20 February 2023
EMA/OD/0000087180
EMADOC-1700519818-997049
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Hemgenix (etranacogene dezaparvovec)
Treatment of haemophilia B
EU/3/18/1999

Sponsor: CSL Behring GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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1. Product and administrative information

Product	
Designated active substance(s)	Recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA
Other name(s)	Hemgenix, recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA
International Non-Proprietary Name	Etranacogene dezaparvovec
Tradename	Hemgenix
Orphan condition	Treatment of haemophilia B
Sponsor's details:	CSL Behring GmbH Emil-Von-Behring-Strasse 76 Marbach 35041 Marburg Hassia Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	uniQure biopharma B.V.
COMP opinion	15 February 2018
EC decision	21 March 2018
EC registration number	EU/3/18/1999
Post-designation procedural history	
Transfer of sponsorship	Transfer from uniQure biopharma B.V. to CSL Behring GmbH – EC decision of 28 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Ilona G. Reischl / Heli Suila
Applicant	CSL Behring GmbH
Application submission	7 March 2022
Procedure start	24 March 2022
Procedure number	EMA/H/C/004827/0000
Invented name	Hemgenix
Proposed therapeutic indication	Treatment of severe Haemophilia B Further information on Hemgenix can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Hemgenix
CHMP opinion	15 December 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Enrico Costa
Sponsor's report submission	28 March 2022
COMP discussion	06-08 October 2022
COMP opinion (adoption via written procedure)	19 December 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA was considered justified based on non-clinical data in valid models of the condition showing significant improvement of circulating factor IX protein levels, and of factor IX activity levels;
- the condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury;
- the condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.
- in addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA will be of significant benefit to those affected by the condition. The product has a mechanism of action that offers the potential to reduce or eliminate the use of exogenous factor IX products currently authorised for the condition, and the sponsor has provided non-clinical data that demonstrate significant improvement of circulating factor IX protein and activity levels in valid models of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Haemophilia B is an X-linked congenital bleeding disorder, characterized by a decrease in Factor IX-plasma levels that produce a variety of bleeding symptoms of different severity. The condition accounts for 10-15% of the total haemophilia patients and predominantly affects males. Haemophilia B is caused by heterogeneous mutations in the FIX gene and is divided into three categories according to the coagulation factor activity present in blood: severe (<1% of normal circulating FIX), moderate (1–5% of normal circulating FIX), or mild (>5% to <40% of normal circulating FIX). Most bleeding occurs internally, into the joints or muscles and some bleeds can be life-threatening and require immediate treatment, generating relating complications: chronic synovitis, muscular atrophy, sites of bleeding in depth. Clinically apparent bleeding in haemophilia B typically correlates with the factor IX activity in plasma, although some patients may have variability in phenotypic bleeding with up to 10% of severe patients with a mild phenotype.

With the deficiency of FIX, activation of FX becomes severely impaired; in consequence, the thrombin burst becomes delayed and insufficient for normal haemostasis. The haemostatic plug formed for affected patients is therefore fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis and prolonged bleeding episodes.

The approved therapeutic indication "*Hemgenix is indicated for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors"* falls within the scope of the designated orphan condition "Treatment of haemophilia B".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The condition is considered life-threatening and chronically debilitating by the COMP due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury. Bleeding starts early in life and can include life threatening haemorrhages, such as intracranial and gastrointestinal haemorrhages. Adult patients are at risk for cerebral- or gastric haemorrhage, which can be life-threatening.

When severe, the disease leads to spontaneous life-threatening bleeding episodes leading to deaths and morbidity from chronic joint disease. When untreated, most individuals with severe haemophilia die from bleeding complications before 25 years of age. Compared to the general population, all-cause mortality is higher (by a factor of 2.69), and median life expectancy is lower (15 years less). Even in the era of adequate factor replacement products, the hallmark of haemophilia B is the lifelong propensity for bleeding.

Since designation, there have been no changes in the chronically debilitating or life-threatening nature of haemophilia B.

Number of people affected or at risk

At the time of initial orphan designation in 2011, the prevalence was estimated to be 0.23 per 10,000 persons in the EU community. The estimate has been re-reviewed as discussed below.

A comprehensive literature review was conducted using PubMed and Embase to identify recent publications (2011-2022) reporting the prevalence of haemophilia B in the European Union, UK, Norway, Iceland and Liechtenstein. Furthermore, the sponsor presents data from the World Federation of Haemophilia (WFH) Global Annual Survey 2020 (WFH, 2020).

