pooled data analysis Congress abstracts and papers corresponding to the above	NMA Narrative reviews Editorials Letters Commentaries Congress abstracts that do not report sufficient data Report data for n≤5 Small studies

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Selection criteria	Inclusion criteria	Exclusion criteria
Language	English	Non-English

Abbreviations: ABR, Annualized bleeding rate; AE, Adverse event; FIX, Factor IX; NMA, Network meta-analysis; OLE, Open-label extension; RCT, Randomized controlled trials; SLR, Systematic literature review.

Table 59: Selection criteria to be used for research question 2 (non-RCTs)

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Males aged 12 and over and/or aged 18 and over with congenital haemophilia B	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	Any intervention or procedure for the treatment of haemophilia B	No intervention or procedures of interest
Outcomes	AEs Discontinuation Discontinuation due to AEs Changes in: ABR FIX activity levels Number of target joints Spontaneous bleeds Traumatic bleeds Joint replacements Mortality rates	No reported outcomes of interest, i.e., only reporting pharmacodynamics genetic, cellular, or molecular outcomes
Study type	Prospective non-RCTs OLE studies Single arm studies Placebo-controlled studies Crossover studies Observational studies Retrospective studies Cross-sectional studies	RCT Economic analyses Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports Case reports or case series of fewer than 10 patients In-vitro, animal, or fetal studies
Publication type	Primary publications Secondary publications Pooled data analysis Congress abstracts and papers corresponding to the above	Systematic reviews NMA Narrative reviews Editorials Letters Commentaries Congress abstracts that do not report sufficient data Report data for n ≤5 Small studies
Language	English	Non-English

Abbreviations: ABR, Annualized bleeding rate; AE, Adverse event; FIX, Factor IX; NMA, Network meta-analysis; OLE, Open-label extension; RCT, Randomized controlled trials; SLR, Systematic literature review.

Searches to identify evidence for all review questions were conducted in the following databases (databases updated daily):

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Table 60: Registers included in the search

Database	Platform	Search strategy	Date of search
Embase	https://www.embase.com/	Structured search	Original: 18th August 2021 Updated: 17th October 2022
MEDLINE	https://www.nlm.nih.gov/medline/index.html	Structured search	Original: 18th August 2021 Updated: 17th October 2022
Cochrane Central Register of Controlled Trials (CENTRAL)	https://www.cochranelibrary.com/central/about-central	Structured search	Original: 18th August 2021 Updated: 17th October 2022
Cochrane Clinical Answers	https://www.cochranelibrary.com/cca/about	Structured search	Original: 18th August 2021 Updated: 17th October 2022

16.1 Search strategy

Table 61 present the search strategies for Embase, MEDLINE and Embase Classic and CENTRAL and Cochrane Clinical Answers.

Table 61: Search terms for clinical SLR in MEDLINE (via Ovid)

No.	Query	Results
#1	[redacted]	9648
#2	[redacted]	22472
#3	[redacted]	1,866,551
#4	[redacted]	2,937,473
#5	[redacted]	633
#6	[redacted]	32

Abbreviations: SLR, Systematic literature review.

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Table 62: Search terms for clinical SLR in Embase (via Ovid)

No.	Query	Results
#1	[redacted]	17,771
#2	[redacted]	39,509
#3	[redacted] OR [redacted]	2,666,150
#4	[redacted]	4,372,948
#5	[redacted]	1,520
#6	[redacted]	88

Abbreviations: SLR, Systematic literature review.

Table 63: Search terms for clinical SLR in Cochrane (CDSR and CENTRAL)

No.	Query	Results
#1	[redacted]	717
#2	[redacted]	1,082
#3	[redacted]	1,017,793

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No.	Query	Results
	[redacted]	
#4	[redacted]	1,942,544
#5	[redacted]	28

Abbreviations: SLR, Systematic literature review.

Table 64: Search for clinical SLR in Centre for Reviews and Dissemination database, DARE, NHS EED, HTA database (v104renork.ac.uk/crd)

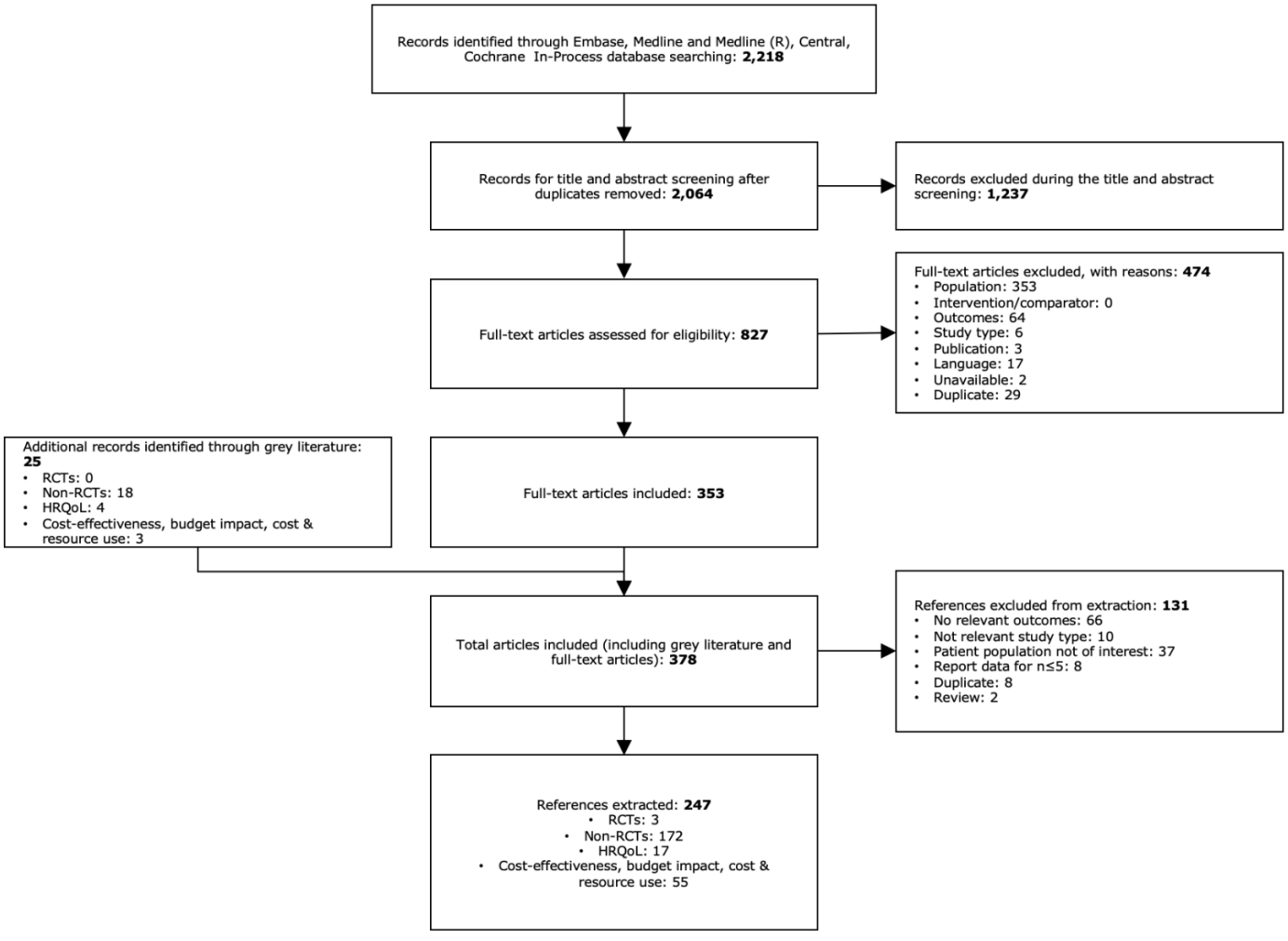
No.	Query	Results
#1	[redacted]	24

Abbreviations: DARE, Database of Abstracts of Reviews of Effects; HTA, Health technology assessment; NHS EED, National Health Service Economic Evaluation Database; SLR, Systematic literature review.

16.2 Systematic selection of studies

The study flow diagrams for the original search and the updated search are presented in Figure 25 and Figure 26.

Figure 25: Original review PRISMA diagram



Abbreviations: HRQoL, Health-related quality of life; RCT, Randomized controlled trial.

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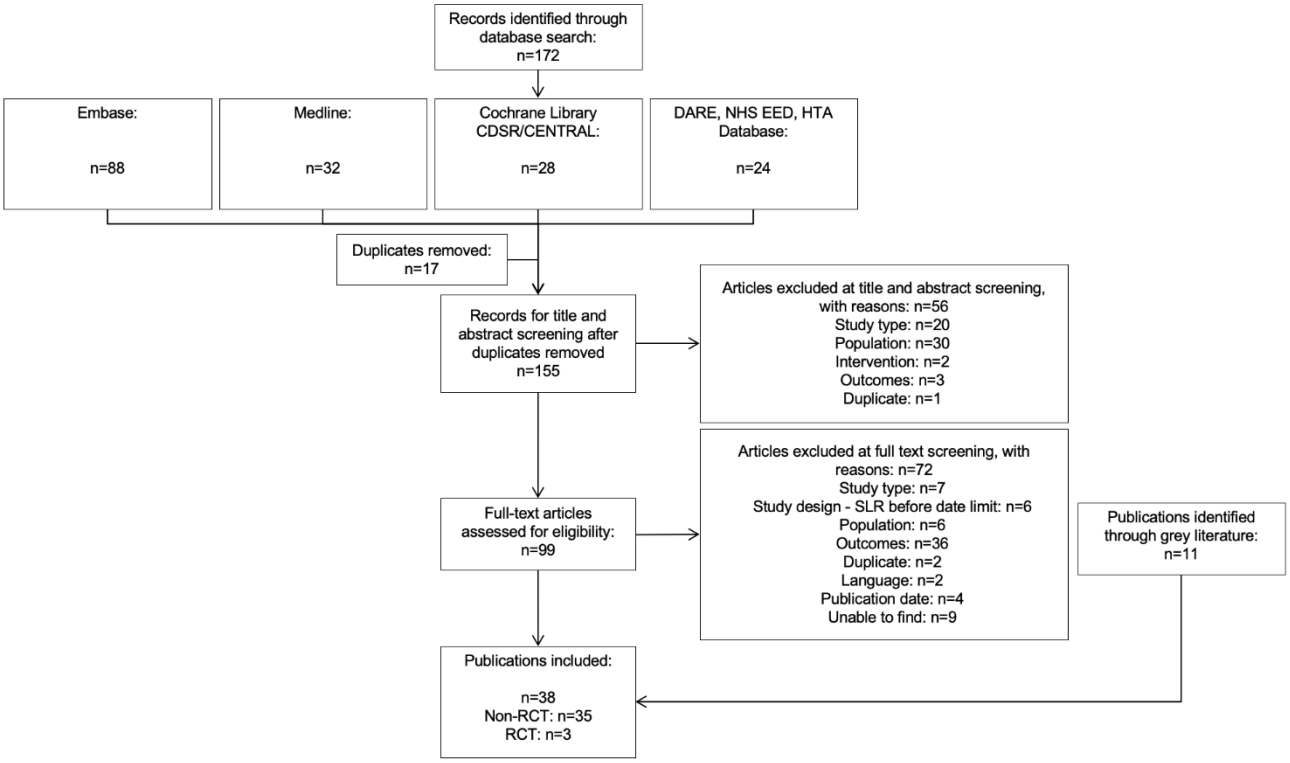
Figure 26: Update review clinical PRISMA diagram



Abbreviations: RCT, Randomized controlled trial; SLR, Systematic literature review.

A full list of excluded articles with the reason for exclusion can be found in Table 65.

Table 65: Excluded publications, update clinical and safety review (n=72 publications)

Reference	Reason for exclusion
Honda K, Nagao T, Kamiya T, Yoshioka A, Miyazaki T, Takeda T, Mori K, Fukutake K, HanabuFIMEA isa H, Taki M, Mohri H. Prospective matched control study concerning the treatment and quality of life of hemophiliacs with inhibitors. [Rinsho Ketsueki] The Japanese Journal of Clinical Hematology. 1998 Jun 1;39(6):416-21.	Duplicate
Ekert H, Brewin T, Boey W, Davey P, Tilden D. Cost–utility analysis of recombinant factor VIIa (NovoSeven®) in six children with long-standing inhibitors to factor VIII or IX. Haemophilia. 2001 May 1;7(3):279-85.	Duplicate
EUCTR 2019. Research study to look at how well the drug concizumab works in your body if you have haemophilia with inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004889-34-BG	Unable to find
EUCTR 2019.Research study to look at how well the drug concizumab works in your body if you have haemophilia with inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004889-34-CZ	Unable to find
EUCTR 2019. Research study to look at how well the drug concizumab works in your body if you have haemophilia without inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004891-36-GB	Unable to find
EUCTR 2020.Research study to look at how well the drug concizumab works in your body if you have haemophilia without inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004891-36-HR	Unable to find
EUCTR 2021.Research study to look at how well the drug concizumab works in your body if you have haemophilia without inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004891-36-HU	Unable to find
EUCTR 2021. Research study to look at how well the drug concizumab works in your body if you have haemophilia with inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004889-34-IT	Unable to find
EUCTR 2019. Research study to look at how well the drug concizumab works in your body if you have haemophilia without inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018-004891-36-PL	Unable to find

Reference	Reason for exclusion
NIHR HSC. Eftrenonacog alfa for haemophilia B. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC). Horizon Scanning Review. 2013. https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32014000554&ID=32014000554	Unable to find
Haute Autorité de Santé. Biologie des anomalies d' l'hémost se : recherche des inhibiteurs des FAH. [Biology of haemostasis disorders: detection and titration of antihaemophilic factor (AHF) inhibitor] Paris: Haute Autorité de Santé (HAS). 2011. https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32016000270&ID=32016000270	Unable to find
Andalusian Agency for Health Technology Assessment. Uso adecuado de Factor VIII en el tratamiento de la hemofilia A. [Appropriate use of Factor VIII for treatment of hemophil–a - A consensus conference] Seville: Andalusian Agency for Health Technology Assessment (AETSA). Informe 7 / 2005. 2005	Language
IQWiG. Therapie von hämophilie-patienten. [Treatment of haemophilia patients] Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). IQWiG-Berichte 305. 2015	Language
Adelaide Health Technology Assessment on behalf of the National Blood Authority. Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX products. Adelaide: Adelaide Health Technology Assessment (AHTA). 2005	Study design - SLR before date limit
Zhou ZY, Hay JW. Efficacy of bypassing agents in patients with hemophilia and inhibitors: a systematic review and meta-analysis. Clinical Therapeutics 2012; 34(2): 434-445	Study design - SLR before date limit
Franchini M, Makris M, Santagostino E, Coppola A, Mannucci PM. Non-thrombotic-, non-inhibitor-associated adverse reactions to coagulation factor concentrates for treatment of patients with hemophilia and von Willebr'nd's disease: a systematic review of prospective studies. Haemophilia 2012; 18(3): e164-e172	Study design - SLR before date limit
Coppola A, Franchini M, Makris M, Santagostino E, Di Minno G, Mannucci PM. Thrombotic adverse events to coagulation factor concentrates for treatment of patients with haemophilia and von Willebrand disease: a systematic review of prospective studies. Haemophilia 2012; 18(3): e173-e187	Study design - SLR before date limit
Chan MW, Leckie A, Xavier F, Uleryk E, Tadros S, Blanchette V, Doria AS. A systematic review of MR imaging as a tool for evaluating haemophilic arthropathy in children. Haemophilia 2013; 19(6): e324-e334	Study design - SLR before date limit
Alfonso I, Emanuela M, Maura M, Kent S, Anthony KC. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database of Systematic Reviews: Reviews 2011; Issue 9.	Study design - SLR before date limit
Chowdary P, Eichler H, Matsushita T, Rose TH, Ruzanski C, Seremetis S. Do106rench106ationion and risk mitigation during concizumab prophylaxis in patients with haemophilia A/B with and without inhibitors in phase 3 clinical trials. Haemophilia. 2022 Feb 1;28(S1):27.	Study type
Lehtinen AE, Baghaei F, Astermark J, Holme PA. Surgical outcomes in patients with haemophilia A or B receiving extended half-life recombinant factor VIII and IX Fc fusion proteins: Real-world experience in the Nordic countries. Haemophilia. 2022 May 16;28(5):713-719.	Study type
Mahlangu J, Lamas JL, Morales JC. Long-term Safety and Efficacy of the Anti-TFPI Monoclonal Antibody Marstacimab in Patients with Severe Hemophilia A or B: Results from a Phase 2 Long-term Treatment Study. Res Pract Thromb Haemost. 2021 Jul 17;5(S2):82.	Study type
Mahlangu J, Luis Lamas J, Cristobal Morales J, Malan DR, Teeter J, Charnigo RJ, et al. Long-term safety and efficacy of the anti-tissue factor pathway inhibitor marstacimab in participants with severe haemophilia: Phase II study results. Br J Haematol. 2022;00:1–9	Study type
Olasupo OO, Lowe MS, Krishan A, Collins P, Iorio A, Matino D. Clotting factor concentrates for preventing bleeding and bleeding-related complications in previously treated individuals with haemophilia A or B. Cochrane Database of Systematic Reviews. 2021(8).	Study type
Pasi KJ, Lissitchkov T, Mamonov V, Mant T, Timofeeva M, Bagot C, Chowdary P, Georgiev P, Gercheva-Kyuchukova L, Madigan K, Van Nguyen H. Targeting of antithrombin in hemophilia A or B with investigational siRNA therapeutic fitusiran—Results of the phase 1 inhibitor cohort. Journal of Thrombosis and Haemostasis. 2021 Jun;19(6):1436-46.	Study type
Shapiro A, Cepo K, Tønder SM, Young G, Jiménez-Yuste V. Safety and efficacy of concizumab prophylaxis following a switch from rFVIIa on-demand treatment: sub-analysis results from the phase 2 explorer4 trial in patients with hemophilia A or B with inhibitors. Res Pract Thromb Haemost. 2021;5(S2):381.	Study type
Miners A H, Sabin C A, Tolley K H, Lee C A. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. PharmacoEconomics 2002; 20(11): 759-774	Publication date

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Reference	Reason for exclusion
Szucs T D, Offner A, Schramm W. Socioeconomic impact of haemophilia care: results of a pilot study. Haemophilia 1996; 2(4): 211-217	Publication date
Lippert B, Berger K, Berntorp E, Giangrande P, Van Den Berg M, Schramm W, Siebert U. Cost effectiveness of haemophilia treatment: a cross-national assessment. Blood Coagulation and Fibrinolysis 2005; 16(7): 477-485	Publication date
Lindvall K, Astermark J, Bjorkman S, Ljung R, Carlsson KS, Persson S, Berntorp E. Daily dosing prophylaxis for haemophilia: a randomized crossover pilot study evaluating feasibility and efficacy. Haemophilia 2012; 18(6): 855-859	Publication date
Heller C, Bidlingmaier C, Escuriola C, Hagedorn N, Oldenburg J, van den Boom J, Malmström H, Santagostino E, Tiede A. Interim analysis of the prevent study: Real world prospective data from children and adolescents with haemophilia A or B treated with recombinant factor VIII FC (rFVIIIFc) or recombinant factor IX FC (rFIXFc). Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):.	Population
Konkle B, Coffin D, Naccache M, Clark C, George LA, Iorio A, Miesbach W, Noone D, Peyvandi F, Pipe S, Recht M. THE WORLD FEDERATION OF HEMOPHILIA GENE THERAPY REGISTRY-A GLOBAL RESOURCE FOR THE LONG-TERM FOLLOW-UP OF HEMOPHILIA PATIENTS TREATED WITH GENE THERAPY. Haemophilia. 2022 Feb 1;28(S1):97-98.	Population
Li Z, Liu G, Yao W, Chen Z, Li G, Cheng X, Zhen Y, Ai D, Huang K, Sun J, Poon MC. Eradication of FIX inhibitor in haemophilia B children using low-dose immune tolerance induction with rituximab-based immunosuppressive agent (s) in China. Haemophilia. 2022 May 3;28(4):625-632.	Population
Ljung R, van den Berg HM. FIX PRODUCT AT FIRST EXPOSURE IN CHILDREN WITH SEVERE HAEMOPHILIA B BETWEEN 2000-2020: DATA FROM PEDNET. Haemophilia. 2022 Feb 1;28(S1):53-54.	Population
Nolan B, Recht M, Rendo P, Falk A, Foster M, Casiano S, Rauch A, Shapiro AD. Prophylaxis with rFIXFc Reduces the Frequency and Delays Time to First Spontaneous Bleed Event in Previously Untreated Patients with Hemophilia B: A Post Hoc Analysis of the PUPs B-LONG Trial. Blood. 2021 Nov 23;138(S1):498.	Population
Fischer K, Steen Carlsson K, Petrini P, Holmstrom M, Ljung R, van den Berg HM, Berntorp E. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. Blood 2013; 122(7):1129-1136	Population
Astermark J, Angchaisuksiri P, Kavakli K, Zak M, Seremetis S. Management of breakthrough bleeds during concizumab prophylaxis in patients with haemophilia A/B with and without inhibitors in phase 3 clinical trials. Haemophilia 2022 Feb 1;28(S1):70-71.	Outcomes
Bhagunde P, Ge S, Iqbal S, Mei B, Andersson S, Kanamaluru V. Fitusiran population pharmacokinetic and pharmacodynamic (PopPK/PD) modeling to support revised dose, dosing regimens & dose mitigation scheme. Res Pract Thromb Haemost. 2021;5(S2):399-400.	Outcomes
Burke T, Shaikh A, Ali TM, Li N, Curtis R, Garcia Diego DA, Recht M, Sannie T, Skinner M, O'Hara J. Association of factor expression levels with health-related quality of life and direct medical costs for people with haemophilia B. Journal of Medical Economics. 2022 Dec 31;25(1):386-92.	Outcomes
Castaman G, Ranta S, Allsup D, Glosli H, Saleh M, Carlsheimer A, Francke A, Santagostino E. B-more, baseline analysis from a 24-month prospective, non-interventional, multicentre study on real-world effectiveness and usage of recombinant factor IX FC (rFIXFc) in haemophilia B. Res Pract Thromb Haemost. 2021;5(S2):419-420.	Outcomes
Chambost H, Rauch A, Repesse Y, Claeyssens S, Castet S' d'Oiron R, Santagostino E, Martinez C. First interim analysis of a 24-mon107renchnch, multicentre, prospective, noninterventional study evaluating the real-world usage and effectiveness of the extended halflife recombinant factor ix fc fusion protein (RFIXFC) in people with haemophilia B (B-sure). Res Pract Thromb Haemost. 2021;5(S2):78-79.	Outcomes
Gustavo Aguilera Covarrubias SL, Leyton Padilla ID, Benard Amador BE, Campos Valerio JB, Reyes Sanchez ER. Prevalence of Bleeding Disorders in Nicaragua in the period 2004-2020. British Journal Of Haematology. 2022 Apr 1;197(S1):224-225.	Outcomes
Ctri. 2020. Prophylaxis Study of PF-06741086 in Adolescent and Adult Hemophilia Patients With or Without Inhibitors. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2020/03/023849	Outcomes
Ctri. 2022. An extension study of Marstacimab in Hemophilia Patients with or Without Inhibitors. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2022/01/039107	Outcomes
Drks. 2020. The effectiveness of manual lymphatic drainage in haemophilic arthropathy (HA). http://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00023198	Outcomes

