Summary of Risk Management Plan for Roctavian (BMN 270; valoctocogene roxaparvovec)

This is a summary of the risk management plan (RMP) for Roctavian. The RMP details important risks of Roctavian, how these risks can be minimized, and how more information will be obtained about Roctavian's risks and uncertainties (missing information).

Roctavian's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Roctavian should be used.

This summary of the RMP for Roctavian should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Roctavian's RMP.

I. The medicine and what it is used for

Roctavian is indicated for the treatment of adult patients with severe haemophilia A (congenital factor VIII [FVIII] deficiency) without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Further information about the evaluation of Roctavian's benefits can be found in the Roctavian EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/roctavian-0

II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of Roctavian, together with measures to minimise such risks and the proposed studies for learning more about Roctavian's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Roctavian, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Roctavian is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Roctavian are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Roctavian. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Hepatotoxicity • Infusion reactions (including hypersensitivity)
Important potential risks	• Thromboembolic events • Development of FVIII inhibitors • Transmission to third parties (horizontal transmission) • Germline transmission • Risk of malignancy in relation to vector integration in the DNA of body cells
Important missing information	• Long-term effect • Use in patients with liver impairment • Use in female patients

II.B. Summary of important risks

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Clinical Trial: Elevations in ALT were reported in 122 of 151 (80.4%) subjects in the All-Treated Population and in 113 of 141 (80.1%) subjects in the Proposed Label Population following administration of BMN 270. In the All-Treated Population, the majority of the ALT elevations reported as adverse events of special interest were Grade 1 or 2, with the highest CTCAE grades reported as Grade 1 in 99 subjects (65.6%), Grade 2 in 22 subjects (14.6%), and Grade 3 in 12 subjects (7.9%). In the Proposed Label Population, the highest CTCAE grades reported were 94 (66.7%) Grade 1, 21 (14.9%) Grade 2, and 11 (7.8%) Grade 3, respectively. No Grade 4 elevations have been reported. No long-term hepatic sequelae reported
Risk factors and risk groups	Patients with uncontrolled chronic hepatic infections, known significant hepatic fibrosis or cirrhosis, or other hepatic disorders or on concomitant hepatotoxic medications including herbal supplements and alcohol may be considered at risk for developing hepatocellular toxicity associated with AAV liver-directed gene therapies.
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.3 Section 4.4 Section 4.8 **PL** Section 2 Section 3 Section 4 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare Professional Guide Patient Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 270-601 (final study report 30 September 2042) 270-801 (final study report 30 June 2044) 270-201 (final study report 31 December 2024) 270-203 (final study report 31 December 2027) 270-205 (final study report 31 December 2028) 270-301 (final study report 30 June 2025) 270-302 (final study report 31 December 2023) 270-303 (final study report 30 September 2027) 270-401 (final study report 31 July 2038) Healthcare professional survey (final study report 30 June 2028) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Infusion Reactions (Including Hypersensitivity)	
Evidence for linking the risk to the medicine	Of the 151 subjects in the All-Treatment Population, 59 (39.1%) experienced at least one AE meeting the criteria for potential infusion-associated reactions. The most commonly reported events included nausea (20 subjects [13.2%]), fatigue (11 subjects [7.3%]), headache (8 subjects [5.3%]), and diarrhoea (4 subjects [2.6%]). Twelve of the 151 (7.9%) subjects experienced infusion-related reactions with initial symptoms developing during or within 6 hours after the end of infusion. Four infusion-related reactions (in 3 subjects) were reported as SAEs (Grade 2 events of presyncope and maculopapular rash; and Grade 3 hypersensitivity and anaphylactic reaction). In addition, 2 subjects experienced SAEs more than 6 hours but within 48 hours of infusion, including one subject who experienced hypersensitivity reaction and one subject who experienced pyrexia.
Risk factors and risk groups	Although the underlying mechanism is not entirely understood, all patents should be closely monitored for development of infusion reactions. Patients with known hypersensitivity to the active substance or to any of the excipients are particularly at risk for developing hypersensitivity reactions
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.2 Section 4.3 Section 4.4 Section 4.8 **PL** Section 2 Section 4 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 270-601 (final study report 30 September 2042) 270-801 (final study report 30 June 2044) 270-201 (final study report 31 December 2024) 270-203 (final study report 31 December 2027) 270-205 (final study report 31 December 2028) 270-301 (final study report 30 June 2025) 270-302 (final study report 31 December 2023) 270-303 (final study report 30 September 2027) See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Thromboembolic Events	
