swissmedic

Date: 13.12.2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Hemgenix®

International non-proprietary name: etranacogene dezaparvovec (contains genetically modified adeno-associated virus-based vector serotype 5 (AAV5))

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): Hemgenix 1x10 e13 gc/mL

Route(s) of administration: for single-dose intravenous infusion only

Marketing authorisation holder: CSL Behring AG

Marketing authorisation no.: 68780

Decision and decision date: approved on 07.12.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ABR	Annualised Bleeding Rate
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AMT-060	Internal company name for the AMT-061 precursor (wild-type FIX)
AMT-061	Internal company name for etranacogene dezaparvovec (Padua FIX), also called CSL222
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FIX	Factor IX
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for etranacogene dezaparvovec in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 04.04.2022.

2.2 Indication and dosage

2.2.1 Requested indication

Etranacogene dezaparvovec is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Haemophilia B (congenital Factor IX deficiency) and with a preexisting neutralising adeno-associated viral vector serotype 5 (AAV5) antibody titre below 1:900 to reduce the frequency of bleeding episodes and the need for Factor IX replacement therapy who:

- currently use Factor IX prophylaxis therapy, or
- have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes

2.2.2 Approved indication

Etranacogene dezaparvovec is an adeno-associated virus vector-based gene therapy indicated for the treatment of male adults with severe/moderately severe Haemophilia B (congenital Factor IX deficiency) and with a preexisting neutralising adeno-associated viral vector serotype 5 (AAV5) antibody titre below 1:900 to reduce the frequency of bleeding episodes and the need for Factor IX replacement therapy who:

- currently use Factor IX prophylaxis therapy, or
- have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.

2.2.3 Requested dosage

For single-dose intravenous infusion only.
The dose of etranacogene dezaparvovec is a single dose of 2×10^{13} genome copies (gc) per kilogram (kg) of body weight (bw) or 2.0 mL/kg bw, administered as an intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline) (see "Dosage/Administration" section. The dose should be calculated as follows: Etranacogene dezaparvovec dose (in mL) = patient body weight (in kilogram) × 2. Etranacogene dezaparvovec can be administered only once.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	15 March 2023
Formal control completed	17 March 2023
List of Questions (LoQ)	26 May 2023
Response to LoQ	3 August 2023

Preliminary decision	22 September 2023
Response to preliminary decision	20 November 2023
Final decision	7 December 2023
Decision	approval

3 Medical context

Haemophilia B is an inherited bleeding disorder characterised by an increased bleeding tendency due to either a partial or complete deficiency in the activity of the essential blood coagulation factor IX. Haemophilia B is an X-linked, recessive condition, and occurs primarily in males. Females are typically carriers with a mild or absent bleeding phenotype.
Intra-articular and intramuscular bleeding is a major clinical manifestation of the disease. Bleeding most commonly occurs in the knees, elbows, and ankles. The pathogenesis of haemophilic arthropathy is multifactorial, with changes occurring in the synovium, bone, cartilage, and blood vessels.
Recurrent joint bleeding causes synovial proliferation and inflammation (haemophilic synovitis), which contribute to end-stage degeneration (haemophilic arthropathy), with pain and limitation of motion severely affecting patients' quality of life (QoL).
The severity of bleeding manifestations generally correlates with the degree of the clotting factor deficiency. Severe forms become apparent early in life.
Based on the historical classification using functional FIX levels, approximately one-third of individuals have a severe disorder characterised by functional FIX levels < 1% of normal, approximately one-third of individuals have moderate haemophilia B, with 1 to 5% of normal, and approximately one-third of individuals have mild haemophilia B with > 5 to < 40% of normal FIX levels.
However, individuals may exhibit a severe bleeding phenotype irrespective of their FIX level, including individuals with current or historical repeated spontaneous bleeding episodes (which may include joint or life-threatening haemorrhage), established joint damage due to haemarthrosis, and / or the current use of factor IX for continuous prophylaxis.
Complications associated with haemophilia negatively impact QoL and short- and long-term productivity during bleeding episodes.
Females may have haemophilia with the same factor VIII (FVIII) or FIX levels as affected males, with the same spectrum of morbidity from haemophilia as affected males, including joint impairment / haemophilic arthropathy levels. Subclinical or asymptomatic joint damage in females occurs regardless of the clinical severity of the haemophilia.
In the population of women receiving care for haemophilia in the United States Hemophilia Treatment Center network between 2012 and 2020, a factor level < 40% (meeting the diagnosis of haemophilia) was reported for 1,667 females, 51 of whom had severe (factor level < 1%), 79 moderate (factor level 1 to 5%), and 1,537 mild (factor level > 5%) haemophilia.
Haemophilia remains a serious and life-threatening condition in which breakthrough bleeds and repeated bleeding in the joints in prophylactic treatment settings lead to sequelae, including haemophilic arthropathy (permanent joint disease). Current treatment options rely on protein replacement therapy by intravenous injection, and have markedly improved patient lifespan and quality of life. However, issues with current options include lack of patient compliance due to needle-based administration, high expenses, and other potential complications (e.g. surgical procedures, inhibitor formation).