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Reference	Reason for exclusion
Faller M, Tønder SM, Porstmann T. Improvement in Health-Related Quality of Life Measures after Long-Term, Daily, Subcutaneous Concizumab Prophylaxis in Patients with Hemophilia A/B with and without Inhibitors: Results from the Main and Extension Parts of Phase 2 Clinical Trials. Blood. 2021 Nov 23;138(S1):1041.	Outcomes
Faraj A, Knudsen T, Desai S, Neuman L, Blouse GE, Simonsson US. Phase III dose selection of marzeptacog alfa (activated) informed by population pharmacokinetic modeling: A novel hemostatic drug. CPT: Pharmacometrics & Systems Pharmacology. 2022 Oct 18.	Outcomes
Faraj A, van Wijk R, Neuman L, Desai S, Blouse GE, Knudsen T, Simonsson US. Dose selection of marzeptacog alfa (activated) in children with hemophilia: A population pharmacokinetic exposure matching strategy. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):349.	Outcomes
Goedhart TM, Bukkems LH, Coppens M, Fijnvandraat KJ, Schols SE, Schutgens RE, Eikenboom J, Heubel-Moenen FC, Ypma PF, Nieuwenhuizen L, Meijer K. Design of a Prospective Study on Pharmacokinetic-Guided Dosing of Prophylactic Factor Replacement in Hemophilia A and B (OPTI-CLOT TARGET Study). TH Open:Companion Journal to Thrombosis and Haemostasis. 2022 Jan;6(1):e60-9.	Outcomes
Hummelshøj Landsy L, Castaman G, Cepo K, Lenting P, Oldenburg J. Immunogenicity in the concizumab phase 2 clinical trials: Clinical impact of antidrug antibodies. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):81-82.	Outcomes
Journeycake J, Cheng D, Chrisentery-Singleton T, Desai V, von Drygalski A, Fedor C, Hirsh N, Patel B, Raffini LJ, Recht M, Sidinio Jr RF et al. Reduced Dosing Frequency Following a Switch to Rix-FP for the Treatment of Hemophilia B: Results from the Athn 2 Study. Blood. 2021 Nov 23;138(S1):1039-1040.	Outcomes
Kloosterman FR, Zwagemaker AF, Bagot CN, Beckers EA, Castaman G, Cnossen MH, Collins PW, Hay C, Hof M, Laros-van Gorkom B, Leebeek FW. The bleeding phenotype in people with nonsevere hemophilia. Blood advances. 2022 Jul 26;6(14):4256-65.	Outcomes
Lee XY, Cepo K, Porstmann T. Concizumab subcutaneous prophylaxis improves health-related quality-of-life measures in patients with congenital hemophilia with inhibitors: phase 2 trial results. Blood. 2019 Nov 13;134:2419.	Outcomes
Markson LE, Young L, Ban L, Chen Y, Zaha R, Fogarty PF. Health care resource use (HRU) among adult persons with hemophilia B (PWHB) and concurrent joint disease (JD) in the United States. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):432.	Outcomes
Navneet NK. A Study on Variances in the Reported Haemophilia Prevalence Throughout the Bihar Region in Tirhut. International Journal of Pharmaceutical and Clinical Research. 2021;13(4)424-429.	Outcomes
Negrier C. Prospective, open-label, multicentre phase II study (PEKAFIX) to evaluate the pharmacokinetic parameters of a plasma derived factor ix concentrate and build a pharmacokinetic Bayesian model. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):380-381.	Outcomes
Negrier C, Young G, Sun J, Wu R, Qiu Z, Andersson S, Mei B, Cano V, Bartelt-Hofer J, Srivastava A. HEALTH-RELATED QUALITY OF LIFE (HRQOL) IMPROVES IN PEOPLE WITH HEMOPHILIA A OR B (PWHA/B) WITH INHIBITORS RECEIVING FITUSIRAN PROPHYLAXIS: RESULTS OF PHASE 3 ATLAS-INH. Haemophilia. 2022 Feb 1;28(S1):57-58.	Outcomes
Samelson-Jones BJ, Sullivan SK, Rasko JE, Giermasz A, George LA, Ducore JM, Teitel JM, McGuinn CE' O'Brien A, Winburn I, Smith LM et al. Follow-up of More Than 5 Years in a Cohort of Patients with Hemophilia B Treated with Fidanacogene Elaparvovec Adeno-Associated Virus Gene Therapy. Blood. 2021 Nov 23;138(S1):3975.	Outcomes
Shehu E, Foley JH, Gray E, Riddell A, Goodale A, Yu IM, Little J, Shattock D, Kitchen S, Chowdary P, Nathwani A, Corbau R. Practical application of FIX-Padua field study results enables a comparison of FIX:C results across AAV gene therapy trials independent of FIX:C assay reported. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):487-488.	Outcomes
Srivastava A, Rangarajan S, Kavakli K, Klamroth R, Kenet G, Khoo L, You CW, Xu W, Malan N, Frenzel L, Bagot CN. Fitusiran, an investigational siRNA therapeutic targeting antithrombin for the treatment of hemophilia: first results from a phase 3 study to evaluate efficacy and safety in people with hemophilia A or B without inhibitors (ATLAS-A/B). Blood. 2021 Dec 4;138(S2):LBA-3.	Outcomes
Teeter J, Charnigo R, Cossons N, Raje S, Hwang E, Le Duigou T. Safety and efficacy of marstacimab for prevention of bleeding episodes in paediatric patients with severe haemophilia A or moderately severe to severe haemophilia B with or without inhibitors. Haemophilia. 2022 Feb 1;28(S1):88-89	Outcomes
Tiede A, Leise H, Horneff S, Oldenburg J, Halimeh S, Heller C, Königs C, Holstein K, Pfrepper C. Safety of intramuscular COVID-19 vaccination in patients with haemophilia. Haemophilia. 2022 May 13;28(5):687-693.	Outcomes

Reference	Reason for exclusion
Ventura E, McDonald B, Makanji H, Cutts S, Polson M, Kangethe A. Real-World Health Plan Data Analysis: Evaluating the Impact of Extended Half-Life Factor Products and Emicizumabkxwh on Annualized Bleed Rate in Patients with Hemophilia. Journal of Managed Care and Specialty Pharmacy. 2021;27(10-B):S43.	Outcomes
Wheeler A, Benson G, Eichler H, Tønder SM, Cepo K, Jimenez-Yuste V, Kavakli K, Wong LL, Matsushita T. SURGERIES and DIAGNOSTIC PROCEDURES in HAEMOPHILIA PATIENTS on CONCIZUMAB PROPHYLAXIS in PHASE 2 CLINICAL TRIALS. Haemophilia. 2022;28(S1):92.	Outcomes
Wheeler AP, Benson G, Eichler H, Tønder SM, Cepo K, Yuste VJ, Kavakli K, Wong LL, Matsushita T. Surgeries and diagnostic procedures in hemophilia patients on concizumab prophylaxis: results from the phase 2 Explorer4 and Explorer5 trials. Blood. 2021 Nov 23;138(S1):345.	Outcomes
Wilkins RA, Stephensen D, Siddle H, Scott MJ, Xiang H, Horn E, Palmer B, Chapman GJ, Richards M, Walwyn R, Redmond A. Twelve-month prevalence of haemarthrosis and joint disease using the Haemophilia Joint Health score: evaluation of the UK National Haemophilia Database and Haemtrack patient reported data: an observational study. BMJ open. 2022 Jan 1;12(1):e052358.	Outcomes
Young G, Chowdary P, Barton S, Long A. DOSE SELECTION AND STUDY DESIGN FOR B-LIEVE, A PHA½1/2 DOSE CONFIRMATION CLINICAL TRIAL OF FLT180A GENE THERAPY FOR PATIENTS WITH HAEMOPHILIA B. Haemophilia. 2022 Feb 1;28(S1):47-48.	Outcomes
Odeyemi I A, Guest J F. Modelling the economic impact of recombinant activated Factor VII compared to activated prothrombin-complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX in the UK. Journal of Medical Economics. 2002; 5: 119-133	Outcomes
Miners A H, Sabin C A, Tolley K H, Lee C A. Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebr'nd's disease. Journal of Internal Medicine. 1998; 244(6): 515-522	Outcomes
Tsai MC, Cheng CN, Wang RJ, Chen KT, Kuo MC, Lin SJ. Cost-effectiveness analysis of carrier and prenatal genetic testing for X-linked hemophilia. Journal of the Formosan Medical Association. 2013: epub	Outcomes
Salaj P, Kubes R, Cetkovsky P, Capova I, Penka M, Ovesna P, Mesterton J, Lindgren P. Economic evaluation of rFVIIa high initial dose compared to rFVIIa standard initial dose in patients with haemophilia with inhibitors using the Czech HemoRec registry. Thrombosis Research. 2013;133(2): 162-167	Outcomes
Pattanaprateep O, Chuansumrit A, Kongsakon R. Cost-utility analysis of home-based care for treatment of Thai hemophilia A and B. Value in Health Regional Issues. 2014;3:73-78.	Outcomes

Table 66: Excluded publications, local adaptation of update clinical and safety review (n=29 publications)

Reference	Reason for exclusion
Shapiro AD, Angchaisuksiri P, Astermark J, Benson G, Castaman G, Eichler H, Jiménez-Yuste V, Kavakli K, Matsushita T, Poulsen LH, Wheeler AP. Long-term efficacy and safety of subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors. Blood advances. 2022 Jun 14;6(11):3422-32.	Non-relevant comparator
Astermark J, Angchaisuksiri P, Benson G, Castaman G, Chowdary P, Eichler H, Jiménez- Yuste V, Kavakli K, Matsushita T, Hvitfeldt Poulsen L, Oldenburg J, Zupancic Salek S, Shapiro A, Wheeler AP, Young G. Longer-term Efficacy and Safety of Concizumab Prophylaxis in Hemophilia A and Hemophilia A/B with Inhibitors: Results from the Main and Extension Parts of Concizumab Phase 2 Trials. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):.	Study type
Young G, Srivastava A, Kavakli K, Ross C, Sathar J, Tran H, Wu R, Sun J, Poloskey S, Qui Z, Kichou S, Andersson SR, Mei B, Rangarajan S. Efficacy and Safety of Fitusiran Prophylaxis, an siRNA Therapeutic, in a Multicenter Phase 3 Study (ATLAS-INH) in People with Hemophilia A or B, with Inhibitors (PwHI). Blood. 2021;138(S1):4.	Non-relevant comparator
Leebeek FWG, Meijer K, Coppens M, Kampmann P, Klamroth R, Schutgens R, Castaman G, Seifried E, Schwaeble J, Halvard Bönig H, Sawyer EK, Miesbach WA. AMT-060 gene therapy in adults with severe or moderate-severe hemophilia B confirm stable fix expression and sustained reductions in bleeding and factor IX use for up to 5 years. Research and Practice in Thrombosis and Haemostasis. 2021;5(S1):.	Phase 1/2 study

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Reference	Reason for exclusion
Miesbach WA, Meijer K, Coppens M, Kampmann P, Klamroth R, Schutgens R, Castaman G, Seifried E, Schwaeble J, Bönig H, Sawyer EK, Leebeek F. AMT-060 Gene Therapy in Adults with Severe or Moderate-Severe Hemophilia B Confirms Stable FIX Expression and Sustained Reductions in Bleeding for up to 5 Years. Hämostaseologie. 2021 Jun;41(S1):S5.	Phase 1/2 study
Miesbach W, Meijer K, Coppens M, Kampmann P, Klamroth R, Schutgens R, Castaman G, Sawyer EK, Leebeek FWG. Five Year Data Confirms Stable FIX Expression and Sustained Reductions in Bleeding and Factor IX Use Following AMT-060 Gene Therapy in Adults with Severe or Moderate-severe Hemophilia B. Res Pract Thromb Haemost. 2021;5(S2):90.	Phase 1/2 study
Chowdary P, Shapiro S, Makris M, Evans G, Boyce S, Talks K, Dolan G, Reiss U, Phillips M, Riddell A, Peralta MR. Factor IX Expression within the Normal Range Prevents Spontaneous Bleeds Requiring Treatment Following FLT180a Gene Therapy in Patients with Severe Hemophilia B: Long-Term Follow-up Study of the B-Amaze Program. Blood. 2021 Nov 23;138(S1):3967	Non-relevant comparator
Chowdary P, Shapiro S, Makris M, Evans G, Boyce S, Talks K, Dolan G, Reiss U, Phillips M, Riddell A, Peralta MR. Phase 1–2 trial of AAVS3 gene therapy in patients with hemophilia B. New England Journal of Medicine. 2022 Jul 21;387(3):237-47	Non-relevant comparator
Alvarez Roman MT, Rivas Pollmar MI, Martin Salces M, Garcia Barcenilla S, Cebanu T, Jimenez Yuste V. HAEMOPHILIA B PATIENTS UNDER RIX-FP PROPHYLAXIS: CLINICAL EXPERIENCE AT HOSPITAL UNIVERSITARIO LA PAZ. Haemophilia. 2022 Feb 1;28:56.	Non-relevant comparator
Burke T, Asghar S, O'Hara J, Chuang M, Sawyer E, Li N. Real-world Outcomes in People with Severe Hemophilia B Receiving FIX Prophylaxis across Europe: A CHESS II Analysis. Res Pract Thromb Haemost. 2021;5 (S2):351-2.	RWE study about Haemophilia
Burke T, Asghar S, O'Hara J, Chuang M, Sawyer EK, Li N. Clinical, humanistic, and economic burden of severe haemophilia B in adults receiving factor IX prophylaxis: findings from the CHESS II real-world burden of illness study in Europe. Orphanet Journal of Rare Diseases. 2021 Dec;16(1):1-9.	RWE study about Haemophilia
Fogarty P, Chhabra A, Winburn I, Rybin D, Byon W, Smith J, Marshall J, Rupon J. Clearance of fidanacogene elaparvovec vector DNA in patients with severe or moderately severe hemophilia B (HB). Research and Practice in Thrombosis and Haemostasis. 2021;5(S1):.	Non-haemophilia related
George LA, Sullivan SK, Rasko JE, Giermasz A, Samelson- Jones BJ, Ducore JM, Teitel JM, McGuinn CE, Rybin D, Murphy JE, Winburn I, Chhabra A, Rupon J. Evaluation of Liver Health after Fidanacogene Elaparvovec Gene Therapy: Data from Study Participants with up to 5 Years of Follow-up. Evaluation of liver health after fidanacogene elaparvovec gene therapy: Data from study participants with up to 5 years of follow-up. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):.	Non-relevant comparator
O'Donovan M, Singleton E, Roche S, McGowan M, Benson J, Bergin C, Bird R, Byrne M, Duggan C, Gilmore R, Ryan K. Single centre, real-world experience of perioperative rFIXFc use in adult patients with haemophilia B undergoing major and minor surgery. Haemophilia. 2021 Nov;27(6):e690-7.	Non-relevant comparator
Pabinger I, Lissitchkov T, Nagao A, Lepatan LM, Li Y, Seifert W, Mancuso ME. Efficacy and Safety of rIX- FP: A Longitudinal Analysis of Patients Treated across the PROLONG- 9FP Clinical Trials Program. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):.	Non-relevant comparator
Olsson A, Myrin-Westesson L, Baghaei F, Holmström M, Olsson E, Magnusson M, Ranta S, Astermark J, Andersson NG, Thanner J, Szamosi J, Sennfält K. Real-world usage of rFIXFc in Sweden: A report from the Swedish national registry for bleedings disorders. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):.	Non-relevant comparator
Pabinger I, Lissitchkov T, Nagao A, Lepatan LM, Li Y, Seifert W, Mancuso ME. Long-term efficacy and safety of rIX-FP prophylaxis in adult patients with haemophilia B on a 21-day dosing regimen. Hamostaseologie. 2021;41(S1):S49.	Non-relevant comparator
Tagliaferri A, Molinari AC, Peyvandi F, Coppola A, Finardi A, Schiavetti I, Rocino A, Castaman G. IDEAL STUDY: A REAL-WORLD ASSESSMENT of TREATMENT REGIMENS, FACTOR IX TROUGH	Non-relevant comparator

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Reference	Reason for exclusion
LEVELS and CONCENTRATE CONSUMPTION in HAEMOPHILIA B PATIENTS RECEIVING ALBUTREPENONACOG ALFA in ITALY. Haemophilia. 2022;28(S1):60.	
Tardy B, Lambert T, Chamouni P, et al. Revised terminal half-life of nonacog alfa as derived from extended sampling data: A real-world study involving 64 haemophilia B patients on nonacog alfa regular prophylaxis. Haemophilia. 2022;28:542–547.	Non-relevant comparator
Kouramba A, Georgopoulou AN, Zannou A, Kosmas P, Galopoulos D, Chatzidavid S, Christidi S, Thivaios GC. Major orthopedic surgeries using extended half-life (EHL) coagulation replacement factors: the experience of a Greek comprehensive haemophilia treatment center (CHTC). Haemophilia. 2022;28(S1):69-70	Non-relevant comparator
Choraria N, Rangarajan S, John MJ, Apte S, Gupta P, Pai S, Chand R, Parvatini S, GSH R, Rupon J, Muley HB, Simoneau D. Safety and efficacy of nonacog alfa prophylaxis and treatment of bleeding episodes in previously treated patients with moderately severe or severe hemophilia b in India. Haemophilia. 2022;28(S1):89	Non-relevant comparator
Oldenburg J, Holzhauer S, Wenning S, Olivieri M, Pfrepper C. Efficacy and Safety Analysis of the Use of rIX- FP in Patients with Hemophilia B: A Prospective, Non- interventional, Surveillance Study from Germany. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):408-409.	Non-relevant comparator
Buczma A, Odnoczko E, Baran B, Gwozdowska A, Zawilski J, Windyga J. Clinical Assessment with the Evaluation of Joint Disease and Haemostatic Treatment in Patients with Severe Haemophilia B. Research and Practice in Thrombosis and Haemostasis. 2021;5(S2):472	Non-relevant comparator
Castaman G, Tagliaferri A, Molinari A, Peyvandi F, Coppola A, Finardi A, Schiavetti I, Vaccari D, Rocino A. IDEAL study: A real- world assessment of pattern of use and clinical outcomes with recombinant factor IX albumin fusion protein (rIX- FP) in patients with haemophilia B in Italy. Research and Practice in Thrombosis and Haemostasis. 2022;6(S1):393.	Non-relevant comparator
Szanto T, Lassila R, Nummi V, Iorio A, Leithinen A. WAPPS- Hemo as a tool for optimizing prophylaxis with extended half- life FIX in patients with severe or moderate hemophilia B. Research and Practice in Thrombosis and Haemostasis. 2022;6(S1):398.	Not-relevant study
Holme P, Glosli H, Thanner J, Sennfält K. Norwegian Real- World Experience with recombinant factor IX Fc (rFIXFc) in Haemophilia B (HB) Patients. Research and Practice in Thrombosis and Haemostasis. 2022;6(S1):412-413.	Not-relevant study
Vandewalle B, Castaman G, Alvarez- Román M, Escuriola Ettingshausen C, Nemes L, Tomic R, Martins P, Rodrigues J, Pinachyan K. Dose optimization for prophylaxis using a pharmacokinetic model for factor IX products in severe hemophilia B. Research and Practice in Thrombosis and Haemostasis. 2022;6(S1):326-327.	Not-relevant study
Peixoto C, Rodrigues F, Pereira A, Campaniço S, Correia S, Afonso P, Pestana J, Moura L, Parusnikova L, Catarino C. Real-world usage of extended half-life FIX in a Portuguese Haemophilia Centre—Prophylaxis must be for moderate and severe hemophilia B patients. Research and Practice in Thrombosis and Haemostasis. 2022;6(S1):349-350.	Not-relevant study
Windyga J, Tran H, Fujii T, Lyu C, Villarreal Martinez L, Sathar J, Stasyshyn O, Zozulya N, Brown Frandsen R, Eskelund C, Apte S, Mahlangu J. Real- world unmet needs of patients with haemophilia A/B with or without inhibitors: Historical haemophilia characteristics from patients entering a non- interventional study. Research and Practice in Thrombosis and Haemostasis. 2022;6(S1):390-391.	Not-relevant study

16.3 Quality assessment

A quality assessment of cost-effectiveness studies identified was conducted using the Drummond and Jefferson criteria (Drummond and Jefferson, 1996).

16.4 Unpublished data

Data from the HOPE-B trial (24-month data cut) was published after the SLR was conducted (Pipe et al., 2022b). A list of planned publications is included in Table 67.

