24 August 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Roctavian (adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene)

Treatment of haemophilia A

EU/3/16/1622

Sponsor: Biomarin International Limited

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)	Adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene
Other name(s)	Roctavian, adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene,
International Non-Proprietary Name	Valoctocogene roxaparvovec
Tradename	Roctavian
Orphan condition	Treatment of haemophilia A
Sponsor's details:	Biomarin International Limited Shanbally Ringaskiddy County Cork P43 R298 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	BioMarin Europe Ltd
COMP opinion	18 February 2016
EC decision	21 March 2016
EC registration number	EU/3/16/1622
Post-designation procedural history	
Sponsor's address change	EC letter of 4 September 2018
Transfer of sponsorship	From BioMarin Europe Ltd to Biomarin International Limited - EC decision of 27 September 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Violaine Closson Carella / Ilona G. Reischl
Applicant	Biomarin International Limited
Application submission	25 June 2021
Procedure start	17 July 2021
Procedure number	EMA/H/C/005830
Invented name	Roctavian
Proposed therapeutic indication	Treatment of severe haemophilia A Further information on Roctavian can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/roctavian
CHMP opinion	23 June 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Karri Penttila
Sponsor's report submission	22 July 2021
COMP discussion and adoption of list of questions	14-16 June 2022

Oral explanation	13 July 2022
COMP opinion	14 July 2022

2 Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene was considered justified based on restoration of bleeding time and reduced bleeding in a preclinical model of the proposed condition;
- the condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening;
- the condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene will be of significant benefit to those affected by the condition. The sponsor has provided *preclinical* data in a model of the condition that demonstrate long-term restoration of factor VIII activity after a single administration, which may result in reduction of the need for on-demand and prophylactic treatment. The Committee considered that this constitutes a clinically relevant advantage.

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

Hemophilia A is characterized by deficiency in factor VIII clotting activity that results in prolonged oozing after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing. The age of diagnosis and frequency of bleeding episodes are related to the level of factor VIII clotting activity.

Hemophilia A is inherited in an X-linked manner. The risk to siblings of an individual proband depends on the carrier status of the mother. Carrier females have a 50% chance of transmitting the F8 pathogenic variant in each pregnancy: sons who inherit the pathogenic variant will be affected; daughters who inherit the pathogenic variant are carriers. Affected males transmit the pathogenic

variant to all of their daughters and none of their sons. Carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the F8 pathogenic variant has been identified or if informative intragenic linked markers have been identified.

Individuals with severe hemophilia A are usually diagnosed during the first two years of life following bleeding from minor mouth injuries and large "goose eggs" from minor head bumps. Without prophylactic treatment, they may average up to two to five spontaneous bleeding episodes each month including spontaneous joint bleeds or deep-muscle hematomas, and prolonged bleeding or excessive pain and swelling from minor injuries, surgery, and tooth extractions.

Individuals with moderate hemophilia A seldom have spontaneous bleeding; however, they do have prolonged or delayed oozing after relatively minor trauma and are usually diagnosed before age five to six years; the frequency of bleeding episodes varies, usually from once a month to once a year. Individuals with mild hemophilia A do not have spontaneous bleeding episodes; however, without pre- and postoperative treatment, abnormal bleeding occurs with surgery or tooth extractions; the frequency of bleeding episodes varies widely, typically from once a year to once every ten years.

Individuals with mild hemophilia A are often not diagnosed until later in life. Approximately 30% of heterozygous females have clotting activity below 40% and are at risk for bleeding (even if the affected family member is mildly affected). After major trauma or invasive procedures, prolonged or excessive bleeding usually occurs, regardless of severity.

The diagnosis of hemophilia A is established in a male proband by identification of decreased factor VIII clotting activity and a normal, functional von Willebrand factor level. (Konkle BA, Huston H, Nakaya Fletcher S. Hemophilia A. 2000 Sep 21 [Updated 2017 Jun 22]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.)

The approved therapeutic indication *"ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5)."* falls within the scope of the designated orphan condition "Treatment of haemophilia A"

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

The seriousness of the condition his acknowledged by the COMP. The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or in surgery, which may also be life-threatening

Number of people affected or at risk

The sponsor has submitted an up-dated prevalence calculation, which relies upon the 2019 data as reported in the latest Annual Global Survey (WFH 2020). Data were collated from national patient organizations using a questionnaire which included hereditary disorder typing. National patient organizations obtained deidentified population data from the relevant regional or national registries in their respective countries.

In this edition of the annual survey, and owing to the on-going COVID-19 pandemic, a greater number of EEA member states than in previous years were unable to provide data. Nevertheless, 20 EEA countries reported data, so a prevalence estimate based on these data remains robust. 'Missing' data is indicated in Table 1, which shows all available per country data used in the current prevalence calculation. In the table, individual country prevalence has been calculated based upon the size of the population reported by the WFH. The WFH used data from the World Bank Group for population size. Several caveats are noted in the WFH Survey report (WFH 2020), including:

- Small differences in numbers of identified cases in countries with smaller populations may impact the apparent prevalence when in fact only a few more/less cases than 'expected' have been identified.
- In countries with universal healthcare all patients with haemophilia are more likely to be identified. In other countries, patients (mild) who do not require treatment may be under-reported.
- The quality, completeness, and accuracy of country registries, from which these data are ultimately derived, influence the prevalence estimate. Over-counting due to double entry (e.g. patients registered at more than one treatment centre) or failure to fully account for births and deaths in a contemporaneous fashion cannot be completely ruled out.

WFH data have previously been accepted by the COMP as providing the best estimate of the prevalence of HA in the EAA. The advantage of the annual WFH survey data is that it provides a longitudinal view of the prevalence of haemophilia demonstrating that it has not significantly changed over time. However, a more than 2-fold difference in reported prevalence is noted across individual EAA countries. There is no scientific reason to believe the prevalence of HA should be significantly different between countries, as most causal mutations are random and should not vary across the globe. Some of the individual country variability may reflect differences in the completeness of national registers but could also reflect variability in quality of medical care and thus life expectancy. It is not possible to quantify the impact of this at an individual EAA country level.

These caveats should be borne in mind when reviewing this prevalence estimate and they inform the Sponsor's preference to rely upon a recently reported estimate of birth prevalence (incidence) and population prevalence of HA (Iorio 2019). In its latest annual report, the WFH used these authors estimates for the overall population prevalence of HA *and* haemophilia B combined, to estimate that approximately 25% of cases of haemophilia may be missing from respective country registries (WFH 2020).