4 Quality aspects

4.1 Drug substance

Etranacogene dezaparvovec, the active substance of Hemgenix, is a recombinant viral vector based on a naturally occurring adeno-associated virus, serotype 5 (AAV5), and is used for delivery of the transgene encoding for the functional human coagulation factor IX into the liver.
The virus capsid of AAV serotype 5 consists of viral capsid proteins, assembled in an icosahedral formation. Wild-type AAV virus is non-pathogenic and naturally replication-deficient, requiring co-infection with helper virus in order to replicate.
In etranacogene dezaparvovec, the virus genome, with the exception of flanking inverted terminal repeats (ITRs), is replaced by the therapeutic transgene expression cassette using recombinant DNA techniques. The transgene expression cassette contains the codon-optimised coding sequence for

human coagulation factor IX, the naturally occurring Padua variant with a single amino acid substitution R338L, under the control of a liver-specific promoter.
When translated *in vivo* and matured through the cleavage of a short leader sequence, the FIX protein is 415 amino acids long.

Etranacogene dezaparvovec is produced in a baculovirus expression system using an insect cell line derived from *Spodoptera frugiperda* cells (Sf9 cells) and recombinant baculovirus-based vectors carrying genes encoding for AAV Rep and Cap, as well as the transgene. The production system is based on a 2-tiered production cell bank and a baculovirus seed system.
The history and characterisation of the Sf9 cell banks, including master and working cell banks, as well as cells at the limit of age, are described.
The generation of the recombinant baculovirus vectors is described, and the respective virus seeds including master and working seeds, were characterised.

During the production of etranacogene dezaparvovec drug substance, the cells from a working cell bank are expanded in several steps to obtain sufficient cell mass, then the cells are co-infected with the recombinant baculoviruses, incubated, lysed, and harvested. The cell harvest is purified by several chromatographic and filtration steps, formulated, and filled into the primary container closure system.
Control of critical steps and process material is achieved using process parameter controls and in-process testing. In-process testing is presented, the methods are described, and justification is provided for the defined limits and acceptance criteria.

Etranacogene dezaparvovec as a drug substance is a clear and colourless solution of viral particles in the formulation buffer.

The manufacturing process performance was validated with several consecutive runs, and a consistent production with an efficient removal of impurities was demonstrated.
Several changes were implemented during development of the manufacturing process, including changes to the manufacturing site and production scale, as well as replacement of the originally used coding sequence for wild-type FIX by that for the FIX Padua variant (R338L) with higher specific activity. Comparability studies including release data and extended characterisation demonstrated comparability between the different processes.
The change of the FIX variant sequence was assessed in non-clinical and clinical bridging studies.

Etranacogene dezaparvovec drug substance and its impurities were sufficiently characterised using state-of-the-art analytical methods.

The specification for release and stability of the drug substance includes relevant tests for e.g. identity, quantification, purity, relevant impurities, and potency. Acceptance limits are based on batch analysis and stability data, as well as clinical experience. Wherever applicable, limits are in conformance with current compendial guidelines. Analytical methods are described, and non-compendial methods have been fully validated in accordance with ICH guidelines.
Batch data analyses from developmental, clinical, and process qualification batches were provided.

No significant changes were observed for etranacogene dezaparvovec drug substance stored under recommended long-term storage conditions in the original container.

4.2 Drug product

The Hemgenix drug product is supplied as a preservative-free, sterile concentrate for infusion with a nominal concentration of $1x10^{13}$ genome copies per mL intended for a single-dose intravenous administration after dilution with 0.9% (w/v) sterile sodium chloride solution.

The drug product is supplied in a 10 mL Type I glass vial with a chlorobutyl rubber stopper sealed with

an aluminium flip-off seal. The materials of the glass vial and rubber stopper comply with compendial requirements.
The total number of vials per single dose corresponds to the dose requirement for each individual patient, depending on body weight.

The drug product is formulated in sterile phosphate buffered saline (PBS), pH 7.1, with 5% sucrose (w/v) and 0.02% polysorbate-20 (v/v).
All excipients are of compendial quality and commonly used for parenteral pharmaceutical preparations.