Table 67: Ongoing publication projects (CONFIDENTIAL INFORMATION)

Study	Study	Short title	Publication timelines*
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]

Note: *All publication timelines are estimates based on the average submission to publishing time at the first-choice target journal.
Abbreviations: PRO, Patient-reported outcomes.

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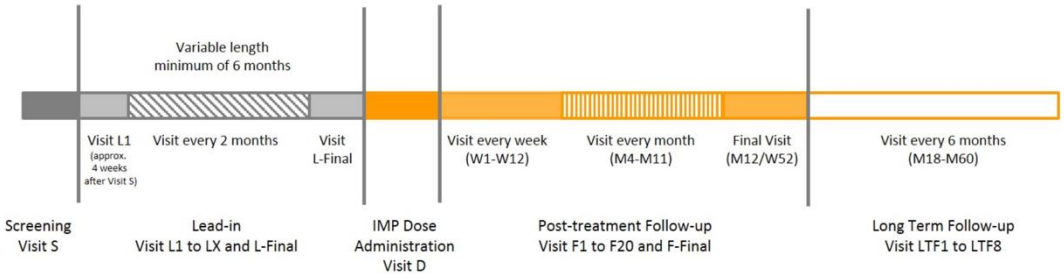
17. Appendix B Main characteristics of included studies

The main characteristics of the studies included in the comparative analysis are detailed in Table 68 and Table 69.

Hemgenix

Table 68: Summary of HOPE-B trial methodology

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02
Location	Multicenter; 33 sites, including 17 sites in the United States (US) and 13 sites in the European Union (EU), the EU sites include 1 site in Denmark and 1 in Sweden.
Trial design	CT-AMT-061-02 (Health Outcomes with Padua Gene; Evaluation in Hemophilia B [HOPE-B]) is an ongoing open-label, single-dose, multi-center, multi-national trial, with a screening phase/period, a lead-in phase/period, a treatment plus a post-treatment follow-up phase/period, and a long-term follow-up phase/period.  At screening (Visit S), subjects were assessed for eligibility and were instructed in how to record bleeding episodes and use of Factor IX (FIX) replacement therapy in a dedicated electronic diary. The approximately 4-week period between screening up to the start of the lead-in phase (Visit L1) was considered a training period where subjects became familiar with recording their use of FIX replacement therapy and bleeding episodes. A pre-defined wash-out period of 3 days for regular-acting FIX products and 10 days for EHL FIX products occurred between screening and the lead-in phase. During the lead-in phase, which lasted for a minimum of 26 weeks (i.e., ≥6 months), subjects recorded their use of FIX replacement therapy and bleeding episodes in their dedicated e-diary. After the lead-in phase, subjects received a single-dose of Hemgenix at the dosing visit (Visit D) and were followed for 1 year (i.e., post-treatment follow-up phase; 52 weeks) to evaluate efficacy and safety. One of the secondary endpoints, endogenous FIX activity at 26 weeks after Hemgenix dosing, was assessed once the last subject had achieved 26 weeks after Hemgenix treatment. Following the post-treatment follow-up phase, subjects continued into the long-term follow-up phase for an additional 4 years, with visits planned every half year (6 months) for evaluation of safety and efficacy parameters. During the long-term follow-up phase, subjects are instructed to document FIX usage and bleeding episode information in study-specific paper diaries. Due to the Coronavirus disease 2019 (COVID-19) pandemic, this trial was adapted to allow for flexibility for remote telemedicine/telehealth visits where possible. Adjustments to the visit location/method or schedule may have been made to accommodate safety concerns and restrictions experienced by individual subjects and sites.
Eligibility criteria for participants	Inclusion criteria Subjects could not have been enrolled in the trial before all of the following inclusion criteria were met: Male Age ≥18 years Subjects with congenital haemophilia B with known severe or moderately severe FIX deficiency (≤2% of normal circulating FIX) for which the subject was on continuous routine FIX prophylaxis* >150 previous exposure days of treatment with FIX protein

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02

Had been on stable prophylaxis for at least 2 months prior to screening

Had demonstrated capability to independently, accurately, and in a timely manner complete the diary during the lead-in phase as judged by the Investigator

Acceptance to use a condom during sexual intercourse in the period from IMP administration until AAV5 had been cleared from semen, as evidenced by the central laboratory, from negative analysis results for at least 3 consecutively collected semen samples (this criterion was applicable also for subjects who were surgically sterilized)

Able to provide informed consent following receipt of verbal and written information about the trial

* Continuous routine prophylaxis was defined as the intent of treating with an a priori defined frequency of infusions (e.g., twice weekly, once every two weeks, etc.) as documented in the medical records.

Exclusion criteria

Subjects were excluded from the trial if any of the following exclusion criteria (including local and central laboratory test results, as specified) were met:

History of FIX inhibitors

Positive FIX inhibitor test at screening and Visit L-Final (based on local laboratory results)

Screening and Visit L-Final laboratory values (based on central laboratory results):

ALT >2 times upper normal limit (i.e., upper limit of normal [ULN])

AST >2 times ULN

Total bilirubin >2 times ULN (except if caused by Gilbert disease)

ALP >2 times ULN

Creatinine >2 times ULN

Positive human immunodeficiency virus serological test at screening and Visit L-Final, not controlled with anti-viral therapy as shown by CD4+ counts ≤200/µL (based on central laboratory results)

Hepatitis B or C infection with the following criteria present at screening:

Currently receiving antiviral therapy for this/these infection(s)
and/or

Positive for any of the following (based on central laboratory results):

Hepatitis B surface antigen (HBsAg), except if in the opinion of the Investigator this was due to a previous hepatitis B vaccination rather than active hepatitis B infection

Hepatitis B virus (HBV) DNA

Hepatitis C virus (HCV) ribonucleic acid (RNA)

Known coagulation disorder other than haemophilia B

Thrombocytopenia, defined as a platelet count below 50 × 109/L, at screening and Visit L-Final (based on central laboratory results)

Known severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease, alcoholism, drug dependency, or any other psychological disorder evaluated by the Investigator to interfere with adherence to the protocol procedures or with the degree of tolerance to the IMP

Known significant medical condition that may have significantly impacted the intended transduction of the vector and/or expression and activity of the protein including, but not limited to:

Disseminated intravascular coagulation

Accelerated fibrinolysis

Advanced liver fibrosis (suggestive of or equal to Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] Stage 3 disease; e.g., a FibroScan™ score of ≥9 kPa was considered equivalent)

Known history of an allergic reaction or anaphylaxis to FIX products

Known history of allergy to corticosteroids

Known uncontrolled allergic conditions or allergy/hypersensitivity to any component of the IMP excipients

Known medical condition that would require chronic administration of steroids

Previous gene therapy treatment

Receipt of an experimental agent within 60 days prior to screening

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02
	Current participation or anticipated participation within one year after IMP administration in this trial in any other interventional clinical trial involving drugs or devices.
Settings and locations where the data were collected	United States Phoenix Children's Hospital, Arizona, Arkansas Children's Hospital, Little Rock, Arkansas, Los Angeles Orthopaedic Hospital, California, Children's Hospital of Los Angeles, Los Angeles, California, University of California, Davis, Sacramento, California University of California, San Diego University of Colorado Denver, Aurora, Colorado, Children's National Medical Centre Haematology and Oncology, Washington, District of Columbia, University of South Florida, Tampa, Florida University of Michigan, Ann Arbor, Michigan Hemophilia Centre of Western New York, Buffalo, New York, University of North Carolina, Chapel Hill, North Carolina, Oregon Health & Science University, Portland, Oregon, University of Tennessee Health Science Centre, Memphis, Tennessee, Vanderbilt University Medical Centre, Nashville, Tennessee, University of Texas Health Science Centre & Medical School, Houston, Texas, University of Utah, Salt Lake City, Utah, Washington Institute for Coagulation, Seattle, Washington, University of Washington, Seattle, Washington, Belgium Clinique's universitaires Saint-Luc, Bruxelles, University Hospital Leuven, Leuven Denmark Righospitalet, Copenhagen Germany Vivantes Klinikum im Friedrichshain, Berlin, Klinikum der Johann Wolfgang Goethe Universitat, Frankfurt am main, Ireland National Coagulation Centre, St James's Hospital, Dublin, Netherlands Amsterdam UMC, AMC, Amsterdam, Universitair Medisch Centrum Groningen, Groningen, Erasmus MC, Rotterdam, Netherlands UMC Utrecht, Van Creveldkliniek, Utrecht Sweden Center for Thrombosis and Hemostasis Skåne University Hospital Malmö, Malmö United Kingdom The Cambridge Haemophilia and Thrombophilia Centre Cambridge University Hospitals NHS Foundation Trust, Cambridge The Royal London Hospital (Barts Health NHS Trust), London, University Hospital Southampton NHS Foundation Trust, Southampton
Trial drugs	Reference therapy in lead-in phase of the study (N=67) FIX prophylaxis therapy used during the lead-in phase, prior to treatment with Hemgenix Active treatment period — dose and mode of administration (N=54) Subjects were planned to receive a single IV infusion of 2×10^{13} gc/kg Hemgenix in a peripheral vein

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02
Permitted and disallowed concomitant medication	The following treatments were not allowed during trial participation: Continuous routine FIX prophylaxis post-treatment if a subject's endogenous FIX activity result was above 5% Treatment in another interventional clinical trial involving drugs or devices for 1 year following treatment administration in this trial Another gene therapy treatment Chronic administration of steroids (oral and/or inhaled) For any known hepatotoxic medications, other alternatives were considered. The Investigator was expected to review the concomitant medications on an ongoing basis for these types of medications. Where possible, subjects were taken off any known hepatotoxic drugs before Visit D. Apart from the above listed treatments, no protocol restrictions applied with respect to concomitant medications: Subjects were permitted to continue administration of their continuous routine FIX treatment on the day of dosing (after the pre-treatment assessments were completed) and continue their continuous routine FIX treatment in the first weeks after dosing to provide sufficient FIX coverage for the initial days post-treatment. During the post-treatment follow-up visits, endogenous FIX activity was assessed. If the endogenous FIX activity result was ≥5%, continuous routine FIX prophylaxis was discontinued, and further management was based on the Investigator's clinical judgement and subject preference. Continuation or re-initiation of continuous routine FIX prophylaxis may have been considered if the endogenous FIX activity was between 2% and 5% in at least two consecutive laboratory measurements, based on the Investigator's clinical judgement and subject preference. If endogenous FIX activity was <2%, continuous routine prophylaxis must have been continued or reinstated. Additional on-demand and/or intermittent prophylactic FIX treatment may have been given after treatment with Hemgenix, if considered necessary. FIX infusions were not recommended for subjects with FIX activity in the non-haemophilic (≥40% of normal) range especially in subjects with a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as increased thrombogenic risk is a known complication of COVID-19
Primary outcomes (including scoring methods and timings of assessments)	Primary outcomes The primary objective was to demonstrate the non-inferiority of Hemgenix during the 52 weeks following establishment of stable FIX expression (Months 6–18) post-treatment follow-up compared to SOC continuous routine FIX prophylaxis during the lead-in phase, as measured by the ABR. Secondary outcomes The secondary objective was to demonstrate additional efficacy and safety aspects of systemic administration of Hemgenix, focused on the following: • Endogenous FIX activity 6 months after a single Hemgenix treatment • Endogenous FIX activity 12 months after a single Hemgenix treatment • Endogenous FIX activity 18 months after a single Hemgenix treatment • Annualized consumption of FIX replacement therapy • Annualized infusion rate of FIX replacement therapy • Discontinuation of previous continuous routine prophylaxis • Trough FIX activity • Prevention of bleedings (comparison for superiority) • Prevention of spontaneous bleeding • Prevention of joint bleeding • Estimated ABR – during the 52 weeks following stable FIX expression (6–18 months) – as a function of pre-treatment anti-AAV5 antibody titers using the luciferase based NAb assay (as a "correlation" analysis) • Correlation of pre-IMP anti-AAV5 antibody titers using the luciferase based NAb assay on FIX activity levels after Hemgenix dosing • Occurrence and resolution of target joints • Proportion of subjects with zero bleeding episodes during the 52 weeks following stable FIX expression (6–18 months) after Hemgenix dosing • International Physical Activity Questionnaire (iPAQ) • EuroQol-5 dimensions-5 levels (EQ-5D-5L) Visual Analog Scale (VAS) Exploratory outcomes Exploratory efficacy objectives investigated the effect of Hemgenix on the following:

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02

- FIX protein levels during the 18 months following Hemgenix dosing
- Haemophilia Joint Health Score (HJHS) scores
- Other Patient Reported Outcome (PRO) questionnaires: Work Productivity and Activity Impairment Questionnaire (WPAI), Brief Pain Inventory (BPI), Hemophilia Activities List (HAL), and Hemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) during the lead-in phase (prophylaxis) and during the 12 months following Hemgenix dosing
- Estimated ABR over time as a function of mean FIX activity (as a "correlation" analysis) over the 18-month post-treatment follow-up
- Rate of traumatic bleeding events during the 52 weeks following stable FIX expression (6–18 months) post-treatment follow-up compared to the lead-in phase
- Subgroup analyses will be carried out for the following endpoints:
- Endogenous FIX activity at 18 months
- Annualized consumption of FIX replacement therapy, excluding replacement for invasive procedures
- Annualized infusion rate of FIX replacement therapy
- ABR comparison between Hemgenix and FIX prophylaxis
- Comparison of the percentage of subjects with trough FIX activity <12% of normal between the lead-in phase and after treatment with Hemgenix over the 52 weeks following stable FIX expression (6–18 months)
- Proportion of subjects remaining free of previous prescribed continuous routine prophylaxis.
- All efficacy endpoints (as exploratory endpoints) at 2, 3, 4, and 5 years after Hemgenix dosing

Safety outcomes

Adverse events (AEs) [Time Frame: 5 years]

- Monitoring of AEs
- Changes in abdominal ultrasound
- Formation of anti-AAV5 antibodies (total immunoglobulin M and immunoglobulin G, NAbs)
- AAV5 capsid-specific T cell response, formation of anti-FIX antibodies
- Formation of FIX inhibitors and recovery
- Serum chemistry parameters
- Serum electrolytes (sodium, potassium)
- Creatinine
- Creatine kinase
- Gamma-glutamyltransferase
- AST
- ALT
- ALP
- C-reactive protein (CRP)
- Albumin
- Total bilirubin
- Glucose (non-fasting)
- Haematology parameters
- Hemoglobin
- Hematocrit
- Platelet count
- Red blood cells
- White blood cells with differential count
- CD4+ count
- Shedding of vector DNA in blood and semen
- Inflammatory markers
- Interleukin-1beta (IL-1β)
- Interleukin-2 (IL-2)
- Interleukin-6 (IL-6)
- Interferon gamma (IFNγ)
- Monocyte chemotactic protein-1 (MCP-1)
- AST and ALT level increases and use of corticosteroids for AST/ALT increases
- Alpha-fetoprotein

Other outcomes used in the economic	N/A

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02
model/ specified in the scope	
Pre-planned subgroups	Pre-planned subgroups: • Age categories: <40 years, 40 to <60 years, ≥60 years • Race and/or ethnicity subgroups • Zero bleeding episodes vs. ≥1 bleeding episodes in lead-in period • Because this subgrouping was defined using information from the lead-in phase, the analysis provided descriptive statistics for only the post-treatment phase. • Presence or absence of target joints at screening • Baseline anti-AAV5 NAb titer categories: positive titer (≥limit of detection [LOD]) vs. negative titer (<LOD) • HIV-negative vs. controlled HIV positive (CD4+ count >200/µL) at baseline • History of hepatitis B or C at baseline • Baseline liver pathology, according to baseline FibroScanTM or equivalent shear wave • elastography, magnetic resonance elastography result: • Degree of fibrosis (≥9 kPA vs. <9 kPa) • Degree of steatosis (Controlled Attenuation Parameter [CAP] score ≥S2 [≥260 dB/m] vs. <S2 [<260 dB/m]) vs. missing Reported subgroup: Full Analysis Set (FAS) baseline NAb titer <700 (to report ABR during lead-in and post treatment period by subgroup)

Sources: 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file],(CSL Behring, 2022i) ClinicalTrials.gov. NCT03569891(ClinicalTrials.gov Identifier).

Refixia

Table 69: Summary of Paradigm™ 2 trial methodology

Trial number (acronym)	NCT01333111
Location	Multicenter; the trial was conducted at 39 sites in 13 countries, as follows: France (1); Germany (3); Italy (2); Japan (5); Macedonia (2); Malaysia (1) Netherlands (1); Russia (2); South Africa(1); Thailand (2); Turkey (3); United Kingdom (4) and United States (12).
Trial design	The aim of this trial is to evaluate the safety and efficacy, including PK (the rate at which the body eliminates the trial drug), of NNC-0156-0000-0009 (Refixia) when used for treatment and prophylaxis of bleeding episodes in PWHB.
Eligibility criteria for participants	Inclusion Criteria: • Male patients with moderately severe or severe congenital haemophilia B with a FIX activity of 2% or below according to medical records • History of at least 150 exposure days to other FIX products • Patients currently treated on-demand with at least 6 bleeding episodes during the last 12 months or at least 3 bleeding episodes during the last 6 months, or patients currently on prophylaxis Exclusion Criteria: • Known history of FIX inhibitors based on existing medical records, laboratory report reviews and patient and legally acceptable representative (LAR) interviews • HIV (Human immunodeficiency virus) positive, with a viral load equal to or above 400,000 copies/mL and/or CD4+ lymphocyte count equal to or below 200/microL • Congenital or acquired coagulation disorders other than haemophilia B • Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records) • Immune modulating or chemotherapeutic medication
Settings and locations where the data were collected	United States Los Angeles, California, United States, 90027-6016 United States, Florida Jacksonville, Florida, United States, 32207

Trial number (acronym)	NCT01333111
	United States, Georgia
	Augusta, Georgia, United States, 30912
	United States, Iowa
	Iowa City, Iowa, United States, 52242
	United States, Maryland
	Baltimore, Maryland, United States, 21287
	United States, Minnesota
	Minneapolis, Minnesota, United States, 55404
	United States, Nebraska
	Omaha, Nebraska, United States, 68198-5456
	United States, New Jersey
	Newark, New Jersey, United States, 07102
	United States, New York
	New York, New York, United States, 10029
	Syracuse, New York, United States, 13210
	United States, Pennsylvania
	Hershey, Pennsylvania, United States, 17033
	United States, Texas
	Houston, Texas, United States, 77030
	Canada, Alberta
	Edmonton, Alberta, Canada, T6G 2B7
	France
	Kremlin-Bicêtre, France, 94270
	Lyon, France, 69003
	Germany
	Bonn, Germany, 53127
	Duisburg, Germany, 47051
	Giessen, Germany, 35392
	Hannover, Germany, 30625
	Hungary
	Budapest, Hungary, H-1134
	Italy
	Firenze, Italy, 50134
	Milano, Italy, 20124
	Japan
	Kawasaki-shi, Kanagawa, Japan, 216-8511
	Nagoya-shi, Aichi, Japan, 466 8560
	Nishinomiya-shi, Japan, 663 8051
	Shinjuku-ku, Tokyo, Japan, 160 0023
	Suginami-ku, Tokyo, Japan, 167 0035
	Macedonia
	The Former Yugoslav Republic of
	Skopje, Macedonia, The Former Yugoslav Republic of, 1000
	Malaysia
	Novo Nordisk Investigational Site
	Kuala Lumpur, Malaysia, 50400
	Netherlands
	Utrecht, Netherlands, 3584 CX
	Russian Federation
	Moscow, Russian Federation, 105077

Trial number (acronym)	NCT01333111
	Saint-Petersburg, Russian Federation, 191119 South Africa Parktown Johannesburg, Gauteng, South Africa, 2193 Thailand Bangkok, Thailand, 10400 Turkey Ankara, Turkey, 06500 Kayseri, Turkey, 38010 Konya, Turkey, 42090 United Kingdom Basingstoke, United Kingdom, RG24 9NA Cardiff, United Kingdom, CF14 4XW London, United Kingdom, NW3 2QG London, United Kingdom, SE1 7EH Manchester, United Kingdom, M13 9WL Oxford, United Kingdom, OX3 7LJ
Trial drugs	Drug: Refixia (NNC-0156-0000-0009) One single dose administered intravenously (into the vein) once weekly. Patients will receive instruction on how to treat any bleeding episode they may experience Drug: Refixia (NNC-0156-0000-0009) Patients will treat themselves with either a low or a high dose dependent on the severity of the bleeding episode
Permitted and disallowed concomitant medication	N/A
Primary outcomes (including scoring methods and timings of assessments)	• Incidence of inhibitory antibodies against FIX defined as titer equal to or above 0.6 BU (Bethesda Units) [Time Frame: 52 weeks after treatment start for patients on prophylaxis] • Incidence of inhibitory antibodies against FIX defined as titer equal to or above 0.6 BU (Bethesda Units) [Time Frame: 28 weeks after treatment start on on-demand treatment]
Other outcomes used in the economic model/ specified in the scope	N/A
Pre-planned subgroups	• Experimental: Prophylaxis, high dose (trial duration 52 weeks) • Experimental: Prophylaxis, low dose (trial duration 52 weeks) • Experimental: On-demand (trial duration 28 weeks)

Sources: Collins et al. (2014).

18. Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

18.1 HOPE-B

The baseline characteristics of the FAS population are described below and presented in [redacted]

Table 70: [redacted]

Table 70: Baseline characteristics of patients recruited to HOPE-B trial

Baseline Characteristic	HOPE-B (N=51)
Severity of hemophilia B, n (%)	
<1 IU/dL	[redacted]
1 – 2 IU/dL	[redacted]
Prior ABR, Mean (SD)	[redacted]
Prior FIX regimen, n (%)	
Prophylaxis	[redacted]
On-demand	[redacted]
Prior presence of target joints, n (%)	
0	[redacted]
≥1	[redacted]
Age, years, Mean (SD)	[redacted]
Prior FIX product class, n (%)	
EHL	[redacted]
SHL	[redacted]
BMI, Mean (SD)	[redacted]
Weight, kg, Mean (SD)	[redacted]
Prior FIX product, n (%)	
rFIX	[redacted]
pdFIX	[redacted]
rIX-FP	[redacted]
Other	[redacted]
Family members with history of FIX inhibitor antibodies, n (%)	

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Baseline Characteristic	HOPE-B (N=51)
No	[redacted]
Yes	[redacted]
Missing/Unknown	[redacted]
HIV status, n (%)	
Positive	[redacted]
Negative	[redacted]
Duration of diagnosed hemophilia B, years, Mean (SD)	[redacted]
Race, n (%)	
White	[redacted]
Non-white	[redacted]
Missing	[redacted]

Note:

[a] Data for covariate were taken at screening for HOPE-B and the comparator trial.