Nevertheless, the reported WFH data suggests the current population prevalence of HA in the EEA is approximately 0.73 in 10,000 (Table 2), very similar to the originally accepted estimate.

To address the potential issues of 'missing' data, and to provide a more accurate estimate for the prevalence of HA, the Data and Demographics Committee of the WFH has published new estimates based on a meta-analysis of high-quality national registers (Iorio 2019). That estimate for the population prevalence of HA, which the Sponsor proposes to rely upon, is described below.

Table 1 Prevalence of haemophilia A in the European Economic Area

Country	Number of inhabitants in 2019[a]	Number of persons with haemophilia A[b]	Prevalence of haemophilia A per 10,000 inhabitants
Austria	8,877,067	693	0.78
Belgium	11,484,055	1,015	0.88
Bulgaria	-	-	*No data*
Croatia	-	-	*No data*
Cyprus	-	-	*No data*
Czech Republic	10,669,709	895	0.84
Denmark	-	-	*No data*
Estonia	1,326,590	106	0.80
Finland	5,520,314	168	0.30
France	67,059,887	6,727	1.00
Germany	83,132,799	3,811	0.46
Greece	10,716,322	839	0.78
Hungary	9,769,949	871	0.89
Iceland	-	-	*No data*
Ireland	4,941,444	664	1.34
Italy	-	-	*No data*
Latvia	1,912,789	66	0.35
Liechtenstein	-	-	*No data*
Lithuania	2,786,844	156	0.56
Luxembourg	-	-	*No data*
Malta	-	-	*No data*
Netherlands	17,332,850	1,115	0.64
Norway	5,347,896	343	0.64
Poland	37,970,874	2,562	0.67
Portugal	10,269,417	744	0.72
Romania	19,356,544	1,615	0.83
Slovakia	5,454,073	529	0.97
Slovenia	2,087,946	220	1.05
Spain	-	-	*No data*

Sweden	10,285,453	769	0.75
Total with data	326,302,882	23,908	0.73

Population is as reported in the WFH Report (sourced from the World Bank Group)

From WFH Annual Survey report (2020 [2019 data]) (WFH 2020)

Table 2 Estimated prevalence (per 100 000 males) of haemophilia, for all severities and severe only

Value	All Severities	Severe Only
Mean estimated prevalence per 100 000 males (95% CI)	17.1 (14.8–19.3)	6.0 (5.8–6.1)
Heterogeneity (I^2), %	99.0	0.0

Source: Iorio 2019

Based on the study of Iorio *et al*, 2019, the prevalence of HA in the EAA is estimated to be 1.71 in 10,000 *male* persons. The ratio of females to males in the EEA is 1.046 (Eurostat). Therefore, **the population prevalence of HA is estimated to be 0.84 in 10,000 persons**. Based on the current size (2020 estimate) of the population of the EEA (EU27+3), **38,059 persons have HA**. This suggests that approximately 5,000 persons may be 'missing' from member States' national haemophilia registries, possibly because they have mild disease, are undiagnosed, and/or have not sought treatment (WFH 2020).

The COMP accepted 0.8 in 10,000 as the final estimate for this prevalence.

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

The sponsor notes that patients with HA are principally treated with FVIII replacement therapy, or bypassing agents if they have inhibitors (either due to acquired HA or in congenital HA patients who develop inhibitors). Two types of FVIII concentrate are available, plasma-derived and recombinant. By-passing agents include recombinant activated factor VII or activated prothrombin complex concentrate (aPCC) (Charlebois 2018; Kruse-Jarres 2019; Windyga 2019). A recombinant porcine FVIII product (susoctocog) is available to treat patients with acquired HA. Emicizumab (Hemlibra), a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure that bridges activated factor IX and factor X to restore the function of missing activated factor VIII is indicated for the treatment of patients with congenital HA with FVIII inhibitors and patients with severe congenital HA without inhibitors. Mild haemophilia A of any type can be treated with desmopressin which affects blood coagulation by briefly increasing the concentration of FVIII (and vWF) in blood (Franchini 2010). Tranexamic acid is used for the treatment of mucosal bleeds, particularly in patients with acquired HA, and more generally in addition to other treatment modalities in PwHA (Antovic 2021).

Patients with inhibitors may also receive treatments aimed at eliminating those inhibitors—immune tolerance induction with high dose FVIII in congenital or acquired HA, and/or immunosuppression

(corticosteroids ± cyclophosphamide or rituximab) in the latter group (Charlebois 2018; Giangrande 2018).

Tabulated lists of centrally approved FVIII products and a representative sample of older (generally plasma-derived) products approved through national/decentralised procedures are provided in Table 3 and Table 4, respectively.

Table 3 Centrally authorised medicinal products for the treatment of haemophilia A

Tradename	Active substance
Factor VIII analogues	
Kogenate Bayer, Helixate NexGen, Advate, Kovaltry / Iblias	Octocog alfa
B-domain truncated/deleted FVIII	
ReFacto AF	Moroctocog alfa
NovoEight	Turoctocog alfa
Nuwiq, Vihuma	Simoctocog alfa
Afstyla	Lonoctocog alfa
FVIII/vWF combination product	
Voncento	Human FVIII + Human vWF (both plasma-derived)
Factor VIII – long acting	
Adynovi	Rurioctocog alfa pegol
Factor VIII – B domain truncated/deleted, long acting	
Elocta	Efmoroctocog alfa
Jivi	Damoctocog alfa pegol
Esperoct	Turoctocog alfa pegol
Treatment of haemophilia A without (severe) or with (all) inhibitors	
Hemlibra	Emicizumab
Treatment of acquired haemophilia A – porcine FVIII	
Obizur	Susoctocog alfa
Treatment of acquired haemophilia A and haemophilia A with inhibitors – FVIII inhibitor bypassing activity	
NovoSeven	Eptacog alfa (activated)
FEIBA	Factor VIII Inhibitor Bypassing Activity

Table 4 Other factor VIII products authorised through decentralised procedure/mutual recognition/national procedures

Active substance / Tradename
Octocog alfa Recombinate
Plasma-derived coagulation factor VIII concentrate Beriate/Beriate P, Betafact, Cluvot, Haemoctin, Haemonine, Immunine, Mononine, Octanate
Plasma-derived human coagulation factor VIII and human von Willebrand factor (VWF) concentrate Immunate, Optivate, Wilate, Fanhdi

The sponsor's approved indication is:

> *ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).*

There is complete overlap with Hemlibra as well as the general indications of the Factor VIIIs which are available.

Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with

- haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors. Hemlibra can be used in all age groups

Significant benefit

The sponsor proposes that their product could replace the need for exogenous sources of Factor VIII. A single dose of BMN 270 leads to endogenous FVIII activity levels that enable patients to discontinue routine FVIII prophylaxis whilst also achieving significant reductions in bleeding episodes and improvements in health-related quality of life relative to their previous experience on FVIII products.

In Protocol Assistance received on 18 May 2017 (EMA/CHMP/SAWP/282886/2017), the Sponsor was advised that: "*In order to establish significant benefit on the basis of a major contribution to patient care, the Applicant should provide clinical evidence that BMN 270 is in the same range with authorized FVIII products with regard to clinical efficacy and safety, and should show that a sustained FVIII levels can be translated into a relevant benefit. The COMP agrees with the Applicant proposal and will take into consideration the totality of data including annual bleeding rate, target joints, reduction of prophylaxis and rescue therapies, quality of life*".

In order to support significant benefit, the sponsor has used their pivotal trials:

- **Study 270-201** (data cutoff 29 March 2021), with ≥5 years of follow-up from the 7 subjects in the 6E13 vg/kg cohort, and ≥4 years follow-up at a lower 4E13 vg/kg dose (6 subjects).
- **Study 270-301** (data cutoff 15 November 2021), with 134 subjects dosed at 6E13 vg/kg (including 22 subjects who enrolled in study 270-301 directly [`Directly Enrolled subjects'] and 112

subjects who enrolled in study 270-301 after completing a non-interventional study 270-902 where subjects baseline bleeding and FVIII usage data under FVIII prophylaxis were prospectively collected [‘270-902 Rollover subjects’]) with follow-up of ≥2 years, of whom 19 subjects were dosed ≥3 years prior to the data cutoff (1 subject lost to follow-up at Week 66).

For the sake of brevity the assessment will focus on Study 270-301 which is an ongoing Phase 3, open-label, single-arm study evaluating the efficacy and safety of BMN 270 6E13 vg/kg in adult subjects with severe HA (Baseline residual FVIII activity levels ≤1 IU/dL) who had: received prophylactic FVIII for ≥ 12 months with ≥ 150 exposure days to FVIII concentrates/cryoprecipitate; no history of FVIII inhibitor; and no detectable pre-existing AAV capsid antibodies. Subjects were instructed to continue FVIII prophylaxis for 4 weeks post BMN 270 infusion; subjects could receive FVIII on demand thereafter as clinically indicated.

Efficacy endpoints were analysed in different study populations with formal hypothesis tests performed sequentially on the primary, first secondary, and second secondary efficacy endpoints. To adjust for multiplicity in testing the primary and secondary efficacy endpoints at the Week 52 analysis, a hierarchical (fixed sequence) testing procedure was used, after applying the fallback procedure to account for the interim analysis. To control the family-wise error rate at the 0.05 level, the Week 52 analysis was performed using the alpha value of 0.05 per the fallback procedure.

- **Primary endpoint**: change from Baseline (under no haemophilia treatment) in median FVIII activity during Week 49-52 post-BMN 270 infusion.

The primary endpoint was tested for superiority (over no haemophilia treatment) using a two-sided one-sample t-test on the modified ITT (**mITT) Population** (2 HIV-positive subjects excluded, N=132). As there was no washout period in this study, for the purposes of this analysis, all subjects were imputed to have a Baseline FVIII activity level of 1 IU/dL.

A subsequent formal Week 104 / Year 2 analysis has now been completed, with results. The hierarchical testing procedure was extended to this later analysis to control the family-wise Type I error rate. Since all pre-specified tests were statistically significant at the Week 52 analysis, the corresponding efficacy endpoints at 2 years were tested in the same sequence under the same significance level (i.e., 0.05).

Prior FVIII usage

Per protocol, all subjects were required to have been treated with a FVIII product prior to study entry, which was discontinued on Day 1 (270-201) or 4-weeks after BMN 270 administration (270-301). The delayed withdrawal of exogenous FVIII was introduced in 270-301 to protect subjects from bleeds in the initial period of increasing endogenous FVIII expression. Most subjects were using conventional (short half-life) FVIII products at study entry (Table 3). Long-acting FVIII products were used by approximately a quarter of subjects in 270-301 overall, but a higher proportion of Directly Enrolled subjects (41%), and zero subjects in 270-201. Across the two studies, the range and extent of prior FVIII product use is sufficient to allow for a 'before and after' comparison for the purposes of the assessment of significant benefit of BMN 270 over FVIII products ().