Evidence for linking the risk to the medicine	No subject had experienced a thromboembolic event as of the data cut.
Risk factors and risk groups	There is no experience in subjects with a history of relevant venous or arterial thromboembolic events or thrombophilia who would potentially be considered to the at-risk population.
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.4 **PL** Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare Professional Guide Patient Guide Patient Card
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Important Potential Risk: Development of FVIII Inhibitors	
Evidence for linking the risk to the medicine	As of the data cutoff, no study patient had developed inhibitors (neutralizing antibody to FVIII).
Risk factors and risk groups	The transgene of BMN 270 encodes the SQ variant of the human coagulation FVIII, and in clinical trials has been evaluated in patients with a minimum of 150 exposure days to FVIII concentrates or cryoprecipitate and have not developed FVIII inhibitors. So although the overall risk of developing inhibitors is very low, given the limited clinical experience in patients with less than 150 exposure days to FVIII concentrates or cryoprecipitate, this population could potentially be considered at risk.
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.4 Section 4.8 **PL** Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare professional guide Patient Guide Patient Card
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Important Potential Risk: Transmission to Third Parties (Horizontal Transmission)	
Evidence for linking the risk to the medicine	Administration of BMN 270 resulted in detectable vector DNA in blood and all shedding matrices evaluated, with peak concentrations observed between 1 and 9 days post BMN 270 administration. At peak levels, the quantity of vector DNA found in patient biofluids was significantly lower than quantities required for clinical effect, as determined in 270-201. The maximum vector DNA concentrations were observed in blood, with the maximum concentration observed to date across 270-201 and 270-301 being 1.78E11 vg/mL. Assuming all vector DNA measured corresponded to intact BMN 270, and assuming a third party weighing 70 kg receives a 1 mL injection of patient's blood, this concentration would be equivalent to a dose of 2.54E9 vg/kg, which is approximately 4 orders of magnitude less than the non-efficacious dose of 2E13 vg/kg. In addition, risk associated with accidental or third-party exposure including environmental is negligible given the non-replicating and non-pathogenic nature of the modified AAV5 vector and benign nature of the FVIII-SQ protein. Development of AAV5 specific antibody, detectable at 2 weeks post-administration, would be predicted to neutralize remaining capsids in the blood and seminal compartments. Therefore, presence of intact vectors or vector capsid fragments in body secretions and excretions is not considered to cause any relevant degree of transduction in contact persons. Presence of residual transgene DNA in saliva, urine, stool, or semen (including in seminal fluid, spermatogonia, leucocytes, epithelial cells) is considered to have no clinical consequences for people exposed.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.4 Section 5.2 **PL** Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare Professional Guide Patient Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 270-201 (final study report 31 December 2024) 270-203 (final study report 31 December 2027) 270-205 (final study report 31 December 2028) 270-301 (final study report 30 June 2025) 270-302 (final study report 31 December 2023) 270-303 (final study report 30 September 2027) 270-401 (final study report 31 July 2038) Healthcare professional survey (final study report 30 June 2028)

Important Potential Risk: Germline Transmission	
Evidence for linking the risk to the medicine	In clinical studies, after administration of BMN 270, transgene DNA was temporarily detectable in semen. The clinical relevance of presence of residual transgene DNA in semen has not been established. In addition, GLP Study BMN270-19-008 and BMN270-19-033 assessed the risk of germline transmission by evaluating, via qPCR, whether transgene DNA is present in the offspring of male mice treated with BMN 270. There were no instances of germline transmission, that is, no transgene DNA was detected in any of the pups sired by male mice dosed with BMN 270.
Risk factors and risk groups	Male patients engaged in sexual intercourse with a woman of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.4 Section 4.6 Section 5.2 **PL** Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare Professional Guide Patient Guide Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 270-201 (final study report 31 December 2024) 270-203 (final study report 31 December 2027) 270-205 (final study report 31 December 2028) 270-301 (final study report 30 June 2025) 270-302 (final study report 31 December 2023) 270-303 (final study report 30 September 2027) Healthcare professional survey (final study report 30 June 2028)