Prevalence reported in the published literature:

Studies conducted in individual EU countries and UK show a range of prevalence from as low as 0.06 per 10,000 people in Poland up to 0.807 per 10,000 people in Ireland (Table 1).

Table 1. European prevalence of Haemophilia reported in the literature (2011-2022)

Country	Study period	Prevalence per 10,000 people	Source
Germany	2010-2011	0.19	Schramm *et al*, 2012
Ireland	1998-2006	0.807	Stonebraker *et al*, 2011a
Italy	2011-2015	0.14	Giampaolo *et al*, 2017
Poland	2009	0.06	Zdziarska *et al*, 2011
France	1991-2015	0.52*	Iorio *et al*, 2019
UK	1991-2015	0.47*	Iorio *et al*, 2019

**Prevalence at birth*

The prevalence of haemophilia B within the EU was reported to be between 2.69 and 8.07 per 100 000 males (Stonebraker et al, 2011a, Stonebraker et al, 2011b). Ireland had the highest reported haemophilia B prevalence with 8.07 per 100 000 males (Stonebraker et al, 2011a).

Schramm *et al*, describes 9,448 patients with bleeding disorders during 2010 and 2011 (Schramm *et al*, 2012), correlating to an estimated prevalence of 0.19 per 10,000 people with Haemophilia B based on a population of 80,222,065 people in Germany (Eurostat).

Giampaolo *et al* report 859 patients with haemophilia B in the Italian National Registry of Congenital Coagulopathies (NRCC). This correlates to a prevalence of haemophilia B in Italy of 0.14 per 10,000 people based on an Italian population of 60,665,551 in 2016 (Eurostat).

Reports of haemophilia in Poland have increased from 2006 to 2011 with a reported 2,366 haemophilia patients in Poland in 2011. Haemophilia B is claimed to be 9.8% of the cases and as such, this would equate to 232 patients with haemophilia B. The population of Poland in 2011 is estimated as 38,062,718 people and as such this would equate to 1 case of haemophilia B in every 164,063 people (0.06 per 10,000 people), (Zdziarska *et al*, 2011).

The proportion of cases of haemophilia B in the population of live male births over a period of time, also called prevalence at birth, was estimated by pooling data from national registries in France and the UK. This study reported prevalence at birth during 1991-2015 as 0.52 and 0.47 per 10,000 male births in France and the UK respectively (Iorio *et al*, 2019). Of note, a birth prevalence around 0.5 in 10,000 males translates to a complete prevalence of approximately 0.18 in 10,000 in the EU (based on recent EUROSTAT data of birth rate and general population).

World Federation of Haemophilia (WFH):

Based on the number of haemophilia patients identified in Europe from the WFH Global Annual Survey 2020 (WFH, 2020), it is estimated that there are 3,733 patients in a population of 236,734,660 in Europe in 2020 with haemophilia B. This equates to a prevalence of 1 in 63,416 people (0.15 per 10,000) for haemophilia B (Table 2).

Table 2. World Federation of Haemophilia global survey results for 2020 by country

Country	Population	People with Haemophilia B
Austria	8,917,205	149
Belgium	11,555,997	8
Czech Republic	10,698,896	0
Estonia	1,331,057	11
Finland	5,530,719	30
France	67,391,582	1,674
Germany	83,240,525	774
Greece	10,715,549	185
Hungary	9,749,763	239
Ireland	4,994,724	228
Latvia	1,901,548	85
Lithuania	2,794,700	27
Slovak Republic	5,458,827	84
Slovenia	2,100,126	30
Sweden	10,353,442	209
Total	***236,734,660***	***3,733***

In conclusion, the range of prevalence reported in the published literature is between 0.06-0.807 per 10,000 people with an approximate average of 0.26 per 10,000 persons. The European data from the WFH Global Annual Survey 2020 (WFH, 2020) reports a prevalence of 0.15 per 10,000 persons for haemophilia B. Based on this data the COMP concluded that a prevalence estimate of less than 0.3 per 10,000 adequately reflects the current prevalence of haemophilia B in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Standard therapy for patients with haemophilia B is Factor IX replacement therapy using recombinant FIX (rFIX) or plasma-derived products, and the sponsor provides a list of the authorised products (Table 1). Depending on the severity of the disease, patients may receive long term substitution (prophylaxis) and on-demand treatment for bleeding episodes. Factor VII is also authorised for use in patients with inhibitors.