Table 5 Prior FVIII replacement therapies

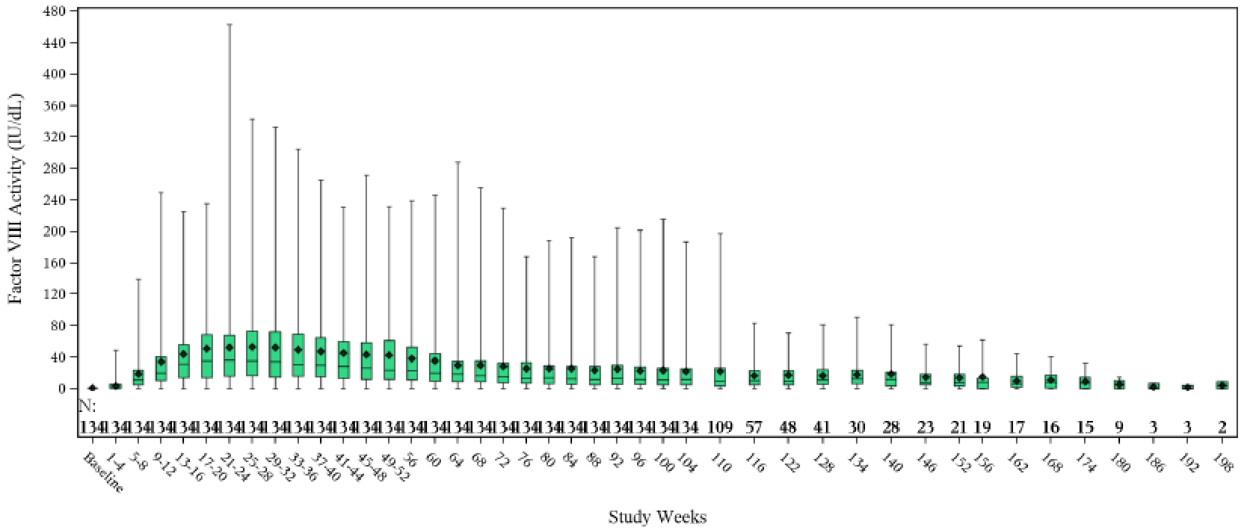
Preferred Drug Name	270-201		270-301			
	4E13 vg/kg (N=6)	6E13 vg/kg (N=7)	Directly Enrolled (N=22)	270-902 Rollover (N=112)	mITT (N=132)	ITT (N=134)
Subjects with reported prior blood coagulation factor use, n(%)	6 (100)	7 (100)	22 (100)	112 (100)	132 (100)	134 (100)
Standard (Short) Half-Life, n(%)	6 (100)	7 (100)	14 (63.6)	69 (61.6)	81 (61.4)	83 (61.9)
Octocog Alfa	0	4 (57.1)	8 (36.4)	48 (42.9)	54 (40.9)	56 (41.8)
Moroctocog Alfa	5 (83.3)	3 (42.9)	5 (22.7)	15 (13.4)	20 (15.2)	20 (14.9)
Turoctocog Alfa	0	0	1 (4.5)	4 (3.6)	5 (3.8)	5 (3.7)
FVIII, Recombinant	1 (16.7)	1 (14.3)	0	2 (1.8)	2 (1.5)	2 (1.5)
Simoctocog Alfa	1 (16.7)	0	1 (4.5)	1 (0.9)	2 (1.5)	2 (1.5)
Lonoctocog Alfa	0	0	0	1 (0.9)	1 (0.8)	1 (0.7)
Extended Half-Life, n(%)	0	0	9 (40.9)	28 (25.0)	36 (27.3)	37 (27.6)
Efmoroctocog Alfa	0	0	8 (36.4)	22 (19.6)	29 (22.0)	30 (22.4)
Rurioctocog Alfa Pegol	0	0	1 (4.5)	5 (4.5)	6 (4.5)	6 (4.5)
Damoctocog Alfa Pegol	0	0	0	1 (0.9)	1 (0.8)	1 (0.7)
Plasma-Derived, n(%)	0	0	1 (4.5)	23 (20.5)	24 (18.2)	24 (17.9)
FVIII (antihemophilic factor)	0	0	1 (4.5)	21 (18.8)	22 (16.7)	22 (16.4)
Wilate	0	0	0	2 (1.8)	2 (1.5)	2 (1.5)
Unknown investigational drug	0	0	1 (4.5)	0	1 (0.8)	1 (0.7)

Note that subjects may have been receiving more than one kind of prior FVIII replacement therapy, such that the subtotals may be greater than the overall total.

Source: 270-301 CSR (November 2020 datacut) Table 14.1.7.1; 270-201 CSR (March 2021 datacut) Table 14.1.7

Of the 134 subjects in the ITT population of 270-301, 33 (24.6%) subjects had a FVIII activity of <5 IU/dL at Week 104. From these 33 subjects, 5 have restarted prophylaxis (as had a further subject with FVIII just above 5 IU/dL), 14 had an ABR of zero, and 8 had an ABR <1 (Data source: 270-301 [November 2021 datacut] Table 14.2.1.1.1; Listing 16.2.6.2.2.10; Listing 16.2.1.1).

Figure 1. Box plot for median Factor VIII activity level using chromogenic substrate assay by 4-week or 6-week window (Study 270-301: ITT population)



Values for FVIII activity were excluded from analysis if obtained within 72 hours (or 3 calendar days if time is not available) since the last infusion of exogenous FVIII replacement therapy. In addition, post-Baseline FVIII activity values were excluded if obtained after FVIII prophylaxis treatment resumed. FVIII activity levels below the LLOQ (Lower limit of quantification) were imputed with 0 IU/dL. Baseline value was the most recent FVIII activity prior to BMN 270 infusion.

FVIII imputation (missing data) based on the smaller of adjacent non-missing values.

The boxes show the interquartile ranges with the lines in the boxes indicating medians. The ends of the whiskers represent the minimum and maximum values and diamonds indicate the means.

Table 6 Patient Annualised Bleeding Rates

	Baseline	**Week 5 and Beyond / Post-FVIII Prophylaxis Period[a]**		
Cohort	**ABR (no/yr)**	**Bleeding Episodes (no.)**	**ABR (no/yr)**	**Follow-Up (Days)**
270-301 Population Enrolled 3+ Years (N=19)				
Mean (SD)	8.91 (21.28)	4.63 (10.20)	1.40 (3.09)	1143.58 (189.64)
Median	0.94	0.00	0.00	1184.00
Min, Max	0.0, 91.5	0.0, 42.0	0.0, 12.8	431.0,1350.01
Zero bleeds in period, n (%)	6 (31.6)	11 (57.9)		
% reduction from Baseline in mean ABR			84.3%	
270-301 Directly Enrolled Population (N=22)				
Mean (SD)	8.41 (19.90)	4.45 (9.50)	1.37 (2.88)	1126.64 (181.02)
Median	0.93	0.00	0.00	1181.00

Cohort	Baseline	Week 5 and Beyond / Post-FVIII Prophylaxis Period[a]		
	ABR (no/yr)	Bleeding Episodes (no.)	ABR (no/yr)	Follow-Up (Days)
Min, Max	0.0, 91.5	0.0, 42.0	0.0, 12.8	431, 1350.0
Zero bleeds in period, n (%)	7 (31.8)	12 (54.5)		
% reduction from Baseline in mean ABR			83.7%	
p-value (t-test), 95% CI mean change in ABR from Baseline			0.1164 (-15.98, 1.90)	
270-301 Rollover Population (N=112)				
Mean (SD)	4.83 (6.47)	1.52 (4.92)	0.75 (2.44)	761.76 (73.11)
Median	2.80	0.00	0.00	739.00
Min, Max	0.0, 33.1	0.0, 34.0	0.0, 17.3	636.0, 1000.0
Zero bleeds in period, n (%)	36 (32.1)	83 (74.1)		
% reduction mean ABR from Baseline			84.5%	
p-value (t-test), 95% CI mean ABR from Baseline			<0.0001 (-5.31, -2.85)	
270-301 mITT Population (N=132)				
Mean (SD)	5.43 (10.04)	1.67 (4.87)	0.75 (2.31)	816.23 (162.71)
Median	2.04	0.00	0.00	741.00
Min, Max	0.0, 91.5	0.0, 34.0	0.0, 17.3	431.0, 1350.0
Zero bleeds in period, n (%)	43 (32.6)	95 (72.0)		
% reduction from Baseline in mean ABR			86.1%	
p-value (t-test), 95% CI mean ABR from Baseline			<0.0001 (-6.42, -2.94)	
270-301 ITT Population (N=134)				
Mean (SD)	5.42 (9.96)	2.00 (5.97)	0.85 (2.52)	821.66 (167.46)
Median	2.30	0.00	0.00	741.00