The manufacturing process for the drug product consists of formulation buffer preparation, thawing of the drug substance aliquots, followed by sterile filtration and compounding, aseptic filling into the final containers, visual inspection, labelling, and secondary packaging.
The process performance qualification was performed with 3 consecutive batches at commercial scale, and validation activities included sterilising filter validation, aseptic process validation, as well as mixing homogeneity and shipping validation.
The specifications for release and stability of the finished product include relevant tests and acceptance criteria, e.g. for appearance, pH, osmolality, subvisible particles, identity, concentration and purity, potency, endotoxins, and sterility.
Analytical methods are described, and non-compendial methods have been fully validated in accordance with ICH guidelines. Batch data analyses from developmental, clinical, and process qualification batches of finished product were provided.

The drug product is stored at 2 to 8 °C in original, unopened containers, protected from light. A shelf-life of 24 months is supported by the available stability data.
After dilution with 0.9% (w/v) sodium chloride solution for injection, the drug product can be stored at room temperature (15 to 25 °C) protected from light and should be administered within 24 hours.

The manufacturing processes for the drug substance and the drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated. Safety of the product with regard to viral and non-viral contamination has been adequately addressed.

5 Nonclinical aspects

5.1 Pharmacology

Etranacogene dezaparvovec (AMT-061) has been developed for the treatment of adult patients with haemophilia B, which is an X-linked bleeding disorder due to a deficiency of the human blood coagulation factor IX (hFIX). The deficiency of hFIX protein results in a decreased capacity for thrombin generation. AMT-061 consists of a recombinant non-replicating adeno-associated viral vector of serotype 5 containing the Padua variant (R338L) of hFIX under the control of a liver-specific promoter (LP1). Following IV infusion, AMT-061 preferentially transduces liver cells, where the vector DNA is maintained mainly in an episomal form. This results in an LP1-directed long-term expression of the hFIX-Padua protein. The recommended human dose is $2x10^{13}$ gc/kg.

In vivo studies were performed in wild-type (wt) C57Bl/6 mice, haemophilia B mice, and rhesus and cynomolgus macaques (non-human primates, NHPs). Only male animals were studied, as mostly men are affected due to the X-linked inheritance. The proof-of-concept (PoC) studies in haemophilia B mice and wt mice showed dose-dependent elevations of hFIX protein levels and FIX activity in plasma after a single IV injection, resulting in a restoration of clotting activity in the haemophilia mice. The protein expression stems mostly from viral vector DNA taken up by hepatocytes. Generally, protein expression occurred 4-5 weeks at the latest after the injection of AMT-061 or AMT-060 (a product that does not express the Padua hFIX), and remained measurable until the end of the study periods, although levels dropped by that time. No differences were noted between AMT-060 and AMT-061, with the exception that AMT-061-derived hFIX protein was more active due to the R338L mutation. The level of hFIX protein was lower in mice treated at a younger age as compared to adult animals. This could be due to fewer genome copies that could successfully be injected in younger, and thus smaller, animals. Data obtained from mice suggest that the drop in the hFIX protein level in some animals is due to the development of anti-hFIX antibodies. This may not be relevant for humans, as the development of anti-FIX antibodies was not an issue in human studies.

Additional studies in mice investigated prednisone as a potential co-medication in the clinical setting. Also, 5 AMT-061 batches that differed with respect to their in vitro potency were investigated. The treatment with prednisone reduced the level hFIX protein, whereas vector DNA levels in the livers were not affected. The in vivo evaluation of the AMT-061 batches showed similar dose dependencies regarding liver transduction, FIX protein levels, and clotting activities, despite the fact that in vitro differences in potency were noted.

Pharmacodynamic studies in NHPs included a PoC study (13 weeks) and 2 safety studies (up to 26 weeks). Single doses of AMT-060 or AMT-061 resulted in hFIX protein expression throughout the study periods, with initial peaks 1 week after administration and a subsequent reduction and stabilisation of the protein level. A clear dose dependence was observed with respect to hFIX protein levels, ranging from 0.3% of normal human levels in the lowest dose group to 15% in the highest. Generally, animals developed anti-AAV5 viral vector antibodies and anti-hFIX antibodies. Two animals in a high-dose group experienced a significant drop in protein levels that might be due to the development of anti-hFIX antibodies. In conclusion, it can be assumed that FIX antibody titres increase over time in these NHPs, resulting in lower plasma hFIX protein levels and activity.

The hFIX protein activity was assessed by a 1-stage aPTT and a chromogenic assay. The NHP FIX activity could not be distinguished from that of hFIX, and the baseline activity was determined before administration of AMT-060 or AMT-061. FIX activity was dose related and correlated with hFIX protein levels. After treatment with the hFIX-Padua encoding AMT-061, a clotting activity up to 400% of normal human levels was noted in the highest dose group.