In the context of this procedure, all authorized factor IX (FIX) products are considered satisfactory methods, which need to be considered for the significant benefit discussion of Hemgenix.

Table 1. List of currently authorized treatments for hemophilia B

Tradename **(active substance, authorisation holder)**	**Authorised indication**	**Method of Administration and Posology for Prophylactic Use**
FIX products		
Alprolix (eftrenonacog alfa, Biogen Idec Ltd)	Haemophilia B Treatment and prophylaxis of bleeding All age groups.	Intravenous injection Starting regimens are either 50 IU/kg once weekly or 100 IU/kg once every 10 days
BeneFix (albutrepenonacog alfa, Pfizer Limited)	Haemophilia B Treatment and prophylaxis of bleeding All age groups.	Intravenous infusion after reconstitution of the lyophilised powder 40 IU/kg at intervals of 3 to 4 days.
Idelvion (albutrepenonacog alfa, CSL Behring GmbH)	Haemophilia B Treatment and prophylaxis of bleeding All age groups.	Intravenous infusion after reconstitution of the lyophilised powder 35 to 50 IU/kg once weekly
Rixubis (nonacog gamma, Baxalta Innovations GmbH)	Haemophilia B Treatment and prophylaxis of bleeding All age groups.	Intravenous infusion after reconstitution of the lyophilised powder 40 to 60 IU/kg at intervals of 3 to 4 days.
Refixia (nonacog beta pegol, Novo Nordisk A/S)	Haemophilia B Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) 12 years and older.	Intravenous infusion after reconstitution of the lyophilised powder 40 IU/kg once weekly
By-passing agents		

Tradename **(active substance, authorisation holder)**	**Authorised indication**	**Method of Administration and Posology for Prophylactic Use**
NovoSeven (eptacog alfa, Novo Nordisk A/S)	Haemophilia B with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU) Treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures	Intravenous bolus injection after reconstitution of the lyophilised powder Not approved for prophylaxis
FEIBA (anti-inhibitor coagulant complex, Shire Pharmaceuticals Ltd)	Therapy and prophylaxis of bleeding in haemophilia B patients with inhibitors to factor IX (FEIBA UK Summary of Product Characteristics (SmPC))	Intravenous infusion after reconstitution of the lyophilised powder 70–100 U/kg body weight every other day

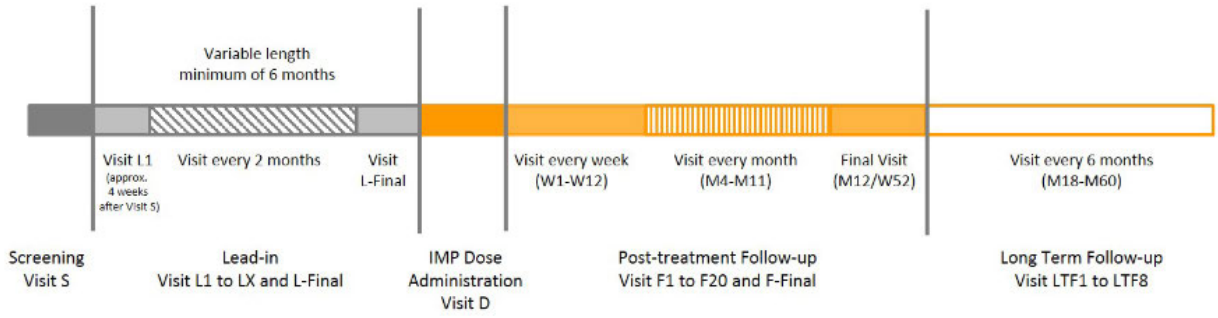
Significant benefit

The sponsor claims that their data from the pivotal licensing studies demonstrates that Hemgenix provides a clinically relevant advantage for patients with severe and moderately severe haemophilia B, as compared to currently authorized standard of care continuous Factor IX routine prophylaxis, including products with extended half-life.