Cohort	Baseline	Week 5 and Beyond / Post-FVIII Prophylaxis Period[a]		
	ABR (no/yr)	Bleeding Episodes (no.)	ABR (no/yr)	Follow-Up (Days)
Min, Max	0.0, 91.5	0.0, 42.0	0.0, 17.3	431.0, 1350.0
Zero bleeds in period, n (%)	43 (32.1)	95 (70.9)		
% reduction from Baseline in mean ABR			84.3%	
p-value (t-test), 95% CI mean ABR from Baseline			<0.0001 (-6.92, -2.85)	

Max, maximum; Min, minimum; SD, standard deviation; ABR, annualized bleeding rate.

a Referred to as the "Post-FVIII Prophylaxis Period" in 270-301 source tables

*The annualized number of bleeding episodes, or annualized bleeding rate is defined as (Number of bleeding episodes during the calculation period / Total number of days during the calculation period) * 365.25.*

Pre-infusion ABR was based historical data collected at Screening visit.

Source: 270-201 CSR (March 2021 datacut) Table 14.2.2.1.2.1; 270-301 (November 2021 datacut) Table 2.2.2.1, Table 14.2.2.2.1.2, Table 14.2.2.2.1.3

The sponsor has also provided an indirect comparison to Hemlibra. This based on a comparison of the Haven 3 trial to study 270-301. Whilst HAVEN 3 is the closest match to the design of 270-301, the study populations, especially in the two emicizumab randomised arms were somewhat different. Apart from the fact that all subjects in those two arms had considerably higher Baseline ABRs (all bleeds) on the order of mean 32-39/year (vs 5.97 and 5.36, respectively in the 270-301 ITT and Rollover Populations), most subjects in those arms had at least one target joint (94% in Arm A and 77% in Arm B vs ~26% in 270-301 populations), with most subjects having >1 target joint. This presumably reflects that the HAVEN 3 randomized population comprised subjects who were previously treated with episodic rather than prophylactic FVIII. Conversely, Arm D in HAVEN 3, the prior FVIII prophylaxis arm, was somewhat more closely matched to 270-301 with a mean (SD) ABR (all bleeds) of 13.9/year and zero target joints in 58.7% of subjects (Hemlibra Assessment Report; EMEA/H/C/004406/II/0002; EMA/125963/2019, Table 27, mean 6.4 bleeds over 24 weeks).

In HAVEN 3, the respective ABRs for all bleeds and treated bleeds following emicizumab weekly (1.5 mg) or Q2W (3 mg) were comparable with the best performing FVIII therapies in indirect side-by-side comparisons. However, recently reported data suggest that the 4-weekly posology (HAVEN 4, subpopulation without FVIII inhibitors) may result in a level of haemostatic control that is worse than that achieved with the best-performing FVIII products (Klamroth 2021), as the data in Table 7 suggests. For this reason, only the two 'optimal' emicizumab regimens are considered further in the significant benefit comparisons with BMN 270.

Table 7 Mean and median ABR (all bleeds and treated bleeds): comparison of BMN 270 with emicizumab (Hemlibra) in patients with severe HA without inhibitors

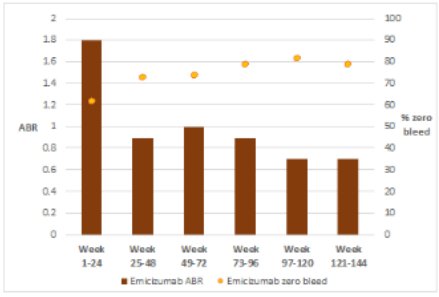
FVIII type	Source[a]		Dose	(median, range; weeks)	Mean (SD/ 95% CI)	Median (IQR)	Mean (SD/ 95% CI)	Median (IQR)
Gene therapy								
BMN 270 FVIII-SQ[b]	270-301 (ITT)		6E13 vg/kg	105.8 (104.0, 123.6)	1.38 (2.73)	0.49 (0.00, 1.51)	0.85 (2.52)	0.00 (0.0, 0.49)
	270-301 (Rollover)			105.6 (90.9, 142.9)	1.23 (2.54)	0.49 (0.0, 17.3)	0.75 (2.44)	0.00 (0.0, 17.3)
	270-201		6E13 vg/kg	261 4 (254.6, 270.6)	-	-	0.77 (1.87)	0.00 (0.0, 0.40)
	270-201		4E13 vg/kg	214.1 (206.6, 221.4)	-	-	1.04 (1.86)	0.36 (0.0, 0.71)
Emicizumab[b]								
Bispecific mono-clonal antibody bridging FIX and FX	HAV-EN 3[d]	Arm A	1.5 mg (per week) [prior episodic]	29.6 (17.3, 49.6)	2.5 (1.6, 3.9)	0.6 (0.0, 3.9)	1.5 (0.9, 2.5)	0.0 (0.0, 2.5)
		Arm D	1.5 mg (per week) [prior prophy-laxis]	33.1 (18.4, 48.6)	3.3 (2.2, 4.8)	1.5 (0.0, 4.3)	1.6 (1.1, 2.4)	0.0 (0.0, 2.2)
		Arm C	3 mg (Q2W)	31.3 (7.3, 50.6)	2.6 (1.6, 4.3)	1.6 (0.0, 4.0)	1.3 (0.8, 2.3)	0.0 (0.0, 1.9)
		Pooled		150.5 (84.4, 153.0)	-	-	1.2 (0.9, 1.6)	-
	HAVEN 4[c,d]		6 mg (Q4W)	25.6 (24.1, 29.4)	4.5 (3.1, 6.6)	2.1 (0.0, 5.9)	2.4 (1.4, 4.3)	0.0 (0.0, 2.1)
				120.4 (89.0, 164.4)	-	-	1.8 (1.2, 2.9)	-

Data source 270-201 CSR (March 2021 datacut) Table 14.2.2.1.2.1; 270-301 (November 2021 datacut) Table 14.2.2.2.1, Table 14.2.4.2.1, Table 14.1.9; MaNangu 2018 (HAVEN 3); Pipe 2019 (HAVEN 4). Pooled HAVEN data for overall negative binomial model-based ABR (Callaghan 2021).
Q2W = every 2 weeks

[a] Data from Week 5 (201) or Post-FVIII prophylaxis (301) to data cutoff in the FAS (201) or ITT or Rollover population (301). The All bleeds endpoint was not assessed in 270-201.
[b] Model-based bleeding data: 1.5 mg dose once per week, 3 mg dose once every 2 weeks, 6 mg dose once every 4 weeks.
[c] HAVEN 4 includes a mixed population of patients (N=41 in expansion cohort) with (12%) and without (88%) inhibitors.
[d] Long-term data from Callaghan 2021.