Important Potential Risk: Risk of malignancy in relation to integration in the DNA of body cells	
Evidence for linking the risk to the medicine	AAV vectors have the potential to integrate into the genome of transduced cells, and integration with AAV can occur without resulting in genotoxicity, clonal expansion, or insertional tumorigenesis. To date, insertional tumorigenesis linked to administration of a AAV vector-based gene therapy has only been observed in non-clinical mouse studies (not in larger animals or humans) (Donsante 2001; Bell 2006; Donsante 2007; Rosas 2012; Wang 2012; Walia 2015; Chandler 2015; Chandler 2017). The clinical relevance of these findings on translatability to humans is unknown. Feedback from scientific forums conducted in 2021 including ASGCT, FDA Advisory Committee, and KOLs, conclude that translatability of vector-mediated insertional mutagenesis and HCC observed in mouse models to humans remains unknown. Clinical experience continues to evolve, with AAV gene therapy administered to 3,328 patients in 101 clinical trials, including some trials with a duration of up to 20 years (Kuzmin 2021). Liver gene transfer studies with AAV vectors showed a favourable safety profile, with no reported AAV treatment-related carcinogenic events (Monahan 2021). Additionally, MAH has not observed any oncogenic events related to BMN 270 (which includes 170 dosed subjects to date). FVIII levels are steady with no evidence of sustained increase following attainment of steady-state levels that would be suggestive of clonal expansion. Vector genomes detected in blood and all shedding matrices evaluated do not show kinetics consistent with clonal expansion. While integration events were also observed in haemophilia A dogs administered AAV-cFVIII associated with clonal expansion, no tumours or oncogenesis were observed in this study for up to 10 years after administration (Nguyen 2021). In ongoing clinical studies with BMN 270, there has been no evidence of clonal expansion based on FVIII trajectories which have shown a gradual decline over time in subjects followed for up to 5 years. Consistent with other AAV gene therapies, vector integration was observed after BMN 270 administration in non-human primate liver samples evaluated for up to 26 weeks after treatment (BMN 270-20-013). Integrations were distributed across the liver cell genome. Some integration sites were located within proto-oncogenes and tumor suppressor genes or located near their transcription starting sites. There was no preferential integration near genes of concern and no clonal outgrowth of cells harbouring integration sites. Furthermore, no test-article-related pre-neoplastic or neoplastic changes were seen in either of the GLP toxicology studies (Studies BMN270-14-030 and BMN270-16-045), including 26 weeks of follow up, with a high dose of 2E14 vg/kg BMN 270 in CD1 mice. There has been no evidence of carcinogenicity or tumorigenesis observed in completed nonclinical studies with BMN 270. Integration site analysis were performed on liver samples from 5 patients in clinical studies. Samples were collected approximately 0.5-4.1 years post-dose. Vector integration into human genomic DNA was observed in all samples. BMN 270 can also insert into DNA of other human body cells (as observed in parotid gland DNA samples from one patient treated with BMN 270 in a clinical study). While the clinical relevance of individual integration events is not known to date, but it is acknowledged that risk of malignancy in relation to vector integration is a potential risk.
Risk factors and risk groups	No specific patient population at risk Patients with significant fibrosis, cirrhosis, chronic hepatitis who are at risk of hepatocellular carcinoma and patients with existing malignancy are contraindicated from receiving treatment with BMN 270.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> **SmPC** Section 4.4 Section 5.3 **PL**