[b] Data for covariate were taken during the lead-in period for HOPE-B and were taken at screening for the comparator trial.

[c] Data for covariate were taken after the lead-in period for HOPE-B and were taken at screening for the comparator trial.

[d] Bleeding history within the last 12 months prior to study entry for Paradigm™ 2. Reported as estimated rate without any source of variability.

[f] Target joints at Hemgenix dosing was identified during lead-in, a target joint was defined as 3 or more spontaneous bleeding episodes in a particular joint within a period of 6 months before trial.

Abbreviations: ABR, Annualized bleeding rate; BMI, Body mass index; dL, Deciliter; EHL, Extended half-life; FIX, Factor IX; HIV, Human immunodeficiency virus; IU, International unit; NA, Not applicable; NR, Not reported; pdFIX, Plasma–derived factor IX; rFIX, Recombinant Factor IX; rIX-FP: Recombinant fusion protein linking recombinant coagulation Factor IX with recombinant albumin; SD, Standard deviation; SHL, Short half-life; SMD, Standardized mean difference.

Sources: CSL Behring (2022e).

18.2 Paradigm™ 2

The baseline characteristics of the population recruited to the Paradigm™ 2 trial are presented in Table 71 below.

Table 71: Baseline characteristics of patients recruited to Paradigm™ 2 trial

Baseline Characteristic	Paradigm™ 2 (N=74)	Paradigm™ 2 - 40IU/kg subgroup (N=29)
Severity of hemophilia B, n (%)		
<1 IU/dL	60 (81.1%)	24 (82.8%)
1 – 2 IU/dL	14 (18.9%)	5 (17.2%)
Prior FIX regimen, n (%)		
Prophylaxis	39 (52.7%)	17 (58.6)
On-demand	35 (47.3%)	12 (41.4)
Prior presence of target joints, n (%)		
Yes	40 (54.1%)	15 (51.7)
No	34 (45.9%)	14 (48.3)
Age, years, Mean (SD)	31.4 (14.2)	30.0 (15.8)
Prior FIX product, n (%)		
Recombinant FIX	21 (53.8%)	10 (58.8)
Plasma FIX product	18 (46.2%)	7 (41.2)
Weight, kg, Mean (SD)	73.7 (14.7)	70.4 (15.1)
Race, n (%)		

Baseline Characteristic	Paradigm™ 2 (N=74)	Paradigm™ 2 - 40IU/kg subgroup (N=29)
White	48 (64.9%)	21 (72.4)
Asian	16 (21.6%)	5(17.2)
Black or African American	5 (6.8%)	3(10.3)
Other	5 (6.8%)	-

Abbreviations: FIX, Factor IX; IU, International unit; rFIX, Recombinant FIX; SD, Standard deviation. Target joints was identified at screening for Paradigm™ 2, a target joint was defined as 3 or more bleeding episodes in a particular joint within a period of 6 months before trial.
Source: Collins et al. (2014).

18.3 Comparability of patients across studies

The HOPE-B and Paradigm™ 2 trials were overall comparable. Please see section 8.2.2 and Appendix F regarding the feasibility assessment for ITC between the two trials.

18.4 Comparability of the study populations with Danish patients eligible for treatment

There are no relevant differences between the study populations in HOPE-B and the expected Danish patient population.

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19. Appendix D Efficacy and safety results per study

19.1 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
HOPE-B trial (NCT03569891)			
Primary outcome measure			
Factor IX activity levels [Time Frame: 26 weeks] (submitted: June 14, 2018)	Assessment of Factor IX activity after a single dose of AMT-061	Factor FIX activity level is correlated with bleeding risk in hemophilia B and used both for severity classification, clinical decision making and monitoring of hemophilia B therapy, ABR. (Germini et al., 2022, Srivastava et al., 2020)	Factor IX activity level is a widely accepted surrogate measure of bleeding risk. ISTH defines severe hemophilia B as activity level of FIX less than 1%, moderate as 1% to 5% and mild as 5% to 40%. For a patient to move from one severity grade to another may seem especially clinically relevant, but there are significant difference in bleeding tendency between patients with similar factor levels and the exact choice of boundaries between severity grades are not based on any specific biological phenomenon.
Annualized Bleeding Rate (ABR) for All Bleeding Episodes (submitted: September 26, 2022)	ABR was calculated as the ratio of the number of bleeds to the number of days in the time interval multiplied by 365.25	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020). Mean or median ABR changes in a population correlate to one or more individuals actual bleeding events, even small changes in mean ABR may relate to a serious bleeding episode in an individual patient. We firmly believe that any statistically significant change in ABR is of clinical relevance. We have also consulted a

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Outcome measure	Definition	Validity	Clinical relevance
			Nordic hematology professor and expert with extensive experience from clinical hemophilia care who shares this view.
Secondary outcome measures			
Difference in Annualized bleeding rate (ABR) [Time Frame: 52 weeks]	Comparison of ABR between prophylaxis used in the lead-in and after administration of AMT-061	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Use of Factor IX replacement therapy [Time Frame: 52 weeks]	Patients will record all use of prophylactic Factor IX replacement therapy in an e-diary, including reason for Factor IX use, date, and time of infusion and total dose	Absent or diminished need for FIX replacement therapy is a measure of how successful etranacogene dezaparvovec has been in replacing factor prophylaxis.	The need for FIX replacement therapy is a cost and a discomfort for the patient.
Factor IX Activity Levels After AMT-061 Dosing [Time Frame: Baseline and 6,12, and 18 months after AMT-061 dosing]	The change in uncontaminated endogenous factor IX activity levels (by the one-stage aPTT assay) at 6 months, 12 months, and 18 months following a single treatment	Factor FIX activity level is correlated with bleeding risk in hemophilia B and used both for severity classification, clinical decision making and monitoring of hemophilia B therapy, ABR.(Germini et al., 2022, Srivastava et al., 2020)	Factor IX activity level is a widely accepted surrogate measure of bleeding risk.

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Outcome measure	Definition	Validity	Clinical relevance
	with AMT-061 will be assessed once the last subject has achieved 6 months, 12 months, and 18 months after AMT-061 treatment, respectively.		
Annualized Exogenous Factor IX Consumption [Time Frame: Lead-in period and months 0-6, 7-12, and 13-18 after AMT-061 dosing]	Annualized consumption of factor IX replacement therapy during the 52 weeks following stable factor IX expression (months 6-18 post treatment), excluding factor IX replacement for invasive procedures, compared to the lead-in phase	Absent or diminished need for FIX replacement therapy is a measure of how successful etranacogene dezaparvovec has been in replacing factor prophylaxis.	The need for FIX replacement therapy is a cost and a discomfort for the patient.
Adjusted Annualized Infusion Rate of FIX Replacement Therapy [Time Frame: Lead-in period and months 7-18 after AMT-061 dosing]	Annualized infusion rate of factor IX replacement therapy during the 52 weeks following stable factor IX expression (months 6-18 post treatment),	Absent or diminished need for FIX replacement therapy is a measure of how successful etranacogene dezaparvovec has been in replacing factor prophylaxis.	The need for FIX replacement therapy is a cost and a discomfort for the patient.

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Outcome measure	Definition	Validity	Clinical relevance
	excluding factor IX replacement for invasive procedures, compared to the lead-in phase		
Percent of Subjects Who Discontinued FIX Prophylaxis and Remained Free of Routine FIX Prophylaxis After AMT-061 Dosing [Time Frame: Months 7-18 after AMT-061 dosing]	Proportion of subjects remaining free of previous continuous routine prophylaxis during the 52 weeks following stable factor IX expression (months 6-18 post-treatment	Absent or diminished need for FIX replacement therapy is a measure of how successful etranacogene dezaparvovec has been in replacing factor prophylaxis.	The need for FIX replacement therapy is a cost and a discomfort for the patient.
Percentage of Subjects With Trough FIX Activity <12% of Normal [Time Frame: Lead-in and 3, 12, and 18 months after AMT-061 dosing]	Comparison of the percentage of subjects with trough factor IX activity <12% of normal between the lead-in phase and after treatment with AMT-061 over the 52 weeks following stable factor IX expression (months 6-18 post-treatment)	Factor FIX activity level is correlated with bleeding risk in hemophilia B and used both for severity classification, clinical decision making and monitoring of hemophilia B therapy, ABR.(Germini et al., 2022, Srivastava et al., 2020)	Factor IX activity level is a widely accepted surrogate measure of bleeding risk.

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Outcome measure	Definition	Validity	Clinical relevance
ABR for FIX-treated Bleeding Episodes [Time Frame: Lead-in and Months 7-18 after AMT-061 dosing]	ABR comparison between AMT-061 and prophylaxis for superiority between the lead-in phase and the 52 weeks following stable factor IX expression (months 6-18 post-treatment)	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Number of Spontaneous Bleeding Episodes [Time Frame: Lead-in period and months 7-18 after AMT-061 dosing]	Rate of spontaneous bleeding events during the 52 weeks following stable factor IX expression (months 6-18 post-treatment) compared to the lead-in phase	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Number of Joint Bleeding Episodes [Time Frame: Lead-in period and months 7-18 after AMT-061 dosing]	Rate of joint bleeding events during the 52 weeks following stable factor IX expression (months 6-18 post-treatment) compared to the lead-in phase	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)

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Outcome measure	Definition	Validity	Clinical relevance
Number of New Target Joints and the Number of New Target Joints Resolved. [Time Frame: Up to 18 months after AT-061 dosing]	A target joint was defined as 3 or more spontaneous bleeding episodes into a single joint within a consecutive 6-month period prior to the dosing visit and which was not resolved by the time of dosing. An identified target joint with ≤2 spontaneous bleeding episodes within a consecutive 12-month period was considered resolved.	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Percent of Participants With Zero Bleeding Episodes During the 52 Weeks Following Stable FIX Expression (6 to 18 Months) After AMT-061 Dosing [Time Frame: Lead-in period and months 7-18 post-treatment of AMT-061]	Proportion of subjects with zero bleeds during the 52 weeks following stable factor IX expression (months 6-18 post-treatment)	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)

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Outcome measure	Definition	Validity	Clinical relevance
International Physical Activity Questionnaire (iPAQ) Overall Score [Time Frame: Lead-in period and up to 12 months after AT-01 dosing]	To calculate MET minutes a week multiply the MET value given (walking = 3.3, moderate activity = 4, vigorous activity = 8) by the minutes the activity was carried out and again by the number of days that that activity was undertaken. A higher score is considered to be more favourable.	The iPAQ was designed to provide an evaluation of daily physical activities in metabolic equivalent of task (MET) minutes/week.	Not to be limited in daily physical activites is relevant to many patients with hemophilia
EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) VAS Overall Score [Time Frame: Lead-in period and up to 12 months after AMT-061 dosing]	The EQ-5D-5L descriptive system of health-related QoL states consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The EQ-5D-5L VAS overall score ranges from 0 to 100. A higher score is considered to be more favourable.	EQ-5D-5L questionnaire is a validated instrument for measurement of Quality of Life (2022)	Quality of Life is relevant to all patients

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Outcome measure	Definition	Validity	Clinical relevance
Number of Adverse events [Time Frame: 5 years]	Follow up and assess any adverse events reported for safety	Safety measure	Adverse events may have serious impact on a patient´s life.

Paradigm 2 trial (NCT01333111)			
Outcome measure	**Definition**	**Validity**	**Clinical relevance**
ABRs in all patients			Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
ABRs in patients with previous prophylaxis treatment (Bleed rate **Time Frame: during the last 12 months before trial and during the trial)**	An ABR during the last 12 months before the trial was calculated on the basis of the patient-reported number of bleeding episodes during this time.	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
ABRs in patients with previous on-demand treatment (Bleed rate Time Frame: during the last 12 months before trial and during the trial)	An ABR during the last 12 months before the trial was calculated on the basis of the patient-reported number of bleeding episodes during this time.	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)

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Outcome measure	Definition	Validity	Clinical relevance
ABRs in all patients by type of bleed (Spontaneous and traumatic bleeding episodes)	Number of bleeding episodes per patient during routine prophylaxis [Time Frame: 52 weeks after treatment start for patients on prophylaxis] The number of bleeding episodes per patient during routine prophylaxis was assessed using the individual annualised bleeding rates (spontaneous and traumatic bleeding episodes per patient per year)	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
The estimated mean FIX trough activity	Factor IX trough levels [Time Frame: 52 weeks after treatment start for patients on prophylaxis] The mean pre-dose factor IX levels was measured with the one-stage clotting assay during the trial. Lowest factor IX	Factor FIX activity level is correlated with bleeding risk in hemophilia B and used both for severity classification, clinical decision making and monitoring of hemophilia B therapy, ABR.(Germini et al., 2022, Srivastava et al., 2020)	Factor IX activity level is a widely accepted surrogate measure of bleeding risk.

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Outcome measure	Definition	Validity	Clinical relevance
	activity recorded during single-dose and steady state, immediately before next dose was given. The analysis was based on a mixed model on the log-transformed plasma factor IX activity with subject as a random effect. The estimated mean factor IX trough level was presented back-transformed to the natural scale		
Number of all bleeds, N (%)	Number of bleeding episodes per patient during routine prophylaxis The number of bleeding episodes per patient during routine prophylaxis was assessed using the individual annualised bleeding rates (spontaneous and traumatic bleeding episodes	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)

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Outcome measure	Definition	Validity	Clinical relevance
	per patient per year).		
Number of joint bleeds, N (%)	Number of joint bleeding Episodes per patient during routine prophylaxis The number of bleeding episodes per patient during routine prophylaxis was assessed using the individual annualised bleeding rates (spontaneous and traumatic bleeding episodes per patient per year).	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Number of target joint bleeds, N (%)	Number of Bleeding Episodes per patient during routine prophylaxis A target joint was defined as 3 or more bleeding episodes in a particular joint within a period of 6 months before trial.	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)

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Outcome measure	Definition	Validity	Clinical relevance
Number of bleeds per site, N (%)	Number of bleeding Episodes Per site per patient during routine prophylaxis. The number of bleeding episodes per patient during routine prophylaxis was assessed using the individual annualised bleeding rates (spontaneous and traumatic bleeding episodes per patient per year).	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Classification of bleeds as mild/moderate/severe, N (%)			Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)
Average dose for treatment of bleeds, (U/kg/bleed)			The dose needed for treatment is a cost
Number of bleeding episodes during trial, N (%)	Number of bleeding Episodes per patient during the tria	The most important indicator of the efficacy of hemostatic therapy is frequency of bleeding, particularly joint and muscle bleeds. (Srivastava et al., 2020)	Bleeding frequency is the primary parameter for treatment decisions and is also used as a predictor of long-term musculoskeletal outcomes.(Srivastava et al., 2020)

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Outcome measure	Definition	Validity	Clinical relevance
Incidence of Adverse Events (AEs)	The incidence of adverse events were summarised by the rate of AEs (i.e., the number of AEs per patient years of exposure or PYE). Number of adverse events per PYE is number of adverse events /total time in trial. All adverse events reported are treatment emergent (any adverse events which occurred after trial product administration)	Safety measure	Adverse events may have serious impact on a patient´s life.

Abbreviations: ABR, Annualized bleeding rate; APTT, Activated partial thromboplastin time; AE, Adverse event; EQ-5D-5L, EuroQol five-dimension 5-level; FIX, Factor IX, iPAQ, International physical activity questionnaire; MET, Metabolic equivalent of task; QoL, Quality of life; SOC, Standard of care;

Sources: 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file],(CSL Behring, 2022i) ClinicalTrials.gov. NCT03569891(ClinicalTrials.gov Identifier). The information for the Paradigm 2 trial is sourced from (Collins et al., 2014, ClinicalTrials.gov, 2023).

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19.2 Results per study

Table 72: FIX activity level after Hemgenix dosing; Results from HOPE-B trial

Results of HOPE-B trial (NCT03569891)												
			Estimated absolute difference in effect				Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Visits**	**N**	**Result (Mean (SD))**	**LS mean[a]**	**95% CI**	**p-value[b]**	**Difference**	**95% CI**	**P value**		
FIX activity (%) from uncontaminated central laboratory one-stage (APTT-based) assay post treatment	Baseline[c]	54	1.19 (0.39)	-	-	-				LS mean from repeated measures linear mixed model with visit as a categorical covariate.	HOPE-B study results overview: 24-month data (EMA, 2023)
	Post-treatment month 6	51	38.95 (18.72)	36.18 (2.432)	31.41, 40.95	<0.0001					
	Post-treatment month 12	50	41.48 (21.71)	38.81 (2.442)	34.01, 43.60	<0.0001					
	Post-treatment month 18	50	36.90 (21.40)	34.31 (2.444)	29.52, 39.11	<0.0001					

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Results of HOPE-B trial (NCT03569891)								
	Post-treatment month 24	50	36.66 (18.96)	34.13 (2.325)	29.57, 38.69	<0.0001		
FIX activity (%) from uncontaminated central laboratory one-stage (APTT-based) assay post-treatment for subjects with pre-existing NAbs to AAV5 (FAS)	Baseline[c]	21	1.24 (0.44)	-	-	-	LS mean from repeated measures linear mixed model with visit as a categorical covariate.	HOPE-B study results overview: 24-month data (EMA, 2023)
	Post-treatment month 6	18	35.91 (19.02)	30.79 (3.827)	23.26, 38.32	<0.0001		
	Post-treatment month 12	18	35.54 (17.84)	31.59 (3.847)	24.02, 39.16	<0.0001		
	Post-treatment month 18	17	31.14 (13.75)	26.83 (3.854)	19.24, 34.41	<0.0001		

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Results of HOPE-B trial (NCT03569891)								
	Post-treatment month 24	17	32.98 (18.51)	28.35 (3.928)	20.62, 36.08	<0.0001		
FIX activity (%) from uncontaminated central laboratory one-stage (APTT-based) assay post-treatment for subjects without pre-existing NAbs to AAV5 (FAS)	Baseline[c]	33	1.15 (0.36)	-	-	-	LS mean from repeated measures linear mixed model with visit as a categorical covariate.	HOPE-B study results overview: 24-month data (EMA, 2023)
	Post-treatment month 6	33	40.61 (18.64)	39.46 (3.172)	33.23, 45.69	<0.0001		
	Post-treatment month 12	32	44.82 (23.21)	43.07 (3.176)	36.83, 49.31	<0.0001		
	Post-treatment month 18	33	39.87 (24.08)	38.72 (3.172)	32.49, 44.95	<0.0001		
	Post-treatment month 24	33	38.55 (19.19)	37.40 (2.933)	31.64, 43.16	<0.0001		

Notes:

[a]LS mean from repeated measures linear mixed model with visit as a categorical covariate.

[b]One-sided p-value ≤0.025 for post-treatment >baseline was regarded as statistically significant.

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[c]Uncontaminated' meant that the blood sampling did not occur within five half-lives of exogenous FIX replacement therapy use. Both the date and time of exogenous FIX replacement therapy use, and blood sampling were considered in determining contamination. FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with zero uncontaminated central laboratory post-Hemgenix values had their change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value; Baseline antibody titer was the most recently collected n on missing antibody titer prior to dosing. Also, the ratio of chromogenic to one-stage (APTT-based) assay was not imputed. Baseline FIX was imputed based on subject's historical haemophilia B severity documented on the case report form. If the subject had documented severe FIX deficiency (FIX plasma level <1%), their baseline FIX activity level was imputed as 1%. If the subject had documented moderately severe FIX deficiency (FIX plasma level ≥1% and ≤2%,) their baseline FIX activity level was imputed as 2%.

[d]With antibodies' was defined as having a titer of >LOD.

[e]Without antibodies' was defined as having a titer of ≤LOD.

Abbreviations: AAV5, Adeno-associated virus vector serotype 5; APTT, Activated partial thromboplastin time; CI, Confidence interval; FAS, Full analysis set; FIX, Factor IX, LOD, Limit of detection; LS, Least squares; Nab, Neutralizing antibody; SD, Standard deviation.

Source: HOPE-B study results overview: 24-month data [data on file] (CSL Behring, 2022i).