It can be observed from Figure 2 that the ABR (treated bleeds) post Week 24 was considerably improved relative to that observed in the first 24-weeks, with an ABR of 0.7 to 0.9 treated bleeds/year and a zero treated bleeds rate of approximately 80%. The sponsor considers that the fairest and most relevant comparison between BMN 270 and emicizumab is that over the longest period of common follow-up for both products, which is approximately 2 years. The COMP agreed that long duration of effect was relevant in establishing significant benefit. These comparisons are presented below.

Figure 2. Comparison of effects of BMN 270 (right) vs emicizumab (HAVEN 3) (left) on ABR (treated bleeds) by 24-week treatment period (emicizumab) or 24/52-week period post-FVIII prophylaxis (BMN 270)



		Post FVIII-Week 26	Week 27-52	Week 53-104
	N	ITT 134; R/O 112		
Mean ABR (treated bleeds)	ITT	1.31	0.64	0.71
	R/O	1.12	0.61	0.71
% zero bleeds	ITT	82.1	91.8	82.1
	R/O	83.9	93.8	83.9

	Week 1-24	Week 25-48	Week 49-72	Week 73-96	Week 97-120	Week 121-144
N	148	144	140	131	104	89
Mean ABR (treated bleeds)	1.8	0.9	1.0	0.9	0.7	0.7
% zero bleeds	62.8	72.9	74.3	79.4	79.8	82.0

ABR (treated bleeds) data for emicizumab is calculated mean in 24-week intervals. Data for BMN 270 is observed mean. R/O = Rollover Population

Source: 270-301 (November 2021 datacut) Table 14.2.2.2.1.3; Callaghan 2021; https://www.emicizumabinfo.com/content/dam/gene/emicizumabinfo/pdf/patient-summaries/hemlibra-and-long-term-effectiveness-and-safety.pdf

Inspection of Figure 2 above reveals generally better total haemostatic control (zero bleeds) following a single dose of BMN 270 than following between 26 (Q2W) and 56 (weekly) doses/year of emicizumab over 2 years. Amongst subjects treated with BMN 270, approximately 73% (ITT: 71%; Rollover: 74% Table) had zero bleeds across the full duration of follow-up and between 82% and 92% had zero bleeds in each treatment interval shown out to Year 2. The zero-bleed rate for the full 3-year follow-up period of HAVEN 3 was not reported by Callaghan 2021. However, total bleeding control (treated bleeds) was clearly inferior to BMN 270 in the first 6 months of emicizumab treatment (63% vs 83%), and thereafter was between 74% and 82% (vs 82-92%). It should also be noted that in Arm D of HAVEN 3 (N=63), which came closest to matching the disease characteristics of subjects in 270-301, only 55.6% of subjects were bleed-free over the first 7.6 months of treatment (Mahlangu 2018, Table S2) vs ~83% in 270-301 (Figure 2). ABR (treated bleeds) was also significantly higher in that period (mean 1.6 vs 1.3 [ITT]).

Although there are no real differences between the two products it should be noted that it could be argued that the gene therapy could dispense with the need for Hemlibra in the severe patients. Unfortunately, the main pivotal trial did not have patient who had been previously treated with Hemlibra so the number of failures needing reintroduction is not known.

From the data submitted it appears that the product can reduce the need for exogenous FVIII use and reduces the annual bleeding rate to a similar extent to Hemlibra and requires one injection as opposed to regular use of Hemlibra. The COMP however noted that the comparability of long-term duration of Roctavian wasn't clear and that the need to use rescue exogenous FVIII over the long term had not been discussed versus Hemlibra. Of particular concern was the sustainability of Roctavian's effect was not clear versus chronic use of Hemlibra. The sponsor further indicated that there are clinically relevant advantages in bleeding outcomes for Roctavian over FVIII replacement and Hemlibra on the basis of the 2-year data from Study BMN 270-301. The sponsor supported this claim with a new matching adjusted indirect comparison (MAIC) to Hemlibra. In order to address the durability of effect, the pharmacokinetic modelling data of Study BMN 270-301 was further supported by provision of 6-year data from Study BMN 270-201 and a discussion on durability of effect versus Hemlibra and use of exogenous FVIII. All aspects were discussed with the sponsor during the oral explanation.

Improved bleed prevention when compared to Hemlibra

For the MAIC, individual patient level data (PLD) from Study 270-301 modified intent-to-treat (mITT) population (n=132) were re-weighted to match aggregate baseline characteristics of HAVEN 3, Group D (Hemlibra1.5 mg/kg weekly, n=63), who were previously treated with FVIII prophylaxis prior to enrolling in the study (Mahlanghu,2018). All available baseline characteristics reported for HAVEN 3 Group D (n=63) that were also captured in 270-301 were used to match cohorts in the base case analysis.

Weighted bleeding outcomes including mean annualized bleeding rate (ABR) and the proportion of participants with zero bleeds from 270-301 were compared with bleeding outcomes reported in HAVEN 3, including:

1. Treated bleeds
2. All bleeds
3. Treated joint bleeds
4. Treated spontaneous bleeds

Bleeding outcomes from 270-301 observed during the Year 1 efficacy evaluation period, i.e., the later of Week 5 or 3 days after the cessation of FVIII prophylaxis through Week 52 were estimated using a negative binomial regression model consistent with the approach used in HAVEN 3 (i.e., stratified by number of bleeds (≥9 vs. <9)) during 6 months prior to enrolment into the study, median 48.0 weeks; range: 35.6-48 weeks). Observed bleeding outcomes captured during the efficacy period (median: 33.1 weeks; range: 18.4-48.6 weeks) in HAVEN 3 for Group D (n=63) were used for comparative purposes. Rate ratios (RR) were used to compare differences in mean ABR, and odds ratios (OR) were used to compare the difference in the proportion of participants with zero bleeding events for Roctavian and Hemlibra prophylaxis for all bleeding outcomes.

In the base case analysis, after matching to available baseline characteristics reported for HAVEN 3 Group D (n=63), the effective sample size (ESS) for Roctavian was n=76.2 (57.7% of the mITT n=132 population, Table 6 from the sponsor's responses to the list of questions).