The main evidence for efficacy stems from the pivotal clinical trial CT-AMT-061-02 (n=54; adult patients with severe or moderately severe FIX deficiency; non-randomized, open-label, single arm study; single dose of AMT-061 of 2×10^{13} gc/kg; intra-patient comparison, i.e. patients treated with Hemgenix are compared to their baseline parameters established during the 6 months lead-in period, where patients were treated with authorized Factor IX prophylaxis therapy; primary endpoint defined as: "*annualized bleeding rate (ABR) comparison between AMT-061 and prophylaxis for non-inferiority between the 52 weeks following stable FIX expression (6-18 months) post treatment (AMT-061) follow-up and the lead-in phase*"; at time of orphan maintenance review up to 2-year efficacy follow-up data available).

Figure 1.

Figure 1 Study Design Diagram



Abbreviations: D = dosing; F = post-treatment follow-up; IMP = investigational medicinal product; L = lead-in; LTF = long-term follow-up; M = Month; S = screening; W = week.
Source: Figure 2 of the Protocol (**Section 16.1.1.7**)

Table 2. Patient's treatment history in the pivotal study CT-AMT-061-02

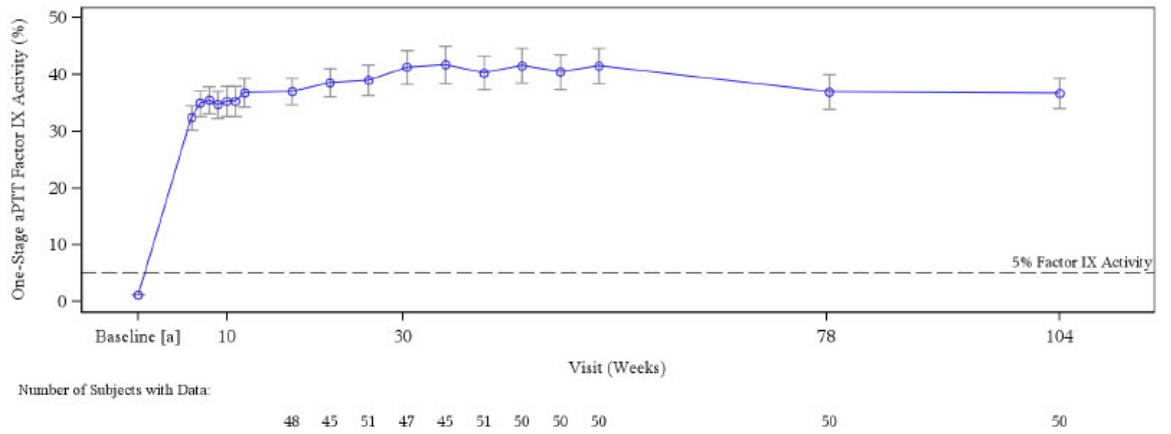
FIX Replacement Therapy Type, n (%)			
Prophylactic	67 (100.0)	54 (100.0)	53 (100.0)
On-demand	5 (7.5)	4 (7.4)	4 (7.5)
Most Recent Pre-Screening FIX Therapy Category, n (%)			
Extended Half-life	40 (59.7)	31 (57.4)	30 (56.6)
Standard Half-Life	27 (40.3)	23 (42.6)	23 (43.4)

The results of this pivotal clinical study show that a single administration of Hemgenix led to clinically relevant increases in endogenous Factor IX activity in the majority (52/54) of subjects and remained stable at 6 months, 12 months, 18 months, and 24 months after treatment, with mean FIX activity levels of approximately 40% (Figure 2). No subject showed supraphysiologic FIX activity.

Figure 2. Endogenous Factor IX activity following treatment with Hemgenix

Protocol: CT-AMT-061-02 AAV5-hFIXco-Padua

Figure 2.1.1.8 Mean Uncontaminated Central Laboratory One-Stage aPTT Factor IX Activity (%) +/- SE Over Time During the Post-Treatment Period
Analysis Set: Full Analysis Set



Number of Subjects with Data:

Baseline [a]	10		30						78	104
48	45	51	47	45	51	50	50	50	50	50

"Uncontaminated" means that the blood sample did not occur within 5 half-lives of exogenous factor IX use. Both the date and time of the exogenous factor IX use (start) and the blood sampling are considered in determining contamination. Factor IX levels beginning with the Week 6 assessment are used in the analysis. Subjects with zero uncontaminated central-laboratory post-AMT-061 values have their post-baseline values set equal to their baseline value.