Table 73: Annualized use of FIX replacement therapy excluding invasive procedures (FAS), IU/year

Results of HOPE-B trial (NCT03569891)										
			Estimated absolute difference in effect				Estimated relative difference in effect		Description of methods used for estimation	References
Outcome	**Post treatment period**	**N (%)**	**Unadjusted mean[a]**	**Adjusted mean[b]**	**95% CI**	**p-value[c]**	**Difference**	**95% CI**	**P value**	
Annualized exogenous FIX replacement therapy consumption, IU/year, n (%)	≥6-month lead-in period	54 (100)	257,339 (149,013)							HOPE-B study results overview: 24-month data (EMA, 2023)
	Month 0–6	54 (100)	12,913 (37,093)							
	Month 7–12	54 (100)	8,399							

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Results of HOPE-B trial (NCT03569891)						
			(29,721)			
	Month 13–18	54 (100)	8,487 (28,770)			
	Month 19–24	53 (98.1)	9,751 (29,140)			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001
	[redacted]	[redacted]	[redacted]	[redacted]	-290,614 -206,172	<0.0001
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Results of HOPE-B trial (NCT03569891)									
	Post-treatment period	**Number of subjects using FIX replacement therapy, n (%)**	**Number of infusions of FIX replacement therapy, n**	**Mean (per subject)**	**Number of person-years observed for usage of FIX replacement therapy**				
Annualized use of FIX replacement therapy excluding invasive procedures (FAS)	≥6-month lead-in period	54 (100.0)	2380	44.1	33.12				
	Month 0-6	14 (25.9)	85	1.6	24.1				
	Month 7 -18	10 (18.5)	70	1.3	26.91				
	Month 7 -24	11 (20.4)	64	1.2	26.12				
	Month 0 -24	13 (24.5)	42	0.8	25.85				
	Post-treatment period	**Cumulative number of infusions of FIX replacement therapy**	**Cumulative number of person-years observed for FIX usage**	**Unadjusted annualized infusion rate[a]**	**adjusted annualized infusion rate[b]**	**(95% CI)[b]**	**rate ratio (post-treatment/ lead-in)[b]**	**two-sided 95% Wald CI**	**p-value[c]**

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Results of HOPE-B trial (NCT03569891)									
Annualized use of FIX replacement therapy excluding invasive procedures (FAS)	≥6-month lead-in period	2,380	33.12	71.87	72.49c	(63.52, 82.71)	–	–	–
	Month 0-6	85	24.1	3.53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 7 -18	134	53.03	2.53	2.53	(0.92, 6.96)	0.03	0.01, 0.10	<0.0001
	Month 7 -24	176	79.18	2.22	2.54	(0.98, 6.59)	0.04	0.01, 0.09	<0.0001
	Month 0 -24	155	51.01	3.04	3.04	(1.14, 8.12)	0.04	0.02, 0.11	<0.0001

Notes:

[a] Unadjusted use was calculated as the ratio of the number of infusions of FIX to the time of observation (in years). Usage related to invasive procedures was not included.

[b] Adjusted use and comparison of use between lead-in and post-treatment periods was estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.

[c] p-values were calculated using a paired t-test comparing post-treatment and lead-in periods. One-sided p-value ≤0.025 for post-treatment lead-in <0 was regarded as statistically significant. For Month 7 to 18, a one-sided p-value ≤0.025 for post-treatment/lead-in of <1 was regarded as statistically significant. For Months 0 to 6 and 7 to 24, p-values were not adjusted for multiplicity.

Abbreviations: CI, Confidence interval; FAS, Full analysis set; FIX, Factor IX; IU, International units; SD, Standard deviation; SE, Standard error.

Source: (CSL Behring, 2022i)

Table 74 shows the results of Paradigm 2 clinical trial (NCT01333111). The results of ABRs, FIX trough activity levels, and frequency of bleeds per bleed sites including joint bleeds are included in the Table 74. According to the authors of the study, the trial was associated with several limitations including the unfeasibility of direct comparisons between the prophylaxis groups and the on-demand group. This was because the patients were free to choose between entering into prophylaxis or receiving on-demand treatment. As the study did not report the results of absolute and relative difference in effect, the table was restructured by removing the columns for the same.

Table 74: Efficacy outcomes reported in the Paradigm 2 trial

Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
ABRs in all patients	Prophylactic treatment with Refixia (10 IU/kg)	30	2.93 (0.99-6.02)	4.56	(3.01-6.90)	*.40*[1]				
	Prophylactic treatment with Refixia (40 IU/kg)	29	1.04 (0.00-4.00)	2.51	(1.42-4.43)	*.01*[1]				
	On-demand treatment	15	15.58 (9.56-26.47)	1.35	N/A	N/A				
	Prophylactic treatment with Refixia (10 IU/kg)	20	4.75	5.13	N/A	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
ABRs in patients with previous prophylaxis treatment (Bleeding rate during the last 12 months before trial)	Prophylactic treatment with Refixia (40 IU/kg)	17	4.00	7.49	N/A	N/A				
	On-demand treatment	2	9.50	9.50	N/A	N/A				
ABRs in patients with previous prophylaxis treatment (Bleeding rates during trial)	Prophylactic treatment with Refixia (10 IU/kg)	20	2.99	4.68	N/A	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	17	1.93	3.33	N/A	N/A				
	On-demand treatment	2	25.69	29.4	N/A	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
ABRs in patients with previous on-demand treatment (Bleeding rate during the last 12 months before trial)	Prophylactic treatment with Refixia (10 IU/kg)	10	14.0	17.9	N/A	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	12	12.5	21.2	N/A	N/A				
	On-demand treatment	13	15.0	22.7	N/A	N/A				
ABRs in patients with previous on-demand treatment (Bleeding rates during trial)	Prophylactic treatment with Refixia (10 IU/kg)	10	2.06[2]	4.30	N/A	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	12	0.52[2]	1.32	N/A	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	On-demand treatment	13	13.0[2]	17.6	N/A	N/A				
ABRs in all patients by type of bleed (Spontaneous bleeding episodes)	Prophylactic treatment with Refixia (10 IU/kg)	N/A	0.97 (0.00-4.01)	3.14	(1.78-5.56)	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	N/A	0.00 (0.00-0.98)	1.22	(0.48-3.10)	N/A				
	On-demand treatment	N/A	11.1 (7.16-15.8)	N/A	N/A	N/A				
ABRs in all patients by type of bleed (Traumatic bleeding episodes)	Prophylactic treatment with Refixia (10 IU/kg)	N/A	0.98 (0.00-1.93)	1.35	(0.81-2.24)	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	Prophylactic treatment with Refixia (40 IU/kg)	N/A	0.00 (0.00-2.04)	1.29	(0.76-2.19)	N/A				
	On-demand treatment	N/A	1.73 (0.00-8.95)	N/A	N/A	N/A				
The estimated mean FIX trough activity	Prophylactic treatment with Refixia (10 IU/kg)	N/A	N/A	8.5 (IU/dl)	7.7-9.3	P< .001				
	Prophylactic treatment with Refixia (40 IU/kg)	N/A	N/A	27.3 (IU/dl)	24.8-30.0	P< .001				
	On-demand treatment	N/A	N/A	N/A	N/A	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
Number of all bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	122[3] (100)	N/A	N/A	N/A	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	69[3] (100)	N/A	N/A	N/A	N/A				
	On-demand treatment	140[3] (100)	N/A	N/A	N/A	N/A				
Number of joint bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	99[3] (81.1)	N/A	N/A	N/A	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	54[3] (78.3)	N/A	N/A	N/A	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	On-demand treatment	107[3] (76.4)	N/A	N/A	N/A	N/A				
Number of target joint bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	49[3] (37.1)	N/A	N/A	N/A	N/A				
	Prophylactic treatment with Refixia (40 IU/kg)	19[3] (27.1)	N/A	N/A	N/A	N/A				
	On-demand treatment	70[3] (49.0)	N/A	N/A	N/A	N/A				
Number of muscle bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	6[3] (4.9)	N/A	N/A	N/A	N/A				

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	Prophylactic treatment with Refixia (40 IU/kg)	7[3] (10.1)	N/A	N/A	N/A	N/A				
	On-demand treatment	24[3] (17.1)	N/A	N/A	N/A		N/A			
Number of mouth/gums/nose bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	7[3] (5.7)	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	2[3] (2.9)	N/A	N/A	N/A		N/A			
	On-demand treatment	3[3] (2.1)	N/A	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
Number of skin and soft tissue bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	7[3] (5.7)	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	2[3] (2.9)	N/A	N/A	N/A		N/A			
	On-demand treatment	2[3] (1.4)	N/A	N/A	N/A		N/A			
Number of bleeding from other location, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	2[3] (1.6)	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	1[3] (1.4)	N/A	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	On-demand treatment	1[3] (0.7)	N/A	N/A	N/A		N/A			
Number of genitourinary bleed, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	1[3] (0.8)	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	N/A	N/A	N/A	N/A		N/A			
	On-demand treatment	2[3] (1.4)	N/A	N/A	N/A		N/A			
Number of muscular bleed, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	N/A	N/A	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	Prophylactic treatment with Refixia (40 IU/kg)	1[3] (1.4)	N/A	N/A	N/A		N/A			
	On-demand treatment	N/A	N/A	N/A	N/A		N/A			
Number of subcutaneous bleed, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	N/A	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	1[3] (1.4)	N/A	N/A	N/A		N/A			
	On-demand treatment	N/A	N/A	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
Number of other bleeds, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	N/A	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	1[3] (1.4)	N/A	N/A	N/A		N/A			
	On-demand treatment	1[3] (0.7)	N/A	N/A	N/A		N/A			
Classification of bleeds as mild/moderate, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	131 (99.2)	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	70 (100.0)	N/A	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	On-demand treatment	143 (100.0)	N/A	N/A	N/A		N/A			
Classification of bleeds as severe, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	1 (0.8)	N/A	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	N/A	N/A	N/A	N/A		N/A			
	On-demand treatment	N/A	N/A	N/A	N/A		N/A			
Average dose for treatment of bleeds, (U/kg/bleed)	Prophylactic treatment with Refixia (10 IU/kg)	N/A	42.4[2]	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	Prophylactic treatment with Refixia (40 IU/kg)	N/A	42.3[2]	N/A	N/A		N/A			
	On-demand treatment	N/A	41.9[2]	N/A	N/A		N/A			
Number of zero bleeding episodes during trial, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	30	5 (16.7)	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	29	13 (44.8)	N/A	N/A		N/A			
	On-demand treatment	15	1 (6.7)	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
Number of one time bleeding episodes during trial, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	30	4 (13.3)	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	29	2 (6.9)	N/A	N/A		N/A			
	On-demand treatment	15	N/A	N/A	N/A		N/A			
Number of two times bleeding episodes during trial, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	30	6 (20.0)	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	29	5 (17.2)	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	On-demand treatment	15	1 (6.7)	N/A	N/A		N/A			
Number of three times bleeding episodes during trial, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	30	4 (13.3)	N/A	N/A		N/A			
	Prophylactic treatment with Refixia (40 IU/kg)	29	2 (6.9)	N/A	N/A		N/A			
	On-demand treatment	15	1 (6.7)	N/A	N/A		N/A			
Number of four times bleeding episodes during trial, N (%)	Prophylactic treatment with Refixia (10 IU/kg)	30	1 (3.3)	N/A	N/A		N/A			

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Results of Paradigm 2 trial (NCT01333111)										
							Estimated absolute difference in effect	Estimated relative difference in effect	Description of the methods used	Reference
Outcome	**Study arm**	**N**	**Median (IQR)**	**Estimated rate**	**95% CI**	**P value**				**(Collins et al., 2014)**
	Prophylactic treatment with Refixia (40 IU/kg)	29	1 (3.4)	N/A	N/A		N/A			
	On-demand treatment	15	1 (6.7)	N/A	N/A		N/A			

Notes:

[1] P-values are from the 1-sided test of the null hypothesis that the estimated rate is at least 4.8, evaluated at the 2.5% level.

[2] IQR was not reported for the median.

[3]The number represents number of bleeds per site. Number of patients for three study arms of 10 U/kg, 40 U/kg, and on-demand groups were 30, 29,and 15 patients, respectively.

[4]A target joint was defined as three or more bleeding episodes in a particular joint within a consecutive 6 months period prior to trial. Percentage is out of the total number of bleeds in the treatment arm.

Abbreviations: ABR, Annual bleed rate; IQR, Interquartile range; N/A: Not available

Source: **(Collins et al., 2014)**

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20. Appendix E Safety data for intervention and comparator(s)

20.1 Hemgenix

20.1.1. TRAEs in Phase III HOPE-B study

At 24 months, Hemgenix continued to be well tolerated with no TRSAEs. During the 24 months post-dose, 54 patients in the phase III HOPE-B study reported a total of 557 AEs, with each patient reported having experienced at least one mild AE. No inhibitors to FIX have been reported, and no relationship between safety and pre-existing NAb titers has been observed. All patients developed a humoral immune response to AAV5 within three weeks of treatment and AAV5 NAb titers remained high through to Month 24 post-treatment. During the 24 months post-dose, all participants experienced at least one treatment-emergent AE (TEAE); of the 557 events, 424 (76%) were mild, 115 (21%) were moderate, and 18 (3%) were severe.TRAEs with an incidence of >5% are reported in XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXX
Table 76 (Pipe et al., 2022b, EMA, 2023).

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Table 75: Overall summary of AEs with incidence of ≥5% by System Organ Class and preferred term (Safety Population)

System Organ Class Preferred Term	Lead-in Period (Including Lead-in Discontinuers) (n=67)		Lead-in Period (Excluding Lead-in Discontinuers) (n=54)		Post-treatment Period (n=54	
	n (%)	# of events	n (%)	# of events	n (%)	# of events
At least 1 AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]		[redacted]		[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]		[redacted]		[redacted]	[redacted]
Upper Respiratory Tract Infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in Extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthritis	[redacted]		[redacted]		[redacted]	[redacted]
Musculoskeletal Chest Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]		[redacted]		[redacted]	[redacted]

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System Organ Class Preferred Term	Lead-in Period (Including Lead-in Discontinuers) (n=67)		Lead-in Period (Excluding Lead-in Discontinuers) (n=54)		Post-treatment Period (n=54	
	n (%)	# of events	n (%)	# of events	n (%)	# of events
Influenza-like Illness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]		[redacted]		[redacted]	[redacted]
Pyrexia	[redacted]		[redacted]		[redacted]	[redacted]
Chest Pain	[redacted]		[redacted]		[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]		[redacted]		[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemorrhoids	[redacted]		[redacted]		[redacted]	[redacted]
Abdominal Pain Upper	[redacted]		[redacted]		[redacted]	[redacted]
Injury, Poisoning, and Procedural Complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ligament Sprain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Limb Injury	[redacted]		[redacted]		[redacted]	[redacted]
Contusion	[redacted]		[redacted]		[redacted]	[redacted]
Infusion Related Reaction	[redacted]		[redacted]		[redacted]	[redacted]

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System Organ Class Preferred Term	Lead-in Period (Including Lead-in Discontinuers) (n=67)		Lead-in Period (Excluding Lead-in Discontinuers) (n=54)		Post-treatment Period (n=54	
	n (%)	# of events	n (%)	# of events	n (%)	# of events
Investigations	[redacted]		[redacted]		[redacted]	[redacted]
ALT Increased	[redacted]		[redacted]		[redacted]	[redacted]
Blood Creatinine Phosphokinase Increased	[redacted]		[redacted]		[redacted]	[redacted]
Aspartate Aminotransferase Increased	[redacted]		[redacted]		[redacted]	[redacted]
C-Reactive Protein Increased	[redacted]		[redacted]		[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]		[redacted]		[redacted]	[redacted]
Dizziness	[redacted]		[redacted]		[redacted]	[redacted]
Respiratory, Thoracic, and Mediastinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Rhinorrhea	[redacted]		[redacted]		[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and Nutrition Disorders	[redacted]		[redacted]		[redacted]	[redacted]
Vitamin D Deficiency	[redacted]		[redacted]		[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	v	[redacted]	[redacted]

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System Organ Class Preferred Term	Lead-in Period (Including Lead-in Discontinuers) (n=67)		Lead-in Period (Excluding Lead-in Discontinuers) (n=54)		Post-treatment Period (n=54	
	n (%)	# of events	n (%)	# of events	n (%)	# of events
Anemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Iron Deficiency Anemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary Disorders	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Hepatic Steatosis	[redacted]		[redacted]		[redacted]	[redacted]

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; n, Number.

Source: 24-Month CSR, CSL Behring (CSL Behring, 2022i).

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Elevations in transaminases in Phase III HOPE-B study

Eleven HOPE-B study subjects had 12 reported AEs of ALT elevation (six mild, five moderate, one severe). Baseline demographics were comparable to subjects without ALT elevation. Mean (±SD) time to first elevated ALT was 46.5 (earliest 22, latest 120) days. Mean elevated ALT duration was 38.2 (±43.5) days. Nine subjects received corticosteroids per protocol, without reported SAEs. Mean (±SD) corticosteroid use duration was 79.8 (±26.6) days (range: 51–130). Mean (±SD) oral corticosteroid dose was 27.2 (5.8) mg/day. All subjects discontinued corticosteroids between Days 85–170 after gene therapy. The mean (±SD) FIX level (% normal) in nine subjects treated with corticosteroids peaked at 22.2 (±10.5) prior to corticosteroid treatment, was 17.1 (±8.09) prior to starting corticosteroid treatment, and was 17.9 (±10.6) two weeks after corticosteroid treatment. The mean (±SD) FIX level in the 11 subjects with elevated ALT was 21.6 (±11.8), 20.3 (±11.5), 18.1 (±9.1), and 18.4 (±9.6) at 6, 12, 18 and 24 months post treatment, respectively. The mean (±SD) FIX level in subjects without increased ALT was 42.4 (±16.2), 45.6 (±20.0), 41.9 (±21.5) and 40.6 (±16.6) at 6, 12, 18 and 24 months post treatment, respectively. The mean (±SD) ABR at Months 7–24 post treatment was 0.8 (±1.0) and 1.1 (±2.0) in the subjects with elevated ALT and without transaminitis, respectively. No subjects returned to continuous FIX prophylaxis (Astermark, 2023).

IRRs in Phase III HOPE-B study

[redacted]

Table 76: Summary of most common TRAEs with an incidence >5% from HOPE-B

TRAE, preferred term	N=54, n (%)	Number of events
ALT increased	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Influenza-like illness	[redacted]	[redacted]
AST increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
IRR	[redacted]	[redacted]

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; IRR, Infusion-related reaction TRAE, Treatment-related adverse event.

Source: HOPE-B study results overview: 24-month data [data on file] (CSL Behring, 2022i).

Treatment discontinuation

[redacted] (CSL Behring, 2022i).

20.2 Refixia - Paradigm™ 2 trial

The mean number of exposure days to Refixia was 54 for patients receiving prophylaxis and 14 for patients receiving on-demand treatment. No patients developed FIX inhibitors, and no deaths, thromboembolic events, or allergic reactions related to Refixia occurred (Collins et al., 2014).

A total of 215 AEs (seven severe, 25 moderate, and 183 mild) in 60 (81%) patients were reported, corresponding to 3.33 AEs per patient year of exposure. The most commonly reported AEs were nasopharyngitis (13 events in 10 patients [13.5%]), influenza (10 events in eight patients [10.8%]), and upper respiratory tract infection (10 events in eight patients [10.8%]). There were four SAEs (hip fracture, worsening of skin ulcer, retroperitoneal hematoma, and abdominal pain)

in four patients (5.4%). These SAEs were reported by the investigator as unlikely to be related to Refixia. No safety concerns were identified from physical examinations or clinical laboratory tests (Collins et al., 2014).

Table 77 and Table 78 are from the EMA Refixia assessment report and respectively show the list of possible or probably AEs identified during the assessment and the most frequent adverse events which occurred in the trial.

Table 77 EMA Refixia Assessment report – List of possible or probably related AEs

Table 2–4 Listing of possibly or probably related adverse events as judged by the investigator - Trials 3639, 3747, 3773, 3775 and 3774 (main phase) - safety analysis set

	Age (years)	Preferred term	ED	Relationship[a]	Serious[b]	Severity	Outcome
Trial 3639							
		Fatigue[c]	1	Possible	No	Moderate	Recovered
		Fatigue[c]	1	Possible	No	Moderate	Recovered
		Myalgia	1	Possible	No	Moderate	Recovered
		Hypersensitivity	1	Probable	Yes	Severe	Recovered
Trial 3747							
		Speech disorder developmental	1	Possible	No	Mild	Recovered
		Speech disorder developmental	2	Possible	No	Mild	Recovered
		Overdose	3	Probable	No	Mild	Recovered
		Incorrect dose administered	9	Probable	No	Mild	Recovered
		Pain in extremity	51	Possible	No	Mild	Not recovered
		Fatigue	1	Possible	No	Mild	Recovered
		Ear pruritus	8	Possible	No	Mild	Recovered
		Headache	8	Possible	No	Mild	Recovered
		Headache	1	Possible	No	Mild	Recovered
		Laryngeal pain	1	Possible	No	Mild	Recovered
		Fatigue	1	Possible	No	Mild	Recovered
		Hot flush	6	Possible	No	Mild	Recovered
		White blood cell count increased	6	Probable	No	Mild	Recovered
		Overdose	14	Probable	No	Mild	Recovered
		Accidental overdose	32	Probable	No	Mild	Recovered
		Incorrect dose administered	1	Probable	No	Mild	Recovered
		Nausea	1	Possible	No	Mild	Recovered
		Palpitations	4	Possible	No	Mild	Recovered
		Fatigue	6	Possible	No	Mild	Not recovered
Trial 3773							
		Pruritus	1	Possible	No	Mild	Recovered
		Serum ferritin increased	90	Probable	No	Mild	Not recovered
Trial 3775							
		Injection site swelling[d]	114	Possible	No	Mild	Recovered
		Injection site rash	27	Probable	No	Mild	Recovered
		Overdose	76	Probable	No	Moderate	Recovered
		Overdose	77	Probable	No	Moderate	Recovered
		Neutropenia	44	Possible	No	Mild	Recovered

Continues

	Age (years)	Preferred term	ED	Relationship[a]	Serious[b]	Severity	Outcome
Trial 3774							
		Headache	1	Possible	No	Mild	Recovered
		Nausea	1	Possible	No	Mild	Recovered
		Abdominal pain	3	Possible	No	Mild	Recovered
		Diarrhoea	7	Possible	No	Mild	Recovered
		Injection site pain	10	Probable	No	Mild	Recovered
		Infusion site pain	30	Probable	No	Mild	Recovered
		Eosinophilia	2	Possible	No	Mild	Recovered
		Wheezing	9	Possible	No	Mild	Recovered

ED: Exposure day
a: The relationship to trial product as judged by the investigator as either probable, possible or unlikely.
b: Denotes if the adverse event is serious or not (yes/no).
c: Two events of fatigue were reported after 1 ED for this patient. These two events were reported two and seven days after the first nonacog beta pegol exposure.
d: This adverse event was reported as a symptom of another adverse event (incorrect route of drug administration) and is not included in the summary statistics. The index adverse event of incorrect route of drug administration was judged to be unlikely related to nonacog beta pegol by the investigator.
For Trial 3774, data are included through the end of main phase for the last patient (7 April 2014).
Cross-reference: Appendix I, Tables 38 and 57

Table 78 EMA Refixia Assessment report – Summary of AEs in more than 5% of patients

Table 2–3 Summary of most frequent adverse events reported in more than 5% of patients adverse events - Trials 3639, 3747, 3773, 3775 and 3774 (main phase) - safety analysis set

	Total N(%)	E[R]
Infections and infestations		
Nasopharyngitis	19(16.5)	35[0.2]
Upper respiratory tract infection	13(11.3)	20[0.1]
Influenza	11(9.6)	18[0.1]
Pharyngitis	7(6.1)	8[<0.1]
Gastroenteritis	6(5.2)	6[<0.1]
Injury, poisoning and procedural complications		
Contusion	15(13.0)	27[0.2]
Skin abrasion	6(5.2)	11[<0.1]
Fall	9(7.8)	11[<0.1]
Laceration	6(5.2)	9[<0.1]
Gastrointestinal disorders		
Vomiting	7(6.1)	14[<0.1]
Nausea[a]	7(6.1)	10[<0.1]
Respiratory, thoracic and mediastinal disorders		
Cough	14(12.2)	23[0.1]
Oropharyngeal pain	9(7.8)	10[<0.1]
Epistaxis	6(5.2)	10[<0.1]
Musculoskeletal and connective tissue disorders		
Pain in extremity[a]	11(9.6)	15[<0.1]
Arthralgia	10(8.7)	14[<0.1]
General disorders and administration site conditions		
Pyrexia	12(10.4)	23[0.1]
Fatigue[a]	8(7.0)	10[<0.1]
Nervous system disorders		
Headache[a]	12(10.4)	23[0.1]

N: Number of patients with adverse event, %: Percentage of patients with adverse event, E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/total patient years of exposure)
a: At least one adverse event with this preferred term was reported by the investigator as probably or possibly related to nonacog beta pegol.