The sponsor noted that matching on mean age had the largest impact on the ESS, which reduced from 132 to 104.1 (78.9%). The impact on ESS of matching on mean age was expected as the minimum age of participants enrolled in the two trials was different (i.e., ≥18 years in BMN 270-301 and ≥12 years in HAVEN 3) with non-overlapping patients between 12 and 18 years between the two studies. The mean age of participants enrolled in BMN 270-301 mITT (n=132), and HAVEN 3 Group D (n=63) were 31.4 and 36.4 years respectively.

A sensitivity analysis was explored omitting the variable mean age from the set of baseline characteristics used to re-weight the mITT population (n=132) in BMN270-301, which resulted in the ESS increasing to 111.5 (84.4%) relative to the base case analysis, while the distribution of weights is well balanced and approximating a normal distribution, which the sponsor considers providing a more reliable re-weighted cohort for comparing outcomes observed in BMN270-301 (mITT, n=132) and HAVEN 3 Group D (n=63). In the sensitivity analysis, the mean age for study BMN 270-301 decreased to 30.3 years from 31.4 years after matching.

Table 6: Patient characteristics from HAVEN 3 and BMN 270-301 before MAIC (unweighted) and after MAIC (weighted) and ESS (base case)

Variable	HAVEN 3 (n=63)	BMN 270-301 (mITT n=132)				ESS (n)	ESS %*
		Unweighted		Weighted			
		Value	p-value	Value	p-value		
Mean Age, years	36.4	31.4	<0.0001	36.4	1.000	104.1	78.9%
Race, % White	74.6%	71.2%	0.4271	74.6%	1.000	131.3	99.5%
Mean BMI	25.56	25.31	0.5236	25.56	0.999	131.6	99.7%
Mean ABR	6.4	6.0	0.6769	6.4	1.000	131.8	99.8%
% with >= 9 bleeds in 24 wks. prior to enrolment	15.9%	9.1%	0.0434	15.9%	1.000	125.0	94.7%
% FVIII product used before trial entry = SHL	84.1%	72.0%	0.0002	84.1%	1.000	123.0	93.2%
Matching All 6 variables	-	-	-	-		76.2	57.7%

mITT, modified intent to treat; ESS: effective sample size; BMI: body mass index; ABR: annualised bleeding rate; SHL: standard half-life; *ESS as a percentage of 270-301 mITT n=132

With regards to the MAIC, the COMP accepted the methodology and the base line characteristics chosen by the sponsor. Age had a substantial impact on the ESS which means that the study populations of the two trials are not balanced. HAVEN 3 had older patients on average and included them from >=12 years whereas BMN 270-301 included patients from 18 years onwards. Age is a relevant covariable (not only because of the results) and disregarding it would not be suitable and the sensitivity analysis was therefore considered important.

Results:

After matching, the mean ABR for treated bleeds, all bleeds and treated joint bleeds were lower for Roctavian compared to Hemlibra. The mean ABR for all bleeds (regardless of whether the bleeds were treated with FVIII) was significantly lower for Roctavian compared to Hemlibra (1.82 vs. 3.30, rate ratio [RR] 0.55, 95% confidence interval [CI] 0.33-0.93) (Table 1 from the sponsors responses to the list of questions).

Table 1: MAIC Results – Mean ABR and rate ratio for all bleed types

Mean ABR	HAVEN 3 (n=63) Value (SE)	BMN 270-301 (mITT n=132) MAIC adjusted (ESS=76.2)		
		Raw ABR (SE)	NB model (SE)	Rate ratio (95% CI)
Treated bleed	1.60 (1.22)	1.43 (0.49)	1.34 (1.37)	0.84 (0.40, 1.74)
All bleeds	3.30 (1.22)	1.97 (0.50)	1.82 (1.19)	0.55 (0.33, 0.93)
Treated joint bleeds	1.20 (1.31)	0.77 (0.26)	0.70 (1.44)	0.58 (0.24, 1.42)
Treated spontaneous bleeds	0.50 (1.47)	0.59 (0.22)	0.53 (1.47)	1.06 (0.36, 3.08)

mITT: modified intent to treat; MAIC: matching adjusted indirect comparison; ESS: effective sample size; ABR: annualised bleeding rate; SE standard error; NB: negative binomial; CI: confidence interval

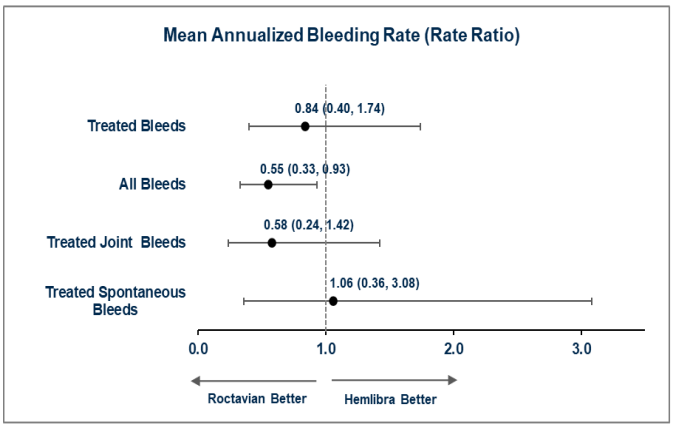
After matching, participants in BMN 270-301 were more likely to be bleed free compared to HAVEN 3 for all bleed types. The proportion of participants with zero treated bleeding events (80% vs. 56%, odds ratio [OR] 3.25, 95% CI 1.53-6.90) and zero treated joint bleeding events (86% vs. 68%, OR 2.75, 95% CI 1.20-6.31) was significantly higher for Roctavian relative to Hemlibra (Table 2 from the sponsors responses to the list of questions).