[a] Baseline factor IX is imputed based on subject's historical hemophilia B severity documented on the CRF. If the subject has documented severe factor IX deficiency (factor IX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject has documented moderately severe factor IX deficiency (factor IX plasma level >= 1% and <= 2%), their baseline factor IX activity level is imputed as 2%. The SE is not provided at baseline.

The display of Number of Subjects With Data begins at Month 4.

Following treatment with Hemgenix and stable FIX expression, ABR was significantly reduced for all bleeding types overall including FIX-treated, spontaneous, traumatic, and joint bleeding episodes (Month 7 to 18 post-dose, primary efficacy endpoint). In the pivotal trial CT-AMT-061-02, the pre-specified non-inferiority analysis encompassing a comparison of ABR between the lead-in (4.19) and post-treatment (1.51) period was significant and non-inferiority to standard of care routine Factor IX prophylaxis could be declared. In addition, the secondary outcome of superiority over FIX prophylaxis could be shown. Importantly, superiority against the specific group of standard of care continuous routine Factor IX prophylaxis products with extended half-life could also be demonstrated. ABR was maintained for all bleeding types from Month 7 to 24 versus the Lead-in Period (64% reduction for all bleeding types vs the Lead-in Period), Table 3.

Table 3. Summary of bleeding episodes and annualized bleeding rate (pivotal study CT-AMT-061-02; full analysis set)

	All Bleeding Episodes			FIX-treated Bleeding Episodes			All Bleeding Episodes for Subjects with anti-AAV5 NAb <3000		
	≥6-month Lead- in Period (N = 54)	Month 7-18 (N = 54)	Month 7-24 (N = 54)	≥6-month Lead- in Period (N = 54)	Month 7-18 (N = 54)	Month 7-24 (N = 54	≥6-month Lead- in Period (N = 53)	Month 7-18 (N = 53)	Month 7-24 (N = 53)
Number of Subjects With a Bleeding Episode n (%)	40 (74.1)	20 (37.0)	27 (50.0)	37 (68.5)	15 (27.8)	19 (35.2)	40 (75.5)	19 (35.8)	26 (49.1)
Number of Subjects with Zero Bleeding Episodes, n (%)	14 (25.9)	34 (63.0)	27 (50.0)				13 (24.5)	34 (64.2)	27 (50.9)
Cumulative Number of Bleeding Episodes, n	136	54	74	118	30	43	136	49	69
Cumulative Number of Person-years Observed for Bleeding Episodes, n	33.12	49.78	74.56	33.12	49.78	74.56	32.60	49.77	74.56
Unadjusted ABR[1]	4.11	1.08	0.99	3.56	0.60	0.58	4.17	0.98	0.93
Adjusted ABR (95% CI)[2]	4.19 (3.22, 5.45)	1.51 (0.81, 2.82)	1.51 (0.83, 4.76)	3.65 (2.82, 4.74)	0.84 (0.41, 1.73)	0.99 (0.48, 2.03)	3.89 (2.93, 5.16)	1.07 (0.63, 1.82)	1.09 (0.67, 1.79)
Rate Ratio (Post-treatment/Lead-in)[2]		0.36	0.36		0.23	0.27		0.28	0.28
Two-sided 95% Wald CI[3]		0.20, 0.64	0.21, 0.63		0.12, 0.46	0.14, 0.54		0.17, 0.43	0.17, 0.46
p-value[4]		0.0002	0.0002		<0.0001	0.0001		<0.0001	<0.0001

Abbreviations: ABR = annualized bleeding rate; CI = confidence interval; FIX = Factor IX; NAb = neutralizing antibody.

Use of exogenous FIX as well as FIX infusion rate fell to approximately 3% of values reported during lead-in. The number of subjects who did not experience any bleeding event more than doubled during month 7-18 [34/54 (63.0%)] compared to baseline [14/54 (25.9%)]. This is considered a clinically relevant improvement over FIX-prophylaxis, because many spontaneous bleeds occur in joints and joint health continues to deteriorate over time despite the current standard of care FIX prophylaxis therapy. In fact, 20.4% of subjects reported joint bleeding episodes post-treatment until month 18, and 27.8% reported joint bleeds until month 24, while 59.3% of subjects reported such events during the lead-in period, which is a clear improvement and represents a clinically meaningful benefit.