Important Potential Risk: Risk of malignancy in relation to integration in the DNA of body cells	
	Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare Professional Guide Patient Guide Patient Card
Additional pharmacovigilance activities	270-601 (final study report 30 September 2042) 270-801 (final study report 30 June 2044) 270-201 (final study report 31 December 2024) 270-203 (final study report 31 December 2027) 270-205 (final study report 31 December 2028) 270-301 (final study report 30 June 2025) 270-302 (final study report 31 December 2023) 270-303 (final study report 30 September 2027) 270-401 (final study report 31 July 2038) Healthcare professional survey (final study report 30 June 2028)

Missing Information: Long-Term Effect	
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.4 PL Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Additional risk minimisation measures: Healthcare Professional Guide Patient Guide
Additional pharmacovigilance activities	270-601 (final study report 30 September 2042) 270-801 (final study report 30 June 2044) 270-201 (final study report 31 December 2024) 270-203 (final study report 31 December 2027) 270-205 (final study report 31 December 2028) 270-301 (final study report 30 June 2025) 270-302 (final study report 31 December 2023) 270-303 (final study report 30 September 2027) 270-401 (final study report 31 July 2038) Healthcare professional survey (final study report 30 June 2028)

Missing Information: Use in Patients with Liver Impairment	
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.2 Section 4.4 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders.
Additional pharmacovigilance activities	None

Missing Information: Use in Female Patients	
Risk minimisation measures	Routine risk minimisation measures: **SmPC** Section 4.6 **PL** Section 2 Other routine risk minimisation measures beyond the Product Information: **Legal Status:** Medicinal product subject to restricted medical prescription. Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders.
Additional pharmacovigilance activities	Embryo-Foetal development toxicity study

II.C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study Short Name	Purpose of the Study
270-601 (A Non-Interventional, Multi-National, Longitudinal Study of Patients Treated with Roctavian (valoctocogene roxaparvovec))	This study is being undertaken to better characterize the long-term effectiveness and safety of Roctavian in patients in a real-world setting. The study aims to assess the long-term effectiveness of the product in a broader population to further inform the risk-benefit balance of Roctavian and to provide information on the long-term impact of treatment with Roctavian. In addition, the study aims to assess the frequency and incidence rate of safety events identified in the Pharmacovigilance and Risk Management Plan including hepatoxicity, thromboembolic events, infusion reactions (including hypersensitivity), malignancies, and development of FVIII inhibitors. Primary Objectives: • To describe the bleeding profile and long-term durability of FVIII expression in patients administered Roctavian • To describe the use of exogenous factor and non-factor replacement treatment(s) in patients administered Roctavian • To describe the change in clinical outcome assessments (ie, Haemophilia-specific quality of life questionnaire [Haemo-QoL-A], EuroQol 5 Dimension 5 Level instrument [EQ-5D-5L], and Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific [WPAI+CIQ:HS]) in patients administered Roctavian Secondary Objectives: • To quantify and characterize the risk of SAEs and suspected ADRs in patients administered Roctavian • To quantify and characterise the risk of targeted adverse events (TAEs) of hepatotoxicity, thromboembolic events, infusion reactions, new malignancies, and development of FVIII inhibitors in patients with haemophilia A administered Roctavian
270-801 (A Retrospective Cohort Study of Patients Treated with Roctavian (valoctocogene roxaparvovec): An Analysis of Patient Registries)	This study is being undertaken to better characterize long-term effectiveness and safety outcomes of patients treated with Roctavian in a real-world setting based on the safety profile outlined in the Pharmacovigilance and Risk Management Plan. **Primary objective**: • To quantify and characterize the risk of targeted adverse events (TAEs) of hepatoxicity, thrombotic events, infusion reactions, new malignancies, and development of FVIII inhibitors among patients with HA administered Roctavian. **Secondary objectives**: • To quantify and characterize the risk of suspected adverse drug reactions (ADRs) in patients administered Roctavian. • To describe the bleeding profile and long-term durability of FVIII expression in patients administered Roctavian. • To describe the use of exogenous factor and non-factor replacement treatment(s) in patients administered Roctavian. • To describe changes in quality of life, as measured by the Euro-QoL Health Status Assessment: 5 Dimensions, 5 Levels of Severity (EQ-5D-5L), in patients administered Roctavian. • To quantify and characterize the risk of TAEs among patients with HA treated with haemostatic treatments, stratified by disease severity and treatment regimen.