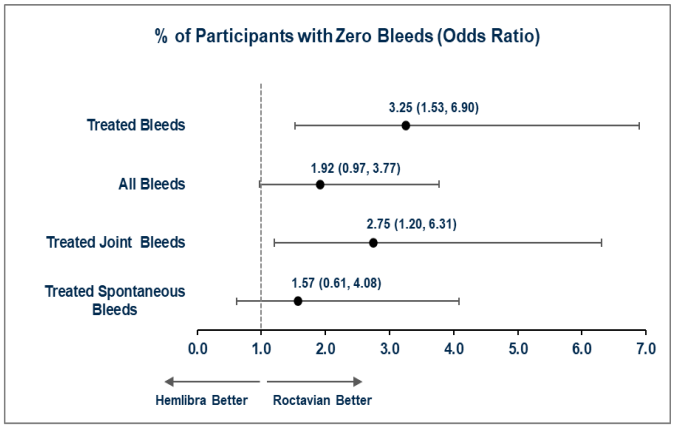
Table 2: MAIC Results – Proportion of participants with zero bleeds (%)

Proportion of participants with zero bleeds (%)	HAVEN 3 (n=63) Value	BMN 270-301 (mITT n=132) MAIC adjusted (ESS=76.2)	
		Value	Odds ratio (95% CI)
Treated bleed	56%	80%	3.25 (1.53, 6.90)
All bleeds	44%	61%	1.92 (0.97, 3.77)
Treated joint bleeds	68%	86%	2.75 (1.20, 6.31)
Treated spontaneous bleeds	83%	88%	1.57 (0.61, 4.08)

mITT: modified intent to treat; MAIC: matching adjusted indirect comparison; ESS: effective sample size; CI: confidence interval

During the oral explanation the sponsor showed a slide comparing annualised bleeding rates to percentage of participants with zero bleeds. This is replicated in the graphs below.





With regards to the distribution of bleeds, the sponsor confirmed during the oral explanation that most patients are bleed-free and that a few patients were responsible for the majority of the bleeds. This is in line with what is known from other studies. As the number of actual bleeds is very small the COMP questioned the clinically relevant treatment effect of Roctavian as compared to Hemlibra. The sponsor was not aware of a universally accepted figure of reduced bleeds that is considered clinically relevant. The generally accepted goal, however, is to have no bleeds at all ("Zero bleeds"). This was agreed by the patient representative engaged by the EMA, who was of the opinion that "zero bleeds" is the best measure and gives the patient a "haemophilia free mind".

Even though the ABR – "all bleeds" was trended to be better for Roctavian than Hemlibra the uncertainty was too high to conclusively agree on a significant benefit based on the reduced ABR. However, a majority of the COMP thought that the data provided (over approximately two years) on the patients with no bleeds at all was convincing and the difference to Hemlibra treated patients

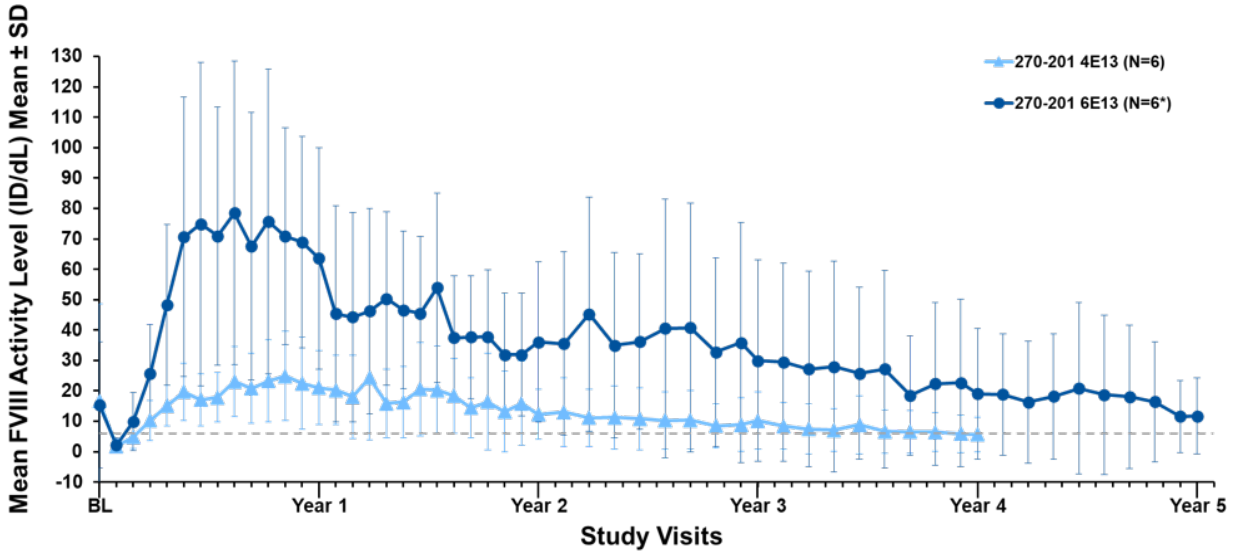
clinically relevant and therefore agreed on a significant benefit based on reduced bleeding. A minority of the COMP were of the opinion that the indirect comparison did not provide a meaningful conclusion regarding annualised bleeding rate nor an improved proportion of patients who were bleed free. In addition, this group felt that longer-term efficacy was driven by outcomes of the 7 subjects from earlier study 270-201 and voiced concern regarding the high percentage of low responders to Roctavian.

Long-term protection of Roctavian using a pharmacokinetic (PK) extrapolation model together with long-term clinical data from Study 201 (up to 6-year follow-up)

In general, the sponsor considered that extrapolation of Hemlibra data beyond 2 years is considered unreliable upon which to base comparisons, as it assumes the 2-years data carries forward and assumes maintained compliance outside the clinical trial setting, a factor which does not affect Roctavian which restores the endogenous FVIII activity.

The COMP was of the opinion that the data past 2 years was not suitable to base the significant benefit on as the numbers of patients is very low and the modelling approach has inherent uncertainties. However, the COMP did voice concerns about the durability of the treatment effect as it seems that based on the data submitted, a gradual decline of FVIII activity was observed. The sponsor claimed that in the long term, a shallower slope is seen and that they are not sure if all patients will have to be treated with factors. The sponsor did confirm that in the study they were aware of some patients who had to be treated with factors e.g. for serious physical action (boxing, football), or before surgery.

Mean FVIII activity levels >5 IU/dL over 5 years, Study 270-201 4E13 (n=6) and 6E13 (n=6) dose cohorts (mean ± SD):



The COMP could not base a significant benefit on data beyond two years.

In conclusion, the COMP accepted, through a qualified majority, that Roctavian provide a clinically relevant advantage as it has been shown that a higher proportion of patients achieve no bleeds as compared to Hemlibra. It was agreed that this constituted a significant benefit and that it could recommend the maintenance of the orphan designation.

4 COMP position adopted on 14 July 2022

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 A (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or during surgery, which may also be life-threatening;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Roctavian 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 shown that a single dose of Roctavian, when compared to treatment with Hemlibra, resulted in a higher proportion of patients with no bleeds. This was demonstrated in an indirect comparison at two years observation time.

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 (reg. prevalence & seriousness) or the second paragraph (reg. economic criterion) 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 Roctavian, adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene, valoctocogene roxaparvovec for treatment of haemophilia A (EU/3/16/1622) is not removed from the Community Register of Orphan Medicinal Products.