The ideal outcome of the therapy in the long-term, in addition to reduction of ABR, would be freedom of previous intravenous FIX substitution therapy. Importantly, 34/53 (64.2%) subjects whose baseline anti-AAV5 nAb titre was <3000 had 0 bleeding episodes during the Month 7 to 18 post-treatment period and 27/53 (50.9) subjects had zero bleeds during Month 7-24 period.

Additionally, consumption of FIX replacement therapy was significantly lower following treatment with etranacogene dezaparvovec after the first year (i.e., between Month 7 and 18) following establishment of stable FIX expression (Month 0 to 6) as compared to standard of care routine FIX prophylaxis during the 6-month Lead-in Period (Table 4).

Table 4. Annualized Use of FIX Replacement Therapy (Infusions/year; Full Analysis Set)

	≥6-month Lead-in Period (N = 54)	Post-treatment Period			
		Month 0-6 (N = 54)	Month 7-12 (N = 54)	Month 13-18 (N = 54)	Month 19-24 (N = 53)
Number of Subjects Using FIX Replacement Therapy, n (%)	54 (100.0)	14 (25.9)	10 (18.5)	11 (20.4)	13 (24.5)
Number of Infusions of FIX Replacement Therapy, n	2380	85	70	64	42
Mean (per subject)	44.1	1.6	1.3	1.2	0.8
Median (Min, Max; per subject)	37.0 (12, 107)	0.0 (0, 34)	0.0 (0, 39)	0.0 (0, 26)	0.0 (0, 13)
Number of Person-years Observed for FIX Usage	33.12	24.10	26.91	26.12	25.85
	≥6-month Lead-in Period (N = 54)	Post-treatment Period			
		Month 0-6 (N = 54)	Month 7-18 (N = 54)	Month 7-24 (N=54)	Year 0-1 (N = 54)
Cumulative Number of Infusions of FIX Therapy	2380	85	134	176	155
Cumulative Number of Person-years Observed for FIX Usage	33.12	24.10	53.03	79.18	51.01
Unadjusted Annualized Infusion Rate1	71.87	3.53	2.53	2.22	3.04
Adjusted Annualized Infusion Rate, n Adjusted Rate	72.49		2.53	2.54	3.04
(95% CI)2	(63.52, 82.71)		(0.92, 6.96)	(0.98, 6.59)	(1.14, 8.12)
Rate Ratio (Post-treatments/Lead-in)2			0.03	0.04	0.04

Two-sided 95% Wald CI3			0.01, 0.10	(0.01, 0.09)	0.02, 0.11
p-value4			<0.0001	<0.0001	<0.0001

Abbreviations: CI = confidence interval; FIX = Factor IX; Max = maximum; Min = mi
Post-treatment period time was the number of days of observation within the time interval, excluding information prior to Day 21.

[1] Unadjusted infusion rate 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.

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

[3] One-sided p-value ≤0.025 for post-treatment/lead-in <1 was regarded as statistically significant. For Month 7-18, p-value adjusted for multiplicity.

Supportive data for efficacy is derived from the dose-response study CT-AMT-061-01 (n=3; adult patients with severe or moderately severe FIX deficiency, open-label, single arm study consisting of a screening phase, a treatment plus post-treatment follow-up phase, and a long-term follow-up phase; study did not contain a lead-in phase so no intra-patient comparisons to previous Factor IX therapy could be done; before treatment with Hemgenix patients received prophylactic and on-demand FIX replacement therapy (Alprolix, Idelvion); single IV dose of 2 × 10E13 gc/kg AMT-061; at time of orphan maintenance review up to 3-year efficacy follow-up data available).

In study CT-AMT-061-01 mean FIX activity level at Week 6, the time of the primary endpoint read-out, was 30.6 % measured by the one-stage assay. Individual FIX activity levels achieved by each subject at Week 6 were 23.9%, 30.0%, and 37.8%. At Week 52, FIX activity level was 40.8% measured by the one-stage assay. Individual FIX activity levels achieved by each subject at Week 52 were 31.3%, 40.8%, and 50.2%. At month 36, the mean FIX activity level was 36.90%, uncontaminated samples were available for 2 subjects and demonstrated that FIX activity levels continued to be elevated, at 32.3% and 41.5%, respectively. The average ABR for the 3 subjects, calculated as the total number of bleeding episodes divided by the time (in years) at risk, was 0.27 over the period of 2.5 years (30 months) of follow-up. The ABRs for spontaneous and traumatic bleeding episodes over 2.5 years (30 months) were both 0.14. The average ABR for the 3 subjects, calculated as the total number of bleeding episodes divided by the time (in years) at risk, was 0.22 over the period of 3 years (36 months) of follow-up. The ABRs for spontaneous and traumatic bleeding episodes over 3 years (36 months) were both 0.11. There were no bleeding episodes between 2.5 and 3 years of follow-up (both bleeding episodes occurred in the first 18 months post-AMT-061 administration). As this trial had no run-in phase specified in the protocol, a comparison to meaningful pre-treatment data is not possible.