Study Short Name	Purpose of the Study
270-401 (A Long-Term Follow-Up Study in Subjects with Hemophilia A Who Received BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in a Prior BioMarin Clinical Trial)	The purpose of this study is to monitor the safety and efficacy of BMN 270 long-term in subjects who received the drug in a clinical study. Subjects will be enrolled in 270-401 following completion of 5 years in the dosing study and will be followed for approximately 10 years in the long-term study (15 years total from BMN 270 dosing).
270-301 (A Phase 3 Open-Label, Single-Arm Study to Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions)	The primary efficacy objective of the study is to: • Assess the efficacy of BMN 270. The secondary efficacy objectives of the study are to: • Assess the impact of BMN 270 on usage of exogenous FVIII replacement • Assess the impact of BMN 270 on the number of bleeding episodes requiring exogenous FVIII replacement therapy. The safety objectives of the study are to: • Evaluate the safety of BMN 270. • Assess the long-term safety of BMN 270.
270-303 (A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients)	The primary efficacy objective of the study is to: • Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 The secondary efficacy objectives of the study are to: • Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis • Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis • Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline The safety objectives of the study are to: • Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids following intravenous infusion of BMN 270 • Assess the long-term safety of BMN 270 with prophylactic corticosteroids

II.C.2 Other studies in post-authorisation development plan

The following studies are also part of the post-authorisation development plan:

Study Short Name	Purpose of the Study
270-201 (A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A)	The primary objectives of the study are: • To assess the safety of a single intravenous administration of a recombinant AAV5 encoding human coagulation FVIII (AAV5-hFVIII-SQ) vector. • To determine the dose of AAV5-hFVIII-SQ required to achieve FVIII at or above 5% of normal activity (≥5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated FVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose. The secondary objectives of the study are: • To describe the immune response to the FVIII transgene and AAV capsid proteins following systemic administration of AAV5-hFVIII-SQ • To assess the impact of BMN 270 on the frequency of FVIII replacement therapy during the study • To assess the impact of BMN 270 on the number of bleeding episodes requiring treatment during the study
270-302 (A Phase 3 Open-Label, Single-Arm Study to Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions)	The primary efficacy objective of the study is to: • Assess the efficacy of BMN 270 defined as FVIII activity, The secondary efficacy objectives of the study are to: • Assess the impact of BMN 270 on usage of exogenous FVIII replacement • Assess the impact of BMN 270 on the number of bleeding episodes requiring exogenous FVIII replacement therapy The safety objectives of the study are to: • Evaluate the safety of BMN 270.
270-203 (A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Preexisting Antibodies Against AAV5)	The primary objective of the study is to: • Assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody Secondary objectives of the study are to: • Assess the efficacy of BMN 270 at Week 26 • Assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy • Assess the impact of BMN 270 on the number of bleeding episodes requiring exogenous FVIII therapy • Evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270 • Assess the impact of BMN 270 on patient-reported outcomes (PROs)

Study Short Name	Purpose of the Study
270-205 (A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Active or Prior Inhibitors)	The primary efficacy objective of the study is to: • Assess the safety of a single IV administration of BMN 270 in HA subjects with active inhibitors (Part A), or prior inhibitors (Part B) The secondary efficacy objectives of the study are to: • Assess the efficacy of BMN 270 as measured by FVIII activity together with the level of inhibitor titre (Part A) and the recurrence of inhibitors (Part B). • Assess the impact of BMN 270 on the use of haemophilia therapy. • Assess the impact of BMN 270 on the number of bleeding episodes requiring pharmacologic intervention • Assess the impact of BMN 270 on quality of life as measured by the Haemo-QoL-A questionnaire The tertiary efficacy objectives of the study are to: • Assess the impact of BMN 270 on quality of life as measured by additional patient-reported outcome (PRO) instruments • Assess the safety and efficacy of emicizumab transition to BMN 270
Healthcare professional survey	To evaluate the effectiveness of educational materials provided as additional risk minimization measures