Cross-reference: Modified from Appendix I, Table 20

21. Appendix F Comparative analysis of efficacy and safety

21.1 Feasibility assessment for ITC of Hemgenix (HOPE-B) versus Refixia (Paradigm™ 2)

21.1.1. Trial design characteristics

The trial designs of HOPE-B and Paradigm™ 2 were overall comparable, with some notable differences as summarized in Table 79: Comparison of trial design features between HOPE-B and Paradigm™ 2. HOPE-B was a multinational, non-randomized, open-label and single-dose trial, while Paradigm™ 2 was multinational, randomized (prophylaxis patients were randomized to receive either 10 IU/kg or 40 IU/kg weekly prophylaxis), and single-blind in design. In Paradigm™ 2, for the prophylaxis groups, patients and investigators were blinded to dose; however, investigators could have been unblinded to measure FIX activity, if needed. In HOPE-B, approximately four weeks following a screening visit, patients entered the lead-in phase for ≥6 months. After the lead-in, patients received a one-time infusion of Hemgenix (2×10^{13} gc/kg) (CSL Behring, 2021c). In contrast, Paradigm™ 2 had a screening period of up to eight weeks, after which the patients were assigned to one of three treatment groups: group 1 received weekly prophylaxis (10 IU/kg), group 2 received weekly prophylaxis (40 IU/kg), and group 3 received episodic (on-demand) treatment (Collins et al., 2014). Only group 2 patients who received weekly prophylaxis with 40 IU/kg were included in this analysis because it is the only dose indicated for prophylaxis in the SmPC; other groups were excluded.

Table 79: Comparison of trial design features between HOPE-B and Paradigm™ 2

Key Trial Design Features	HOPE-B (Hemgenix)	Paradigm™ 2 (Refixia)	Assessment of Difference
Phase	3	3	None
Design	Non-randomized	Randomized	HOPE-B is a single-dose trial, prophylaxis patients in Paradigm™ 2 were randomized to receive either 10 IU/kg or 40 IU/kg weekly prophylaxis
Blinding	Open-label	Single-blind	
Countries	Belgium, Denmark, Germany, Ireland, Italy, Netherlands, Sweden, United Kingdom, United States	Canada, France, Germany, Hungary, Italy, Japan, Macedonia, The Former Yugoslav Republic of, Malaysia, Netherlands, Russian Federation, South Africa, Thailand, Turkey, United Kingdom, United States	Similar, but HOPE-B has narrower set of countries
Screening Period	~4 weeks	2 to 8 weeks	Similar
Lead-In Period	≥6 months	None	HOPE-B has Lead-In which provides monitored prophylaxis use to patients
Treatment Groups of Interest (N)	Gene therapy ITC analysis set: N=51b	40 IU/kg group (weekly prophylaxis) N=17, 40 IU/kg weekly prophylaxis group who received prior prophylaxis N=29, Full 40 IU/kg weekly prophylaxis group	HOPE-B one-time infusion, Paradigm™ 2 routine injections
Regimen and Dose in Prophylaxis Groups of Interest	One-time infusion of 2×10^{13} gc/kg	40 IU/kg of Refixia	
Follow-up Time in Groups of Interest	24 months after infusion	52 (±2) weeks after first injection	HOPE-B has longer follow-up and patients require ~3 to 6 months to reach full efficacy

Note:

[a] Prophylaxis patients were randomized to receive either 10 IU/kg or 40 IU/kg weekly prophylaxis in Paradigm™ 2.

[b] ITC analysis set population to exclude one patient with extreme nAB titer who would not be eligible to receive Hemgenix, and one Italian patient due to informed consent forms.

Abbreviations: gc, Gene copies; IU, International units; ITC, Indirect treatment comparison; kg, Kilograms.

Source: Collins et al. (2014), CSL Behring (2021c).

21.1.2. Study eligibility criteria

Comparison of key eligibility criteria that were identified to be of prognostic significance between HOPE-B and Paradigm™ 2 are presented in Table 80. HOPE-B enrolled a narrower patient population than the Paradigm™ 2 trial in terms of the lower bound of age (≥18 years versus 13 to 70 years in Paradigm™ 2), prior exposure time period to FIX protein (>150 versus ≥150 days), and levels of ALT (excluding >2 ULN versus >3 ULN). HOPE-B enrolled a broader population with respect to BMI (no restriction versus ≤35 in Paradigm™ 2). Importantly, HOPE-B required patients be on stable prophylaxis for at least two months prior to screening, while Paradigm™ 2 enrolled a mix of patients who were on either prophylaxis or on-demand FIX therapy prior to study entry. Other criteria such as FIX activity and history of FIX inhibitors were similar across the two trials. Overall, comparison of key eligibility criteria revealed that the two trials had sufficient overlap in patient populations to conduct an ITC.

Table 80: Comparison of select key eligibility criteria between HOPE-B and Paradigm™ 2

Eligibility Criteria	HOPE-B (Hemgenix)	Paradigm™ 2 (Refixia)	Assessment of Difference
Key Inclusion Criteria			
Age (years)	≥18	13-70 years	HOPE-B does not have pediatric patients and Paradigm™ 2 has a maximum age 70 years
Weight (kg)	No restriction	No restriction	Unclear
BMI	No restriction	≤35	HOPE-B has a broader population, with no BMI restriction
FIX activity	≤2%	≤2IU/dL	None
Previous exposure days of treatment with FIX protein (days)	>150	≥150 days	None
FIX use prior to screening	Have been on stable prophylaxis for at least 2 months prior to screening and during lead-in	Subjects have received prophylaxis or on-demand FIX products[b]	HOPE-B has narrower population, being all prophylaxis-experienced patients
Key Exclusion Criteria			
History of FIX inhibitors	Excluded	Excluded	None
ALT	>2 ULN	>3 ULN	HOPE-B has a narrower population
AST	>2 ULN	No restriction[c]	HOPE-B has a narrower population
Total Bilirubin	>2 ULN[a]	No restriction[c]	HOPE-B has a narrower population

Note:

[a] Except for the Netherlands where the lower age limit was 18 years.

[b] Patients currently treated on-demand with at least 6 bleeding episodes during the last 12 months or at least 3 bleeding episodes during the last 6 months, or patients currently on prophylaxis.

[c] Inferred because parameters AST and Total Bilirubin were not mentioned in the exclusion criteria.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; dL, Deciliter; FIX, Factor IX; IU, International unit; ULN, Upper limit of normal.

Source: Collins et al. (2014), CSL Behring (2021c).

21.1.3. Baseline patient characteristics

A comparison of key baseline characteristics, corresponding to ranked factors, between patients from HOPE-B and Paradigm™ 2 for the analysis sets of interest is presented in Table 81. Differences are quantitatively summarized via

SMDs and can be interpreted as a relatively small difference if SMD <0.2 or relatively large difference if SMD ≥0.2. Baseline characteristics are named to align with the definition and baseline timepoint used in HOPE-B (see Section 8.3) and differences in definitions for Paradigm™ 2 are annotated where required, with key differences summarized here. Prior ABR was calculated during lead-in phase from HOPE-B where subjects received monitored prophylaxis and close monitoring, while this was captured as bleeding history within the last 12 months prior to study entry for Paradigm™ 2. The degree to which this difference in measurement affects interpretation is unclear. However, the mean ABR prior to screening captured from CRFs in HOPE-B was very similar to that captured during lead-in (4.06 versus 4.10, respectively). In HOPE-B, a target joint was defined as a joint which the subject has spontaneously bled into at least 3 times in a 6-month period and data used in this report reflect the definition applied to the lead-in period, while in Paradigm™ 2, the criteria for target joint was 3 or more bleeding episodes in a particular joint within a period of 6 months before trial.

Comparisons were made between the selected HOPE-B population and both the subgroup of patients from Paradigm™ 2 who received pre-study prophylaxis and the full Paradigm™ 2 population including a mix of pre-study prophylaxis and on-demand patients. For the prior-prophylaxis subgroup comparison, Paradigm™ 2 reported the estimated rate of bleeds prior to screening and prior FIX product, while prior FIX product class (EHL versus SHL) was inferred given that Paradigm™ 2 occurred before the commercial availability of EHL products. HOPE-B had a lower average ABR during lead-in phase than the number of bleeds prior to screening for Paradigm™ 2 (4.10 versus 7.49, respectively) (Collins et al., 2014). Additionally, 41.2% of the population from HOPE-B was on a SHL prior FIX product while 100% of all prior FIX products were assumed to be SHL for Paradigm™ 2. HOPE-B also had a wider range of prior FIX product, while Paradigm™ 2 only contained rFIX and pdFIX.

For the full population of Paradigm™ 2, many more baseline characteristics were reported. Populations were very similar in severity of haemophilia B, with 80.4% of patients with <1 IU/dL for HOPE-B versus 82.8% for Paradigm™ 2. Although the mean prior ABR was not reported for the full population of Paradigm™ 2, it would be expected to be much larger than that of HOPE-B, given 41.4% of patients in Paradigm™ 2 were receiving on-demand therapy prior to study and a much higher percentage of patients in Paradigm™ 2 had at least one target joint (3.9% for HOPE-B versus 51.7% for Paradigm™ 2). Patients in HOPE-B were on average older and heavier, reflecting the differential inclusion criteria whereby Paradigm™ 2 allowed adolescent patients and HOPE-B did not. The percentage of patients who were positive with HIV at baseline was lower in HOPE-B compared to Paradigm™ 2 (5.9% versus 10.3%, respectively) (Collins et al., 2014).

These noted differences in baseline factors ranked to be prognostic or treatment effect modifying may bias a relative treatment effect if not adjusted for or balanced between studies.

Table 81: Comparison of baseline characteristics between HOPE-B and Paradigm™ 2

Baseline Characteristic	Comparison with Prior Prophylaxis Subgroup from Paradigm™ 2			Comparison with Full Population from Paradigm™ 2		
	HOPE-B (N=51)	Paradigm™ 2 (N= 17)	SMD	HOPE-B (N=51)	Paradigm™ 2 (N=29)	SMD
Severity of haemophilia B[a], n (%)						
<1 IU/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 – 2 IU/dL	[redacted]			[redacted]	[redacted]	
Prior ABR[b,d], Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior FIX regimen[b], n (%)			[redacted]			
Prophylaxis	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
On-demand	[redacted]			[redacted]	[redacted]	
Prior presence of target joints[b,f], n (%)		[redacted]	[redacted]			[redacted]
0	[redacted]			[redacted]	[redacted]	
≥1	[redacted]			[redacted]	[redacted]	

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Baseline Characteristic	Comparison with Prior Prophylaxis Subgroup from Paradigm™ 2			Comparison with Full Population from Paradigm™ 2		
	HOPE-B (N=51)	Paradigm™ 2 (N= 17)	SMD	HOPE-B (N=51)	Paradigm™ 2 (N=29)	SMD
Age[c], years, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior FIX product class[b], n (%)			[redacted]			[redacted]
EHL	[redacted]	[redacted]		[redacted]	[redacted]	
SHL	[redacted]	[redacted]		[redacted]	[redacted]	
BMI[a], Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight[a], kg, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior FIX product[b], n (%)			[redacted]		[redacted]	[redacted]
rFIX	[redacted]	[redacted]		[redacted]		
pdFIX	[redacted]	[redacted]		[redacted]		
rIX-FP	[redacted]	[redacted]		[redacted]		
Other	[redacted]	[redacted]		[redacted]		
Family members with history of FIX inhibitor antibodies, n (%)		[redacted]	[redacted]			[redacted]
No	[redacted]			[redacted]	[redacted]	
Yes	[redacted]			[redacted]	[redacted]	
Missing/Unknown	[redacted]			[redacted]	[redacted]	
HIV status[a], n (%)			[redacted]			[redacted]
Positive	[redacted]			[redacted]	[redacted]	
Negative	[redacted]			[redacted]	[redacted]	
Duration of diagnosed haemophilia B[c], years, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n(%)		[redacted]	[redacted]			[redacted]
White	[redacted]			[redacted]	[redacted]	
Non-white	[redacted]			[redacted]	[redacted]	
Missing	[redacted]			[redacted]	[redacted]	

Note:

[a] Data for covariate were taken at screening for HOPE-B and the comparator trial.

[b] Data for covariate were taken during the lead-in period for HOPE-B and were taken at screening for the comparator trial.

[c] Data for covariate were taken after the lead-in period for HOPE-B and were taken at screening for the comparator trial.

[d] Bleeding history within the last 12 months prior to study entry for Paradigm™ 2. Reported as estimated rate without any source of variability.

[f] Target joints was identified at screening for Paradigm™ 2, defined as a target joint was defined as 3 or more bleeding episodes in a particular joint within a period of 6 months before trial.

[g] Based on data available, the prior FIX product class (EHL vs. SHL) was assumed to be SHL for all patients from the 40 IU/kg weekly prophylaxis group of Paradigm™ 2.

Abbreviations: ABR, Annualized bleeding rate; BMI, Body mass index; dL, Deciliters; EHL, Extended half-life; FIX, Factor IX; HIV, Human immunodeficiency virus; IU, International unit; NA, Not applicable; NR, Not reported; pdFIX, Plasma–derived factor IX; rFIX, Recombinant Factor IX; rIX-FP, Recombinant fusion protein linking recombinant coagulation Factor IX with recombinant albumin; SD, Standard deviation; SHL, Short half-life; SMD, Standardized mean difference.

Sources: CSL Behring (2022e).

21.1.4. Outcomes

The three bleeding outcomes (ABR, AsBR and % 0 ABR), and two PROs (EQ-5D and Haem-A-QoL total score CFB) were assessed for this analysis. Annualized joint bleeding rate, % 0 AsBR, % 0 AjBR and annual FIX consumption were not reported for Paradigm™ 2. The definition of ABR from HOPE-B was carefully examined against the definition reported in Paradigm™ 2 (see Section below). Annualized spontaneous bleeding rate was defined and calculated as for ABR, but with restricting bleeding events to those that were spontaneous only, for the respective definitions.

21.1.4.1 Annual bleeding rate definitions

A summary of ABR definition reported by Paradigm™ 2 (Collins et al., 2014) and ABR definition selected from HOPE-B (CSL Behring, 2021c) is presented in able 82. For HOPE-B, the definition for ABR from sensitivity analysis 6 was selected as this best matches the definitions defined in other comparator trials, including Paradigm™ 2. This definition was chosen because bleeds were counted only when they met the following two criteria: (1) were treated with exogenous FIX, and (2) were validated to be "new and true". This at least partially aligns with the definition used in Paradigm™ 2, where only those bleeds that were treated were analyzed (Collins et al., 2014). The key remaining differences or uncertainties (due to lack of reporting for Paradigm™ 2) between the definitions are:

- The definitions of time at risk,
- The type of bleeds being counted, and
- The timing of bleeds being counted.

For Paradigm™ 2, subjects reported the number of doses and the amount of Refixia used to treat bleeds, though it was unclear whether bleeds had to be considered new and true. HOPE-B considered bleeds that were both treated with exogenous FIX and determined to be new and true. This is a potential source of bias in the comparison. For Paradigm™ 2, the time at risk was not clearly defined and is another potential source of bias in the comparison. Finally, the ABR for Refixia was based on only counting spontaneous and traumatic bleeding events, while the ABR for Hemgenix was any bleeding event. This difference is likely to bias indirect comparisons of ABR in favor of Refixia given that more types of bleeding events were included in calculations for HOPE-B. However, given most bleeding events are likely to be classified as spontaneous or traumatic, any bias is expected to be minimal. Overall, it is uncertain whether these remaining differences are likely to bias the ITC of ABR between Hemgenix and Refixia in a meaningful way

The % 0 ABR outcome available for comparison has the same limitations as the ABR and AsBR outcomes. However, the shorter follow-up time in Paradigm™ 2 (52 (±2) weeks) compared to median follow-up time from 7 – 24 Month period within the 24-month data-cut of HOPE-B (approximately 1.5 years in the ITC analysis set, calculated by time at risk reported in HOPE B IPD) is likely to bias the comparison of these % 0 ABR outcome in favor of Refixia, because patients in Paradigm™ 2 have a shorter time for a bleed to occur.

able 82: ABR definitions for the HOPE-B (Hemgenix) versus Paradigm™ 2 (Refixia) comparison

Trial	ABR Definition
HOPE-B[a]	Bleed count: Any bleeding events between stable FIX expression and study completion or early withdrawal that were both treated with exogenous FIX and determined to be new and true Time at risk: Time between stable FIX expression and study completion or early withdrawal, excluding time within 5 half-lives subsequent to exogenous FIX use
Paradigm™ 2	Bleed count: Spontaneous and traumatic bleeds that were treated. Time at risk: Unclear

Note: [a]Definition was selected from a series of analyses for the HOPE-B trial. This definition represents that from sensitivity analysis 6.

Abbreviations: ABR, Annualized bleeding rate; FIX, Factor IX.

Source: CSL Behring (2022i), Collins et al. (2014).

21.1.4.2 Comparison of bleeding outcomes between HOPE-B and Paradigm™ 2

For the HOPE-B and Paradigm™ 2 trials, bleeding outcomes, including ABR and AsBR are shown in Table 83. Rates for HOPE-B are based on Month 7 – 24 post-treatment follow-up period data and estimated with an intercept-only Poisson regression model to match the methodology for the rates reported for Paradigm™ 2. Although HOPE-B sensitivity analysis 6 outcome definition was deemed most comparable to that reported for Paradigm™ 2, the ABR and AsBR values based on the primary endpoint definition of HOPE-B are also included in this table for comparison. For all bleeding outcomes and for both definitions of ABR from HOPE-B, the unmatched and unadjusted (naïve) rate ratio shows that Hemgenix is favored over Refixia. Proportions of patients with zero ABR are reported in Table 79 and favor Hemgenix wherever a comparison is possible.

Table 83: Bleeding outcomes (ABR, AsBR) for HOPE-B and Paradigm™ 2 Trials

	Comparison with Prior Prophylaxis Subgroup from Paradigm™ 2			Comparison with Full Population from Paradigm™ 2			Treatment Favored
Outcome	HOPE-B (N=51)[a]	Paradigm™ 2 (N=17)[b]	Naïve Rate Ratio	HOPE-B (N=51)[a]	Paradigm™ 2 (N=29)[b]	Naïve Rate Ratio	
ABR, per Sensitivity Analysis 6 from HOPE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABR, per Primary Analysis from HOPE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AsBR, per Sensitivity Analysis 6 from HOPE-Bc	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AsBR, per Primary Analysis from HOPE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note:

[a] Rates per person year estimated from Poisson, intercept-only model to match the methods for reported rates from Paradigm™ 2.

[b] Estimated rates for prophylaxis patients are based on a Poisson regression model.

[c] AsBR per sensitivity analysis 6 of HOPE-B was derived in HOPE-B for this analysis and values are not present in the clinical study report.

Abbreviations: ABR, Annualized bleeding rate; AsBR, Annualized spontaneous bleeding rate; NR, Not reported; NA, Not applicable.

Source: Collins et al. (2014), CSL Behring (2022), CSL Behring (2022i).

Table 84: Bleeding outcomes (% 0 ABR) for HOPE-B and Paradigm™ 2 Trials

	Comparison with Prior Prophylaxis Subgroup from Paradigm™ 2			Comparison with Full Population from Paradigm™ 2			Treatment Favored
Outcome	HOPE-B (N=51)[a,b]	Paradigm™ 2 (N=17)[b]	Naïve Odds Ratio	HOPE-B (N=51)[a,b]	Paradigm™ 2 (N=29)[b]	Naïve Odds Ratio	
% 0 ABR, per Sensitivity Analysis 6 from HOPE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% 0 ABR, per Primary Analysis from HOPE-B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note:

a Proportions evaluated from Month 7 – 24 post-treatment follow-up period of HOPE-B.

b Proportion of patients with 0 ABR.

Abbreviations: ABR, Annualized bleeding rate; AsBR, Annualized spontaneous bleeding rate; NR, not reported; NA, Not applicable.

Source: Collins et al. (2014); CSL Behring (2022)CSL Behring (2022i).