No dedicated studies were submitted with respect to **safety pharmacology**. Safety pharmacology endpoints (CNS, cardiovascular, respiratory, kidney function) were included in the toxicity studies in cynomolgus monkeys with AMT-060 and AMT-061. No risks were identified. Only with respect to heart rate were the values for the AMT-061 highest dose group ($9x10^{13}$ gc/kg) lower than those for the

control group, with the lowest value observed during Week 26 (190 bpm). However, due to the lack of a pretreatment baseline it was difficult to conclude whether this was a true test article-related effect. There was no clear indication of a treatment-related effect on PR, QRS, QT, QTcB, or waveform morphology. No effects were seen after treatment with AMT-060.

5.2 Pharmacokinetics

Pharmacokinetic studies included the evaluation of biodistribution, shedding, and persistence of AMT- 061 and AMT-060 in mice and NHPs in several PD and toxicity studies. All methods used were sufficiently validated and in compliance with GLP, when necessary. Bridging studies confirmed that the assays were able to detect AMT-060 and AMT-061. The analysed organs include liver, adrenal glands, brain, heart, kidneys, lungs, lymph nodes, muscle, pancreas, salivary glands, spleen, thymus, thyroid, testes, epididymis, seminal vesicles, and prostate. With respect to excretion/shedding, plasma/serum, urine, saliva, and semen were evaluated.

In mice, vector DNA in plasma was highest 1 day after treatment and thereafter decreased steadily. In 1 study it was shown that vector DNA decreased from 10^{10} copies/mL to 10^{4} copies/mL within 13 weeks. This DNA concentration profile was independent of the formulation with or without PS-20.

The plasma hFIX protein levels were dose dependent and followed a biphasic pattern, reaching maximum levels 4-5 weeks after treatment, followed by a subsequent fall-off and stabilisation until the end of the studies. The kinetics of this biphasic pattern were similar, but not identical, in all studies, and differed depending on the age of the animals (lower protein levels in young animals. Generally, the plasma profiles were similar between AMT-061 and AMT-060 and independent of the formulation with or without PS-20. The kinetics profiles of the viral vector and hFIX protein may depend on the development of anti-vector and anti-hFIX antibodies.

The biodistribution of the vector DNA depends on the capsid proteins. AAV5 capsids are supposed to target the vector to the liver, which was confirmed in a dose-dependent manner in studies in mice. However, all other organs/tissues analysed were also positive for vector DNA. Even though there is a tendency of reduced levels over time, vector DNA was measurable at all investigated time points. Neither prednisone, nor PS-20, nor the type of product (AMT-060, AMT-061) had a measurable influence on the vector DNA distribution. Where analysed, the vector DNA in mice always persisted until the end of the studies (18 months as the longest time point in mice). Vector DNA was found in the testis, epididymis, and seminal vesicles, pointing to a risk of inadvertent germline transmission. However, a specific germline transmission study in mice did not reveal a risk, as no AMT-060 was detected in any of the female tissues examined (uterus, fetus, and placenta) from untreated females following mating with treated males.

In NHPs, the vector DNA plasma profile is biphasic. The AUC increased dose-dependently. At higher doses (above 10^{13} gc/kg), the T1/2 was around 25-29 days. At lower doses (10^{12} gc/kg and lower) the T1/2 was substantially shorter (around 30-70 hours). At the highest doses, vector DNA plasma levels were still detectable at least 6 months after treatment.

The plasma hFIX protein levels were dose dependent and also followed a biphasic pattern. Four days after vector infusion, circulating hFIX protein was detected in all dose groups, and the average levels reached a maximum around Days 7 or 8 after infusion. Subsequently, the hFIX protein levels decreased and stabilised for the duration of the follow-up period. The kinetics profiles of the viral vector and hFIX protein may depend on the development of anti-vector and anti-hFIX antibodies.

Biodistribution analysis showed that vector DNA dose-dependently distributed systemically throughout all organs, with highest levels in the liver and adrenal glands, followed by spinal cord and spleen.

Vector DNA was also found in the testis, epididymis, and seminal vesicles. In the off-target organs, the other analysed tissues, vector DNA was at least 1 or 2 logs lower than in the liver. In the target organ, the liver, the vector DNA was distributed regularly throughout the liver lobes. The transduction of hepatocytes was dose dependent and estimated to be between 17% and 46%. The vector DNA in the liver and other organs decreased over time, but persisted throughout the whole study periods (26 weeks was the longest time point analysed). No differences were observed between AMT-060 and AMT-061.

The mRNA expression is driven by a liver-specific promoter. This was confirmed by the quantification of hFIX mRNA by RT-qPCR in liver, adrenal glands, spleen, kidney, heart, and spinal cord, showing strong dose-dependent mRNA expression only in the liver. No differences were observed between AMT-060 and AMT-061.