In study CT-AMT-061-01 the annualized mean FIX replacement use was 306,204.9 IU/year in the 1 year prior to screening. All subjects discontinued use of routine prophylaxis Factor IX use between 1 and 4 days post-Hemgenix administration. Over 3 years (36 months) of follow-up, the annualized mean FIX use was 714.6 IU/year for the period following discontinuation of routine prophylaxis (post-continuous FIX prophylaxis period). 3/3 patients remained free of intravenous FIX prophylaxis over 3 years post-Hemgenix administration. The annualized on-demand FIX usage for participant 1, 2, and 3 was 0, 0, and 2144 IU/year over 3 years, respectively.

In conclusion, the COMP is of the opinion that Hemgenix provides a clinically relevant advantage as it has been shown that a single administration results in a significant reduction in annualized bleeding rate (ABR). In the pivotal trial CT-AMT-061-02, non-inferiority to FIX prophylaxis could be declared on the primary efficacy endpoint (i.e. "*Annualized bleeding rate comparison between AMT-061 and prophylaxis for non-inferiority between the lead-in phase and the 52 weeks following stable FIX expression, Months 6 to 18 post-treatment*"). In addition, the secondary outcome of superiority over

FIX prophylaxis could also be shown. Superiority against the specific group of FIX products with extended half-life could also be demonstrated. ABR was maintained for all bleeding types from Month 7 to 24 versus the Lead-in Period (64% reduction for all bleeding types vs the Lead-in Period). About 50% of patients had zero bleeds during the Month 7-24 period following Hemgenix administration. Importantly, a significant reduction of patients experiencing joint bleeds through month 24 following Hemgenix administration has been observed as compared to previous FIX prophylaxis therapy (i.e. 27.8% vs 59.3%). This is especially noteworthy as recurrent joint bleeding contributes to haemophilic arthropathy which severely affects patients' quality of life (pain and limitation of motion). Furthermore, a single administration of Hemgenix resulted in a substantial reduction in the use of exogenous Factor IX products through month 24 post-dose. In fact, use of exogenous FIX as well as FIX infusion rate fell to approximately 3% of values reported during patient's previous FIX prophylaxis therapy (lead-in period). FIX activity peaked at 12 months and while a limited decline could be observed at 18 months, the FIX activity levels have been maintained at 24 months. Supportive data from the dose-response study CT-AMT-061-01 in 3 patients showed that annualized bleeding rates remained low even through month 36 following the administration of Hemgenix. Also, over 3 years (36 months) of follow-up, the annualized mean exogenous Factor IX use fell to below 1% of values reported during patient's previous FIX prophylaxis therapy, in the 12 months period prior to the administration of Hemgenix (study CT-AMT-061-01).

Considering all the above, the COMP agreed that the data presented by the sponsor supports significant benefit for the purpose of orphan designation maintenance and that Hemgenix provides a clinically relevant advantage for patients.

4. COMP position adopted on 19 December 2022

The Committee for Orphan Medicinal Product (COMP) considered that the designated orphan condition "Treatment of haemophilia B" (hereinafter referred to as "the condition").

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of haemophilia B (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Hemgenix may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The sponsor has provided clinical data that demonstrate superior efficacy with regards to a reduction in annualized bleeding rate compared to standard of care with authorized Factor IX products, including those with extended half-life. A single administration of Hemgenix significantly reduced or eliminated the need for exogenous Factor IX products over a period of at least 18 months. Also, a significant reduction of patients experiencing joint bleeds for at least 18 months following Hemgenix administration has been observed, as compared to exogenous factor IX prophylaxis therapy. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Hemgenix, recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA, etranacogene dezaparvovec for treatment of haemophilia B (EU/3/18/1999) is not removed from the Community Register of Orphan Medicinal Products.