21.1.4.3 Comparison of PRO outcomes between HOPE-B and Paradigm™ 2

The health-related quality of life of patients in the HOPE-B and Paradigm™ 2 trials was assessed as change from baseline in Haem-A-QoL total score and EQ-5D index score to a post-treatment timepoint deemed most comparable between studies (CSL Behring, 2022e). The post-treatment timepoint selected for Paradigm™ 2 was the end of trial (i.e., presumed to be the last visit at which an assessment was made; reporting was not clear). The post-treatment timepoint selected for HOPE-B was 24 months, which was the latest timepoint for which Haem-A-QoL or EQ-5D data was collected in the 24-month data-cut of HOPE-B. To align with Paradigm™ 2 and strengthen the comparison, patients from HOPE-B who did not report Haem-A-QoL or EQ-5D data at 24 months were given their last-reported post-treatment Haem-A-QoL or EQ-5D value (i.e., 12 months post-treatment or six months post-treatment if 12 months post-treatment data was missing). Patients were considered to have missing values If last-reported post-treatment data was not available.

Between the 18-month and 24-month data-cuts of HOPE-B, an additional data-handling rule was implemented whereby Haem-A-QoL total scores were no longer calculated if more than seven of the 43 Haem-A-QoL domains were missing data. For the current analysis, this resulted in the 24-month data-cut having one less patient with a valid post-treatment Haem-A-QoL total score and two patients with different Haem-A-QoL total score baseline timepoints (and therefore values), relative to what was available in the 18-month data-cut analysis.

Mean change from baseline for both outcomes in HOPE-B and Paradigm™ 2 full population are presented in Table 85. along with the unmatched and unadjusted (naïve) difference in means, showing similarity between Hemgenix and Refixia. Note that a higher Haem-A-QoL total score represents greater impairment. This means that within a single study, a lower (more negative) change from baseline represents a greater improvement for the patients.

Table 85: Change from baseline in Haem-A-QoL and EQ-5D for HOPE-B and Paradigm™ 2 trials

Outcome	HOPE-B (N=51)	Paradigm™ 2 (N=29)	Naïve Difference in Means	Treatment Favored
Haem-A-QoL, change from baseline[a]	XXXX	XXX	XXX	XXXXXX
EQ-5D, change from baseline[a]	XXXX	XXX	XXX	XXXXXXXX

Note:

[a] Post-treatment data used was the latest timepoint available (i.e., end of trial). For HOPE-B, data from 24-month post-treatment timepoint was the latest timepoint available and patients from HOPE-B who did not report Haem-A-QoL or EQ-5D data at 24 months were given their last-reported post-treatment Haem-A-QoL or EQ-5D value (i.e., 12 months post-treatment or 6 months post-treatment if 12 months post-treatment data was missing). Baseline Haem-A-QoL and EQ-5D data for HOPE-B was the final lead-in period visit; the latest timepoint with such data available before the post-treatment period. If Haem-A-QoL or EQ-5D data was unavailable at the final lead-in period visit, the next latest timepoint before the post-treatment period was used. One patient did not have any post-treatment Haem-A-QoL data and was considered as missing value.

Abbreviations: EQ-5D, EuroQol-5 dimensions-5 levels; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults.

Source: CSL Behring (2022e).

22. Appendix G Extrapolation

Extrapolation was not performed on the clinical efficacy data (i.e. ABR) used in the model (section 9.2). However, a mixed linear model was used to estimate the durability of effect. As discussed in section 9.4, duration is an important component of gene therapy. It determines for the period in which therapy maintains its full effect and at which point the clinical effect decreases over time.

To assess the durability, statistical analysis was performed to estimate the long-term durability of FIX activity levels after receiving Hemgenix, using data from the Phase IIb and Phase III clinical trials for Hemgenix (Shah et al., 2023, Von Drygalski et al., 2019, CSL Behring, 2022i, CSL Behring, 2024). Statistical approaches are commonly used to make such prediction and given the limited data set, linear mixed models was assessed as being a good option for modelling durability because it allows for information sharing across subgroups and since not all of the include participants had

FIX activity levels recorded at each visit, this approach provides a simple alternative to handle missing data under the missing at random assumption without imputation. The covariates included in the model included time since analysis baseline (6-months-infusion) and pre-infusion AAV5 NAb status (negative or positive), with each participant having their own intercept and slope.

Two modelling approaches were used: Bayesian and Frequentist. The Bayesian approach is probabilistic and views the model parameters as random variables while the analysis data is fixed. The Frequentist approach views the parameters in the model as fixed values and data as a random sample of the population. As discussed in section 9.4 the Bayesian model was chosen due to its ability to account for uncertainty in future observations and the inherent uncertainty on durability of haemophilia B treatments. The durability model results for a FIX level of <2% and <5% are presented in Table 86.

Table 86: Durability of clinical effect

Year	FIX level <2%	FIX level <5%
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
10	[redacted]	[redacted]
15	[redacted]	[redacted]
20	[redacted]	[redacted]
25	[redacted]	[redacted]
30	[redacted]	[redacted]
35	[redacted]	[redacted]
40	[redacted]	[redacted]
45	[redacted]	[redacted]
50	[redacted]	[redacted]
55	[redacted]	[redacted]
60	[redacted]	[redacted]

Abbreviations: FIX, Factor IX.

Source: (CSL Behring, 2024).

A linear relationship was assumed between the log FIX activity and time based on the first 18 months of data.

For modelling, FIX levels were transformed from their original scale to log scale. This serves three main purposes. Firstly, the FIX activity levels on the original scale are presumed to have a log-normal distribution and the model fits the observed data well on the log scale. Secondly, the log-transformed outcome is robust to outliers and measurement error, thus reducing bias in predicting long-term FIX activity. Finally, the model estimates and predictions of FIX activity are always positive when transformed back to the original scale, thus remaining biologically plausible. Thus, the data were extrapolated up to 60 years assuming the same linear relationship on the log-scale (**Fejl! Henvisningskilde ikke fundet.**). Bayesian R squared was calculated according to Gelman (Gelman, 2018).

23. Appendix H Literature search for HRQoL data

A SLR of HRQoL studies was conducted to support heath technology assessment (HTA) submissions for Hemgenix for the treatment of adult patients with congenital haemophilia B with moderately severe or severe haemophilia B (FIX activity ≤2% of normal) for which the subject is on continuous routine FIX prophylaxis. The objective of this SLR was to identify HRQoL studies conducted in haemophilia B. Specifically, the objectives were:

1. What studies have been published into the HRQoL and PROs of adult male PWHB and their caregivers. How were these measured and what were the key findings?
2. What cost-effectiveness analysis evidence is available for treatment of haemophilia B?
3. What budget impact evidence is available for haemophilia B treatments?
4. What are the direct and indirect costs and resource use associated with the management of adult male PWHB?

23.1.1. Search strategy

The selection criteria specified in Table 87 was used to inform the inclusion of studies at first and second pass stages of the reviews. Studies published as abstracts, conference presentations or press releases were eligible if adequate data were provided in line with the inclusion criteria.

Table 87: Selection criteria to be used for HRQoL studies

Selection criteria	Inclusion criteria	Exclusion criteria
Population	• Males aged 18 and over with congenital haemophilia B	• Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	• Any intervention or procedure for the treatment of haemophilia B	• No intervention or procedures of interest
Outcomes	• Any relevant patient reported outcome, e.g.: • SF-36 • EQ-5D, (EQ-VAS) score • Haemophilia-Specific QoL (Haemo-QoL) • Haemophilia Joint Health Score (HJHS) • Impact on carers • Other PRO or HRQoL instruments	• No reported outcomes of interest
Study type	• RCTs • Non-RCTs • Observational studies • HRQoL elicitation studies • HRQoL validation studies • Economic evaluations: • Cost-utility analysis • EEACT	• Individual case study reports
Publication type	• Article, conference abstract, conference paper, article in press	• Short survey • Reviews • Letters • Comment articles
Language	• English	• Non-English

Abbreviations: EEACT, Economic evaluation alongside a clinical trial; FIX, Factor IX; HJHS, Hemophilia joint health score; HRQoL, Health-related quality of life; PRO, Patient reported outcomes; RCT, Randomized controlled trials; SLR, Systematic literature review.

Searches to identify evidence for all review questions were conducted in the following databases (databases updated daily):

Table 88: Registers included in the search

Database	Platform	Search strategy	Date of search
Embase	https://www.embase.com/	Structured search	Original: 18th August 2021 Updated: 17th October 2022
MEDLINE	https://www.nlm.nih.gov/medline/index.html	Structured search	Original: 18th August 2021 Updated: 17th October 2022
Cochrane Central Register of Controlled Trials (CENTRAL)	https://www.cochranelibrary.com/central/about-central	Structured search	Original: 18th August 2021 Updated: 17th October 2022
Cochrane Clinical Answers	https://www.cochranelibrary.com/cca/about	Structured search	Original: 18th August 2021 Updated: 17th October 2022

Grey literature searches included clinicaltrials.gov, searches of the manufacturer's repository of evidence, websites of manufacturers of comparator products, bibliographic searching of any SLRs identified during screening, and the following relevant congresses over the last two years:

Table 89: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
British Society for Haematology	62nd Annual Scientific Meeting of the British Society for Haematology 3–5 April 2022, Hybrid Meeting https://onlinelibrary.wiley.com/toc/13652141/2022/197/S1	Manual search	• hemophilia b: 0 • haemophilia b: 1 • blood clotting factor 9: 0 • factor ix: 1
European Haematology Association	EHA2022 Congress, Hybrid, 9-12 June 2022 https://journals.lww.com/hemasphere/Fulltext/2022/06003/Abstract_Book_for_the_27th_Congress_of_the.1.aspx	Manual search	• hemophilia b: 1 • haemophilia b: 0 • blood clotting factor 9: 0 • factor ix: 0
American Society of Haematology	63rd ASH Annual Meeting and Exposition December 11-14, 2021 https://ashpublications.org/blood/issue/138/Supplement%201	Manual search	• hemophilia b: 56 • haemophilia b: 14 • blood clotting factor 9: 9 • factor ix: 27
European Haemophilia Consortium	EHC 2021 Virtual Conference, 4-8 October 2021 Unable to find	Manual search	N/A
European Association for Haemophilia and Allied Disorders	15th Annual Congress of EAHAD, 2-4 February https://onlinelibrary.wiley.com/toc/13652516/2022/28/S1	Manual search	• hemophilia b: 11 • haemophilia b: 17 • blood clotting factor 9: 0 • factor ix: 14
International Society of	ISTH 2022 Congress, July 9-13, 2022 https://onlinelibrary.wiley.com/toc/24750379/2022/6/S1	Manual search	• hemophilia b: 35 • haemophilia b: 14

Conference	Source of abstracts	Search strategy	Words/terms searched
Thrombosis and Haemostasis (ISTH)	https://academy.isth.org/isth		• blood clotting factor 9: 0 • factor ix: 32
World Federation of Hemophilia (WFH)	8–11 May 2022, Montreal and Virtual https://onlinelibrary.wiley.com/toc/13652516/2022/28/S3	Manual search	• hemophilia b: 4 • haemophilia b: • blood clotting factor 9 • factor ix
The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	https://www.ispor.org/heor-resources/presentations-database/search	Manual search	2019 to 2022: • hemophilia b: 21 • haemophilia b: 16 • blood clotting factor 9: 0 • factor ix: 12
National Institute for Health and Care Excellence (NICE)	National Institute for Health and Care Excellence (NICE) (via https://www.nice.org.uk/) NICE was searched in original review, so these numbers of hits are for results from August 2021 only.	Manual search	• hemophilia b: 4 • haemophilia b: 4 • blood clotting factor 9: 0 • factor ix: 1
Pharmaceutical Benefits Advisory Committee (PBAC)	• Pharmaceutical Benefits Advisory Committee (PBAC) (via https://pbac.pbs.gov.au/) PBAC was searched in original review, so these numbers of hits are for results from August 2021 only.	Manual search	• hemophilia b: 0 • haemophilia b: 0 • blood clotting factor 9: 0 • factor ix: 0
Canadian Agency for Drugs and Technologies in Health (CADTH)	• Canadian Agency for Drugs and Technologies in Health (CADTH) (via https://www.cadth.ca/) CADTH was searched in original review, so these numbers of hits are for results from August 2021 only.	Manual search	• hemophilia b: 2 • haemophilia b: 2 • blood clotting factor 9: 1 • factor ix: 1
Scottish Medicines Consortium (SMC)	• Scottish Medicines Consortium (SMC) (via https://www.scottishmedicines.org.uk/) SMC was searched in original review, so these numbers of hits are for results from August 2021 only.	Manual search	• hemophilia b: 3 • haemophilia b: 3 • blood clotting factor 9: 0 • factor ix: 0
All Wales Medicines Strategy Group (AWMSG)	All Wales Medicines Strategy Group (AWMSG) (via http://www.awmsg.org/)	Manual search	• hemophilia b: 3 • haemophilia b: 3 • 9*: 0 • ix* : 1 * 9 and ix shortened from blood clotting factor 9 and factor ix as this website was searching for each word not together, for example 'factor OR ix' not 'factor AND ix' with the full term 'factor ix'.
National Centre for Pharmacoeconomics (NCPE)	National Centre for Pharmacoeconomics (NCPE) (via https://www.ncpe.ie/)	Manual search	• hemophilia b: 278 • haemophilia b: 278

Conference	Source of abstracts	Search strategy	Words/terms searched
			• blood clotting factor 9: 219
clinicaltrials.gov	https://clinicaltrials.gov/	Manual search	
Manufacturer's repository of evidence	Publications or congress abstracts to be provided by CSL	Manual search	
Websites of manufacturers of comparator products	• BeneFIX: https://www.benefix.com/ • Rixubis: https://www.rixubis.com/ • Ixinity: https://www.ixinity.com/ • Alprolix: https://www.alprolix.com/ • Idelvion: https://www.idelvion.com/ • Rebinyn: https://www.rebinyn.com/	Manual search	

Table 90: Search terms for economic and QoL SLR in MEDLINE (via Ovid)

No.	Query	Results
#1	[redacted]	9648
#2	[redacted]	402299
#3	[redacted]	362177
#4	[redacted]	1307761

No.	Query	Results
#5	[redacted]	1936294
#6	[redacted]	561
#7	[redacted]	37

Table 91: Search terms for economic and QoL SLR in Embase (via Ovid)

No.	Query	Results
#1	[redacted]	17771
#2	[redacted]	1074753
#3	[redacted]	671507
#4	[redacted]	2146696
#5	[redacted]	3449331
#6	[redacted]	2249
#7	[redacted]	106

Table 92: Search terms for economic SLR in Cochrane (CDSR and CENTRAL)

No.	Query	Results
#1	[redacted]	717
#2	[redacted]	30729

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No.	Query	Results
	[redacted]	
#3	[redacted]	118310
#4	[redacted]	229535
#5	[redacted]	336247
#6	[redacted]	34

Table 93: Centre for Reviews and Dissemination database, DARE, NHS EED, HTA database (via york.ac.uk/crd)

No.	Query	Results
#1	[redacted]	24

Table 94: Econlit

No.	Query	Results
#1	[redacted]	0

Abbreviations: DARE, Database of Abstracts of Reviews of Effects; HTA, Health technology assessment; NHS EED, National Health Service Economic Evaluation Database; SLR, Systematic literature review.

Table 95: ScHARRHUD database (https://www.scharrhud.org/index.php?home)

No.	Query	Results
#1	[redacted]	2

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram illustrated in Table 96 demonstrates how references were reviewed and extracted in the original reviews and Table 97 for the update review.

In the original review (searched for clinical, economic, cost and resource use and HRQoL evidence simultaneously) the database searches retrieved 2,218 references, of which 154 were duplicates, leaving 2,064 unique references for first

pass screening. Of the 827 full texts assessed at second pass, 378 were included, including 25 identified through grey literature, and 247 were extracted overall. Overall, three RCTs, 172 non-RCTs, five cost-effectiveness studies, four budget impact studies, 17 HRQoL studies and 46 cost and resource use studies met the selection criteria following the first and second pass of the clinical studies review and were extracted.

In the HRQoL update review the database searches retrieved 203 references, of which 15 were duplicates. Of the 188 titles and abstracts screened with the eligibility criteria, 104 references did not meet the criteria. Hence, full texts of the remaining 84 references were retrieved and reviewed based on the eligibility criteria, after which 10 publications were included, including one identified through grey literature searches.

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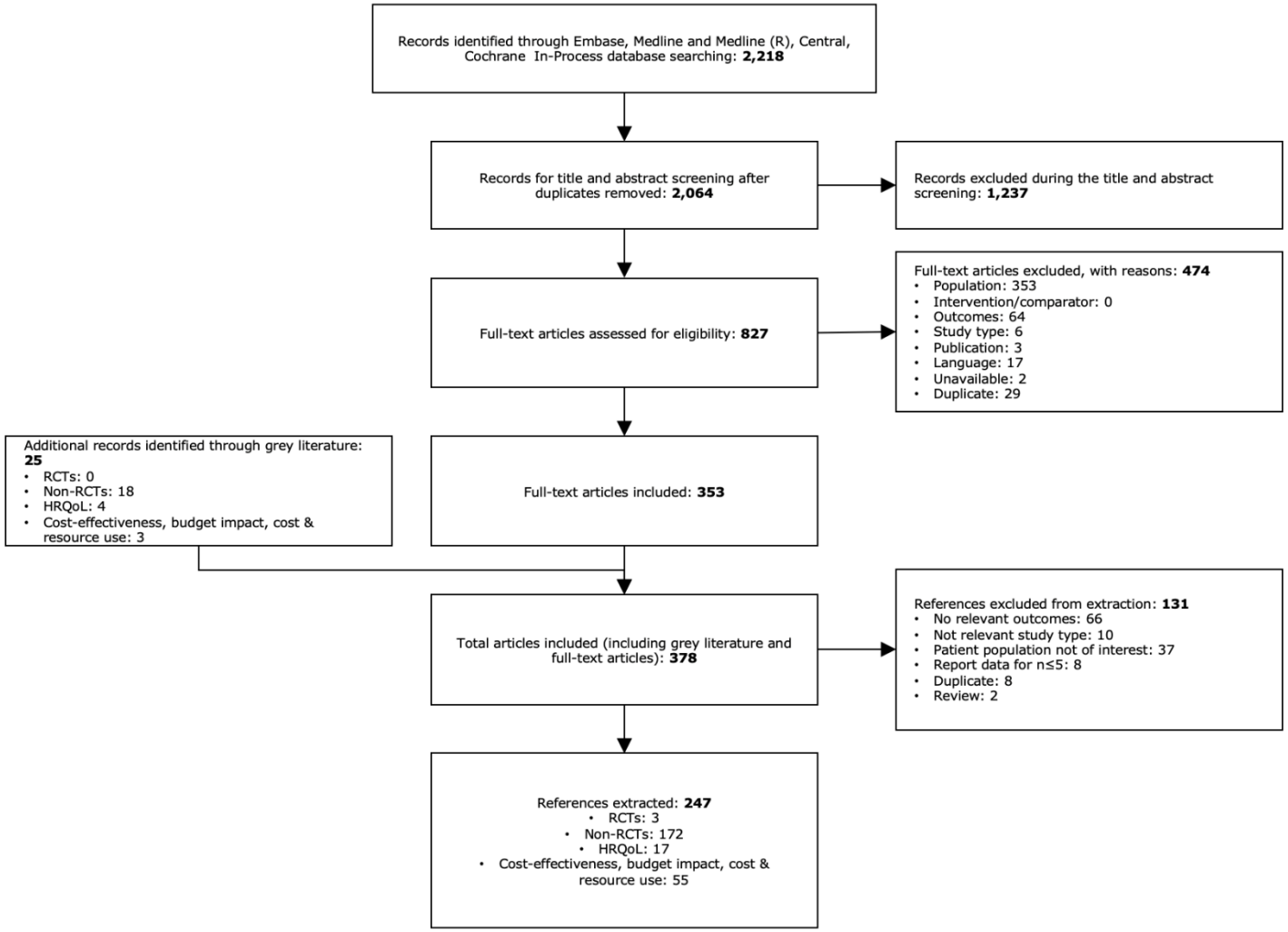
Table 96: Original review PRISMA diagram



Abbreviations: HRQoL, Health-related quality of life; RCT, Randomized controlled trial.

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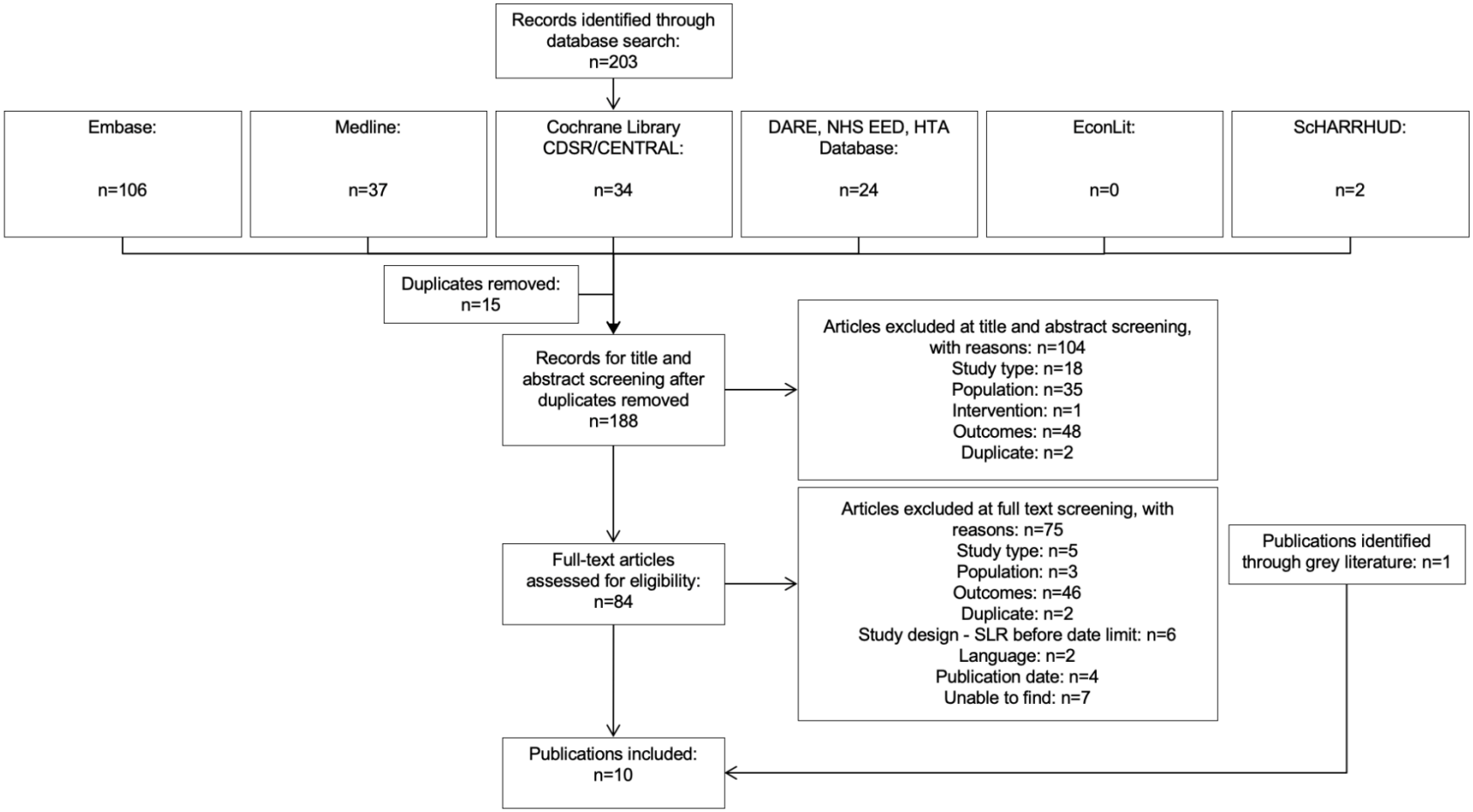
Table 97: Update review QoL PRISMA diagram



Abbreviations: QoL, Quality of life; SLR, Systematic literature review.