Excretion of AMT-060 was analysed in saliva and urine, and of AMT-061 in urine only. The clearance curves in saliva and urine followed the clearance profile for serum, albeit with vector DNA concentrations multiple logs lower than in serum. Vector DNA in saliva was no longer detectable between Weeks 8 and 12. Vector DNA levels in urine were below the LOD around Week 8.

5.3 Toxicology

Single IV dose GLP studies were performed in mice and NHPs to analyse the toxicity and biodistribution of AMT-061 and AMT-060. The doses ranged from a low pharmacological effect level, corresponding to a 10-fold human dose ($2x10^{13}$ gc/kg) in mice, to a 5-fold human dose in NHPs. These studies also included the analysis of hFIX expression and activity. Furthermore, haematology/clotting and cytokine analyses were conducted. To evaluate the haemostatic safety related to high levels of circulating hFIX and FIX activity, thrombin/antithrombin III (TAT) complex and D-dimer levels were measured. AMT- 060 and AMT-061 showed comparable safety profiles, and no differences were apparent between the formulations with or without PS-20.

Studies in mice with study durations up to 6 months. The established NOAEL always corresponded to the highest applied dose (up to $2.3x10^{14}$ gc.kg), and no target organ toxicities were identified. Six out of more than 1,000 mice died prematurely, due to experimental procedures or unknown reasons in the control or low-dose groups. Given the absence of a correlation with the applied dose, the deaths were concluded to be unrelated to treatment with AMT-060 or AMT-061.

One effect noted was an AMT-060-meditated increase in spleen weights, which might be attributable to an immune response towards the viral vector. Other effects include pulmonary thrombus formation in 2 animals (1 animal treated with AMT-060 and 1 animal treated with AMT-061) from the same study in the high-dose group ($5x10^{13}$ gc/kg). In the second dose group, with a maximum dose of $2.3x10^{14}$ gc/kg, no effects with regards to thrombus formation were noted. As the incidence of pulmonary thrombosis was low and the severity was minor, it was not considered to be an adverse effect by the applicant.

A paternal germline transmission study was conducted in mice. AMT-060-treated males were paired with untreated females on Day 6 after treatment. Although high levels of AMT-060 were detected in male gonadal tissues, no AMT-060 was detectable in untreated females or their offspring. No adverse effects on male reproductive organs were detected.

Studies in NHPs showed mild transient elevations of the liver enzymes AST (up to 4.5x of control) and ALT (up to 3.0x of control), observed 2 to 4 days after treatment and which were most likely related to the uptake of the viral vector by hepatocytes. AST and ALT activities were normal by Day 8. Some effects on the clotting cascade were noted in the highest dose group. APTT was shortened, while PT was longer, as a consequence of the high FIX clotting activity levels. Plasma TAT complex and D-dimer levels were not elevated. AMT-060 and AMT-061 showed comparable profiles.

No notable histopathological findings were recorded. Even though viral vector DNA was found in the central nervous system, including brains and spinal cord, dorsal root ganglia (DRG) toxicity was not included in the histopathological analyses. No adverse findings in spinal cord (cervical, lumbar, and thoracic) histopathology, including absence of spinal cord axonopathy, were reported in the NHP study with etranacogene dezaparvovec dose up to $9x10^{13}$ gc/kg, with a 26-week follow-up. The DRG analysis is planned to be performed in an ongoing study in juvenile NHPs.

An integration site (IS) analysis was performed based on LAM-PCR and next-generation sequencing with liver tissue obtained from mice and NHPs treated with AMT-060. The IS analyses of liver tissue indicated a low and near random distribution of IS without specific carcinogenicity concerns.

The analysis identified 8,646 unique ISs for the mice, of which 7,537 ISs could be exactly mapped to a definitive position in the host genome. In total, 1,541 unique ISs were retrieved for cynomolgus macaques, of which 1,392 could be exactly mapped to the macaque genome. The retrieved integrants were randomly distributed throughout the host genome in the cynomolgus macaque genome, while in mice some clustering of AAV integrations sites was noted. No enrichment of integrations next to, or within, genes listed in cancer gene databases has been observed for either mouse or NHP, and the observed integration profile did not raise specific carcinogenicity concerns.

5.4 Nonclinical conclusions

The submitted studies include a clear proof-of-concept. The AMT-060 and AMT-061 were sufficiently characterised with respect to vector kinetics and biodistribution. The toxicity evaluation did not reveal critical findings. From the preclinical perspective, this application can be approved.

6 Clinical aspects

6.1 Clinical pharmacology

The kinetics of FIX activity, FIX protein, clearance of vector DNA, and immunogenicity, along with safety and tolerability of AMT-060, were evaluated in the first-in-human Phase 1/2 study (Study CT-AMT-060-01) in subjects with moderately severe or severe haemophilia B. The kinetics of FIX activity, FIX protein, clearance of vector DNA, and immunogenicity, along with efficacy and safety of etranacogene dezaparvovec, were evaluated in Studies CSL222_2001 (CT-AMT-061-01) and CSL222_3001 (CT-AMT-061-02). Due to the nature of the gene product, no conventional clinical pharmacology studies were conducted.

Pharmacokinetics

No relative bioavailability studies have been conducted in humans to evaluate the effect of formulation changes or food on either etranacogene dezaparvovec or AMT-060-derived FIX protein and FIX activity.

Clinically relevant and statistically significant increases in FIX activity were observed after administration of etranacogene dezaparvovec. Following a single-dose administration of etranacogene dezaparvovec, FIX activity levels gradually increased, and subjects achieved mean ± standard deviation (SD) uncontaminated (i.e. excluding measurements within 5 half-lives of FIX replacement therapy) FIX activity levels of 38.95 ± 18.72%, 41.48 ± 21.71%, 36.90 ± 21.40%, and 36.66 ± 18.96% of normal, respectively, at 6 months, 12 months, 18 months, and 24 months post-dose (Study CSL222_3001 (CT-AMT-061-02)).

The time to onset of FIX protein expression was quick, with expression detectable by the first uncontaminated measurement (at Week 3 in Study CSL222_3001 (CT-AMT-061-02) and Week 1 in Study CT-AMT- 061-01). The mean FIX protein levels ranged from 19.35 to 25.25% across visits, and the mean ratio of FIX activity to FIX protein level was stable at approximately 7 to 8.5 between Month 6 and Month 24 (Study CSL222_3001 (CT-AMT-061-02)).

The time of maximum levels of vector DNA in blood and semen was observed between 4 and 7 hours, and between Weeks 5 and 27 post-dose, respectively, in Study CSL222_3001 (CT-AMT-061-02). The earliest that subjects were no longer shedding vector DNA from blood and semen was 17 weeks and 6 weeks post-dose, respectively. The median time to absence of shedding in semen was 47.3 weeks, while the median time to absence of shedding in blood was 52.3 weeks (Study CSL222_3001 (CT-AMT-061-02)).

Durability analysis of FIX activity and FIX protein concentration derived from etranacogene dezaparvovec showed that FIX levels were stable up to 18 months, with no statistically significant differences in the least square mean FIX levels at almost all time points up to 2 years (24 months) compared to baseline at Month 6. Durability analysis of FIX activity and FIX protein concentration derived from AMT-060 showed that FIX levels at almost all timepoints up to 5 years were not statistically significantly different from the Month 6 baseline, suggesting stable levels of FIX up to 5 years. A sensitivity analysis taking Month 3 as the baseline was consistent with the primary analysis (Month 6 baseline) for both etranacogene dezaparvovec and AMT-060.

Special populations / Intrinsic factors

The effect of intrinsic and extrinsic factors on uncontaminated FIX activity was evaluated in the pharmacokinetic population, defined as subjects receiving a full dose of etranacogene dezaparvovec and having at least 1 post-dose FIX activity measurement in Study CSL222_3001 (CT-AMT-061-02). A trend toward higher mean FIX activity with increasing age was observed. The impact of age on FIX activity as an independent variable could not be established due to the lower sample size for the ≥ 60-years of age subgroup (N = 7).

Overall, pre-existing anti-AAV5 NAbs up to a titre of 1:678 (53/54 [98.1%] in Study CSL222_3001 (CT-AMT-061-02)) immediately before dosing, total IgG and IgM antibodies to AAV5, and AAV5 capsid-specific T-cell response had no clinically relevant impact on the FIX activity, and there was no clinically relevant impact of pre-existing anti-AAV5 NAbs on safety in Studies CSL222_3001 (CT-AMT-061-02) and CSL222_2001 (CT-AMT-061-01).

Subjects with mild renal impairment (N = 7/53; PK population) had slightly higher mean FIX activity (up