None of the HRQoL publications which were identified in the SLR were used in the current cost-effectiveness model.

23.1.2. Quality assessment and generalizability of estimates

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers, or by consulting a third reviewer if necessary. Data from each publication were extracted into a data collection form (Excel-based with tables suitably formatted to align with NICE SLR template) and developed in line with the University of York CRD and NICE reporting requirements (Centre for and Dissemination, 2009, Nice, 2015).

Each RCT identified in the SLR underwent a comprehensive quality assessment using NICE guidelines (Centre for and Dissemination, 2009, Nice, 2015).

23.1.3. Unpublished data

The QoL data used in the model (24-month data cut from the HOPE-B trial) is unpublished.

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24. Appendix I Mapping of HRQoL data

For the HRQoL data used in the health economic model no mapping of HRQoL data was conducted. The only transformation conducted on the post-treatment 24 month utilities values for Hemgenix, taken from the HOPE-B data, was to appropriately weight the values using the Jensen et al. 2021 Danish EQ-5D-5L value set (Jensen et al., 2021).

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25. Appendix J Data of import tance publish ed after

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25.1.1. Hemgenix Phase III study (HOPE-B) 36 months post dose

Recently 36-month follow-up data have become available and presented (Pipe et al., 2023); of 54 participants who received etranacogene dezaparvovec, 52 completed 36 months of follow-up. The results are summarized as follows:
Mean annualized bleeding rate (ABR) for all bleeds during Months 7-36 post-treatment was significantly reduced by 64% (mean ABR 1.52) compared with the ≥6-month lead-in period (mean ABR 4.17; P=0.0004). Total number of bleeds (all types) were 136 during the ≥6-month lead-in period and decreased to 55 during Year 1, 48 during Year 2, and 37 during Year 3 post-treatment. Median [range] bleeds per participant decreased from 2.0 [0-10] during the lead-in period and remained stable to 0.0 [0-4] during Year 1, 0.0 [0-10] during Year 2, and 0.0 [0-8] during Year 3. Superior bleeding protection was in line with the level of transgene-derived endogenous FIX expression.

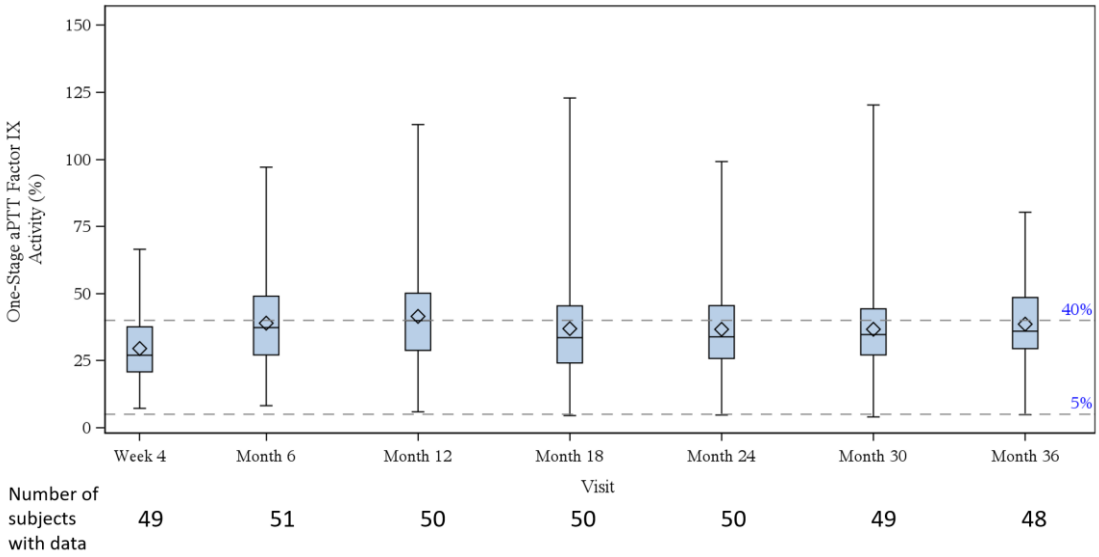
The mean ±SD (median; range) endogenous FIX activity level (i.e. in the absence of exogenous FIX exposure) of participants was 41.5 IU/dL ±21.7 (39.9; 5.9-113, n=50) at Year 1, 36.7 IU/dL ±19.0 (33.9; 4.7-99.2, n=50) at Year 2, and sustained at 38.6 IU/dL ±17.8 (36.0; 4.8-80.3, n=48) at Year 3 post-treatment (see **Fejl! Henvisningskilde ikke fundet.**). Pharmacodynamic profile was not significantly different in participants with AA5 NAb undetected or titer ≤1:678.

At 3 years post-treatment, 51 (94%) remained free of continuous FIX prophylaxis. One participant who lacked efficacy (highest AAV5 NAbs titer of 1:3212) and 1 who received a 10% partial dose of treatment did not discontinue prophylaxis; 1 participant eventually had his FIX levels declined to 2-5% range; his bleeding phenotype returned, and he resumed prophylaxis per protocol at month 30 post-treatment. During Year 2 and Year 3 post-treatment, 37 (70%) and 39 (75%) participants received no FIX infusion, respectively. Overall mean annualized FIX consumption decreased by 96% over 3 years post-treatment compared to the ≥6-month lead-in period (–246,763 IU/kg/participant, including those receiving FIX prophylaxis post-treatment; P<0.0001).

During the 3 years post-dose, all participants experienced at least 1 treatment-emergent AE (TEAE); of 709 events, 541 (76%) were mild, 137 (19%) were moderate, and 31 (4%) were severe. There were no serious AEs related to treatment. A total of 38/54 (70%) participants experienced 96 TRAEs, of which 95% occurred before 6 months post-treatment. The most common TRAE was an increase in alanine transaminase (ALT), for which 9

(16.7%) participants received supportive care with reactive corticosteroids for a mean duration of 81.4 days (SD: 28.6; range: 51-130 days). No new deaths, no new HCC, and no late treatment-related ALT elevations or thromboembolic events were reported.

Figure 28.27 Uncontaminated endogenous FIX activity after Hemgenix administration



25.1.2. AMT-061 (Hemgenix) Phase IIb study 48 months post dose

The three first patients to receive etranacogene dezaparvovec (Hemgenix) have now been followed for 48 months after treatment (von Drygalski et al., 2024):

- At month 48 (longest follow-up of treated patient to date), uncontaminated samples were available for all 3 subjects treated. Mean ± SD FIX activity was stable at 45 ±2.76 %, and median FIX activity was at 44.1%, as measured by one-stage aPTT-based assay. The 3 patients, individual factor FIX activity levels were measured at 44.1 %, 48.1 % and 42.8 % by a central laboratory one-stage aPTT-based assay, see **Fejl! Henvisningskilde ikke fundet.**.
- At 4 years after administration data cut-off, there were no new bleeding episodes reported between 36 and 48 months of follow-up. Consistent with absence of new bleeding episodes, the ABR for the cumulative period of 4 years decreased from 0.22 to 0.17.
- At year 4 of follow-up data cut-off, all subjects remained prophylaxis-free, consistent with the mean FIX activity levels and absence of bleeding. Year 4, FIX consumption was zero for all participants.

Except for one patient who experienced 2 mild AEs possibly treatment related shortly after dosing, no treatment related AEs have been reported in this study and after four years there are still no thrombosis events.

Figure 29. Mean FIX activity levels over time in AMT-061 (Hemgenix) Phase IIb study

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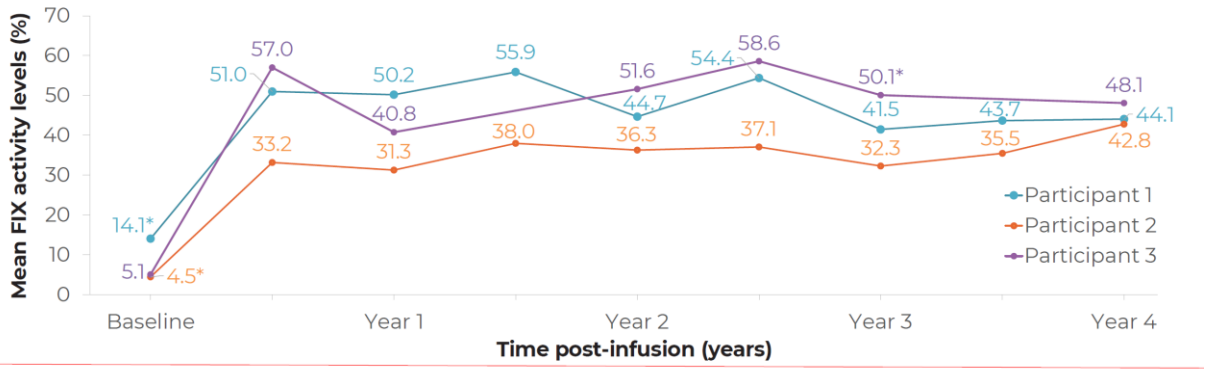

FIX activity measured by using a one-stage aPTT assay. Samples at baseline may have included activity from exogenous FIX replacement. *Contaminated result from a blood sample obtained within 5 half-lives of previous FIX therapy. aPTT, activated partial thromboplastin time; FIX, factor IX.

25.1.3. AMT-060 Phase I/IIa study 6 years post dose and findings in patients more than 10 years after treatment with scAAV2/8-LP1-Hfixco Adeno-Associated Virus Gene Therapy

Etranacogene dezaparvovec (Hemgenix) is the end-result of small but important progressive modifications to improve efficacy and safety during more than ten years of research. The basic concept of *in vivo F9* gene transfer to hepatocytes using an AAV derived vector, to achieve effective endogenous FIX production compensating for congenital FIX deficiency (haemophilia B), remains unchanged since trials at St Jude hospital (Nathwani et al., 2011). As Hemgenix shares many properties with its predecessors (Figure 30), it is relevant to consider available long-term data from early gene therapy trials when discussing the expectations concerning the long-term results of Hemgenix.

Figure 28. Evolution of AAV vectors for haemophilia B gene therapy

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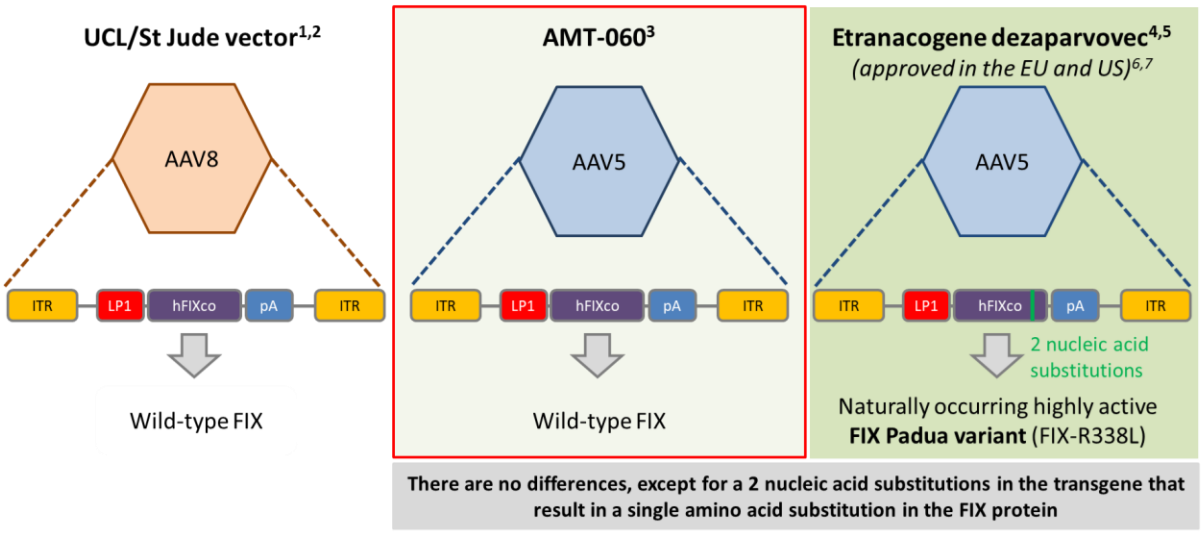
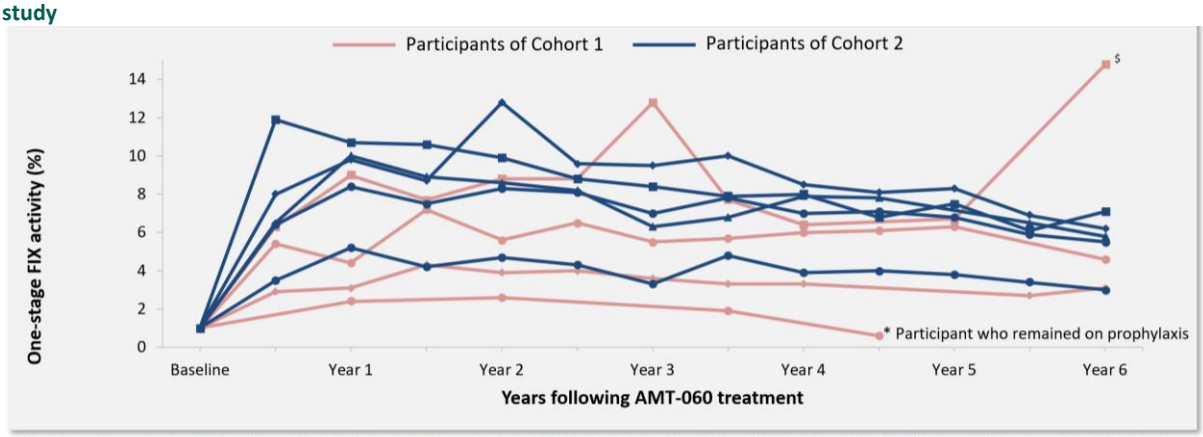


AAV, adeno-associated virus; FIX, factor IX; ITR, inverted terminal repeat; LP1, liver promoter 1; pA, poly A; rAAV, recombinant adeno-associated virus.
1. Nathwani AC et al. N Engl J Med 2011:365(25):2357–65; 2. Nathwani AC et al. N Engl J Med 2014;371(21):1994–2004; 3. Miesbach W et al. Blood 2018;131(9):1022–31; 4. von Drygalski A et al. Blood Adv 2023;7(19):5671–79; 5. Pipe SW et al. N Engl J Med 2023;388(8):706–18; 6. HEMGENIX Summary of Product Characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/hemgenix-epar-product-information_en.pdf (Accessed January 2024); 7. HEMGENIX Prescribing Information. Available at https://labeling.cslbehring.com/PI/US/Hemgenix/EN/Hemgenix-Prescribing-Information.pdf (Accessed January 2024).

Hemgenix is the same as AMT-060 except for a 2 nucleic acid substitution so that the Hemgenix transgene codes for the Padua FIX variant instead of ordinary (wild-type) FIX. The Padua FIX activity is approximately six times higher per unit protein than wild type FIX resulting in much higher plasma FIX activity after Hemgenix treatment than after AMT-060 when using the same dose and hepatocyte FIX protein production is similar (see chapter 6.3.1.). 10 patients were included in the AMT-060 phase I/IIa; 5 patients received $5 \cdot 10^{12}$ gc/kg and 5 patients received the higher dose $2 \cdot 10^{13}$ gc/kg which was later chosen for the phase IIb and the phase III HOPE-B trials. $2 \cdot 10^{13}$ gc/kg is the dose recommended in the SPC for Hemgenix. AMT-060 phase I/IIa study was a 5-year-study, but after completion the participants were offered inclusion into an extension study. All initial patients, except one patient in the $5 \cdot 10^{12}$ gc/kg cohort, participated in the extension study. Recently 6-year AMT-060 post-dose data were presented for these nine patients (Miesbach et al., 2024). Despite much lower median FIX activity than seen after Hemgenix the FIX one-stage activity remained stable 6-years post AMT-060 and all patients except one in the $5 \cdot 10^{12}$ gc/kg cohort remain free from prophylaxis (Figure 31). No new safety concerns were reported during year 6 (no TRAE) and safety profile remains favorable.

Figure 29. Median FIX activity at Year 6 of follow-up was 4.6% in Cohort 1 and 5.8% in Cohort 2 in AMT-060 Phase I/IIa study



FIX activity, using the one-stage aPTT assay. Only uncontaminated (blood sampling did not occur within 5 half-lives of exogenous FIX use) values are included. Baseline FIX was imputed based on participant's historical haemophilia B severity.
$ potentially contaminated by exogenous FIX, query open
FIX, clotting factor IX; SD, standard deviation.

It is now more than 12 years since the first haemophilia B patients received AAV based gene therapy targeting hepatocytes in the scAAV2/8-LP1-Hfixco gene therapy study at the St Jude Hospital. The 10 patients received $2 \cdot 10^{11}$ vg/kg (n=2) cohort 1, $6 \cdot 10^{11}$ vg/kg (n=2) cohort 2, and $5 \cdot 10^{12}$ vg/kg (n=6) cohort 3. Follow up data presented

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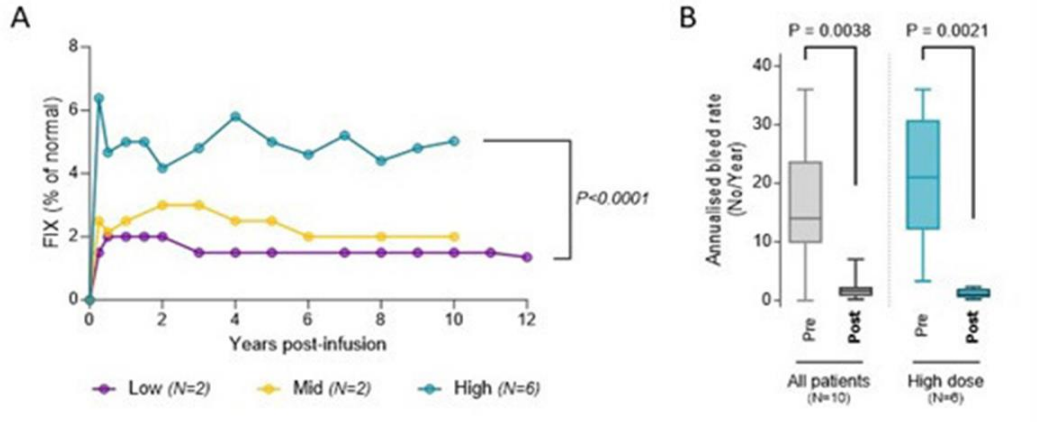
at the ASH meeting in December 2023 (Reiss et al., 2023) demonstrated still stable and therapeutic FIX activity levels (**Fejl! Henvisningskilde ikke fundet.**).

Figure 30. Factor IX activity (panel A) and annualized bleed rates over a 10 year period following systemic administration of scAAV2/8-LP1-hFIXco at 2·1011 vg/kg (low, n=2), 6·1011 vg/kg (mid, n=2), and 5·1012 vg/kg (high, n=6) dose levels



25.1.4. Impaired quality of life in Nordic patients with severe haemophilia B

There is a new QoL publication from the previously described B-NORD study cohort (section 6.1), which includes patients with severe haemophilia B (FIX <1%) registered at HTCs in Denmark, Finland, Norway and Sweden (Kihlberg et al., 2021, Kihlberg et al., 2023). HRQoL was assessed using the EQ-5D-3L questionnaire and joint health using haemophilia joint health score (HJHL). Participants were without current inhibitors, had a mean age of 40 years (SD 18 years), and all but one (98%) were on prophylactic treatment with factor concentrates. As many as 33% of the patients experienced problems with anxiety/depression. Moreover, while 46% reported problems with mobility, more than half (62%) of the patients reported problems with pain/discomfort. There was no difference in HRQoL scores between patients treated with EHL and those managed with SHL FIX products. Linear regression adjusted for age demonstrated that an increase in severity of joint damage was associated with a significant decrease in both EQ-5D index and EQ VAS score, confirming that impaired joint health has a significant negative impact on HRQoL (Kihlberg et al., 2023). To conclude, despite that the Nordic severe haemophilia B population is well-treated with the majority of patients being on prophylaxis, impaired QoL is reported with a high frequency of pain, mobility problems and anxiety/depression, indicating that areas of insufficient care exist (Kihlberg et al., 2023).

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