to 37% relative difference) compared to those with normal renal function during Months 6 to 18 post-dose. Only 1 subject with moderate renal impairment in the study had FIX activity similar to that in subjects with normal renal function. The impact of moderate renal impairment, severe renal impairment, and end-stage renal disease on FIX activity could not be fully assessed due to either limited ("moderate") or no ("severe" and "end stage renal disease") subject representation of these subgroups. Subjects with steatosis controlled attenuation parameter scores of ≥ S2 (≥ 260 decibels per metre [dB/m]), < S2 (< 260 dB/m) and missing scores showed no clinically meaningful differences in the mean FIX activity levels.
Evaluation of the impact of race, ethnicity, body mass index, and baseline FIX activity at the time of historical diagnosis on FIX activity showed that all subgroups within each of these variables had clinically meaningful increases in FIX activity post dose.
Thirteen out of 53 subjects who received a full dose of etranacogene dezaparvovec experienced alanine aminotransferase (ALT) elevation (> upper limit of normal [ULN] or > 2 × baseline value over the initial 90 days post dose), and 9 subjects were treated with corticosteroids for ALT elevation of either > ULN (n = 8) or > 2 × baseline value (n = 1). Subjects with ALT elevation had approximately 44% and 41% lower mean FIX activity (statistical significance not tested) at Months 18 and 24, respectively, compared to subjects that did not have ALT elevation. The 9 subjects that were treated with corticosteroids for ALT elevations exhibited approximately 63% and 62% lower mean FIX activity (statistical significance not tested) at Months 18 and 24, respectively, compared to subjects who did not receive corticosteroid co-administration. The mean FIX activity in the limited number of subjects (n = 9) treated with corticosteroids for ALT elevations was > 15% of normal, and the subjects were able to maintain FIX activity levels in the mild haemophilia B range.
Different drug product batches used in Study CSL222_3001 (CT-AMT-061-02) showed no notable differences in the mean FIX activity at 6, 12, and 18 months after etranacogene dezaparvovec administration.
Preclinical studies and clinical studies with etranacogene dezaparvovec or its predecessor AMT-060 showed no effect on electrocardiogram readings. The impact of etranacogene dezaparvovec on cardiac repolarisation in subjects with moderately severe or severe haemophilia B has not been evaluated in a clinical study. No vital sign abnormalities were observed in clinical studies.

6.2 Dose finding and dose recommendation

The safety and efficacy of 1 doses (5 x 10^{12} and 2 x 10^{13} gc/kg) of AMT-060, a recombinant AAV5 containing the codon-optimised hFIX complementary deoxyribonucleic acid (cDNA) under the control of a liver-specific promoter, were evaluated in trial CT-AMT-60-01.

6.3 Efficacy

A single dose of etranacogene dezaparvovec reduced the incidence of all bleeding episodes by 64% (p = 0.0002) and the incidence of FIX-treated bleeding episodes by 77% (p < 0.0001) during Months 7 to 18 post-dose (period of 52 weeks from establishment of stable FIX expression) compared to the ≥ 6-month lead-in period of standard of care FIX prophylaxis in the FAS of all subjects treated in Study CSL222_3001 (CT-AMT-061-02). The reduction in ABR was maintained through to Month 24 post-dose, with a 64% reduction in all bleeding episodes (p = 0.0002; p-value not adjusted for multiplicity) and a 73% reduction in FIX-treated bleeding episodes (p = 0.0001; p-value not adjusted for multiplicity) in the FAS during Months 7 to 24 post-dose compared to the ≥ 6-month lead-in period.
Both non-inferiority and superiority were met for ABR for all bleeding episodes at Months 7 to 18 post-dose in subjects who were anti-AAV5 NAb-negative at baseline (last pre-dose value) and for subjects with a baseline anti-AAV5 NAb titre < 1:700, tested using the clinical study assay (FAS and Per Protocol [PP] population). These results were also observed at Months 7 to 24 post-dose.
Etranacogene dezaparvovec showed stable FIX expression with clinically relevant and statistically significant increases in FIX activity at all timepoints assessed (Months 6, 12, 18, and 24 post-dose) in subjects with a severe bleeding phenotype when used according to the proposed label.
Across Studies CSL222_2001 (CT-AMT-061-01) and CSL222_3001 (CT-AMT-061-02), 78 subjects were screened, 8 subjects were screen failures, 70 subjects were enrolled, and 57 subjects received treatment with etranacogene dezaparvovec (Integrated Summary of Safety [ISS] Safety population).

6.3.1 Pivotal studies

Study CSL222_2001 (CT-AMT-061-01)

Three subjects with severe haemophilia B received a single IV dose of 2×10^{13} gc/kg etranacogene dezaparvovec and have been followed up for 3 years post-dose (data cutoff: 14 December 2021 (CT-AMT-061-01 (CSL222_2001) 3-year CSR).

The primary objective was to confirm that a single dose of 2×10^{13} gc/kg etranacogene dezaparvovec resulted in FIX activity levels of ≥ 5% at 6 weeks after dosing. The secondary efficacy objectives assessed the effect of etranacogene dezaparvovec on endogenous FIX activity at 52 weeks post-dose, discontinuation of previous continuous FIX prophylaxis, total usage of FIX replacement therapy, ABR, and specific types of bleeding events (e.g., spontaneous bleeds, joint bleeds, traumatic bleeds). Efficacy measurements included FIX activity level, FIX protein levels, FIX replacement therapy, bleeding episodes, and Patient Reported Outcomes (PRO) to evaluate QoL.

At 6- and 52-weeks post-AMT-061 administration, the subjects expressed mean ± standard deviation (SD) uncontaminated endogenous FIX activity levels of 30.6 ± 6.97% and 40.8 ± 9.45% of normal, respectively, as measured by the one-stage (aPTT-based) assay. Uncontaminated endogenous FIX activity levels were available for all 3 subjects at 24 months and 30 months post-AMT-061 administration, demonstrating mean ± SD one-stage FIX activity levels of 44.2 ± 7.66% and 50.0 ± 11.40%, respectively, at these 2 timepoints. At Month 36, 3 years post-AMT-061 administration, uncontaminated samples were available for 2 subjects and demonstrated that FIX activity levels continued to be elevated compared to baseline, at 32.3% and 41.5%, respectively. No trends in FIX activity levels were noted with this small dataset.

Two of 3 subjects did not experience bleeding episodes post-AMT-061 administration. The third subject had 2 lower leg muscle bleeding episodes that were treated with FIX; one was spontaneous and the other was traumatic. The ABR over 3 years (36 months) of follow-up was 0.22, and the ABRs for spontaneous and traumatic bleeding episodes over 3 years (36 months) of follow-up 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).

All 3 subjects discontinued use of continuous prophylaxis FIX during the study within 1 to 4 days of AMT-061 administration. The annualised mean FIX use was 714.6 IU/year over 3 years (36 months) of follow-up for the post-continuous prophylaxis period, with all of this use by a single subject. This subject required on-demand FIX replacement therapy post-AMT-061 administration per protocol for the following: due to elective surgeries (2 major hip surgeries associated with an ongoing SAE of worsening avascular necrosis - left hip [preferred term: osteonecrosis]); for 2 reported bleeding episodes; and 2 separate times for self-administered infusions due to unreported reasons.

Annualised Exogenous Factor IX Use by Period and Time Interval (All Subjects Treated; Table 10, CSR AMT-061-01)

Period	Time Interval/Visit	Factor IX Use (IU/kg/year)	Factor IX Use (IU/year)
Pre-AMT-061	Over the 1 year prior to screening, n	3	3
	Mean (SD)	3675.9 (1445.0)	306,204.9 (112,272.4)
	Min; Max	2510; 5293	223,429; 434,000
	Over the 30 days prior to screening, n	3	3
	Mean (SD)	3127.7 (908.5)	260,285.8 (65,916.5)
	Min; Max	2118; 3880	188,516; 318,121
	During screening, n	3	3
	Mean (SD)	3542.0 (647.4)	299,330.7 (70,896.9)
	Min; Max	3058; 4277	250,726; 380,682
Post-AMT-061 Administration	Overall, n	3	3
	Mean (SD)	13.7 (13.0)	1157.2 (1076.0)
	Min; Max	0; 26	0; 2128
Post-Continuous Prophylaxis	Overall, n	3	3
	Mean (SD)	8.7 (15.1)	714.6 (1237.8)
	Min; Max	0; 26	0; 2144
	Year 1, n	3	3
	Mean (SD)	6.9 (12.0)	568.3 (984.4)
	Min; Max	0; 21	0; 1705
	Year 2, n	3	3
	Mean (SD)	13.8 (23.9)	1133.3 (1963.0)
	Min; Max	0; 41	0; 3400

Factor IX activity measured using the chromogenic assay was lower than using the 1-stage (aPTT-based) assay. Using the chromogenic assay, mean ± SD uncontaminated FIX activity levels were 17.5 ± 3.64% and 22.2 ± 5.98% at Weeks 6 and 52, respectively. At Month 30, 2.5 years post-AMT- 061 administration, the mean ± SD uncontaminated FIX activity level was 22.3 ± 5.90%. Samples were available for 2 subjects at Month 36, 3 years post-AMT-061 administration, with uncontaminated FIX activity levels of 17.0% and 22.8%.

HJHS scores decreased for 2 subjects from 35 and 36 at Baseline to 31 and 32 at Month 36; the third subject only had reported scores of 1 and 6 at Baseline and Month 24, respectively.

Generally, QoL improved for 2 subjects based on responses to the patient-reported outcome questionnaires. The third subject showed a decrease in QoL at Week 26 and Week 52, including worsening pain and problems with pain and mobility as indicated via the BPI and EQ 5D 5L, which was likely due to pre-existing avascular necrosis of the bilateral hip (preferred term: osteonecrosis) and 2 associated elective major hip surgeries during the study; improvement was noted at Month 24. This subject also showed a decrease in QoL at Week 36, including worsening pain and problems with pain/discomfort as indicated via the BPI and EQ-5D-5L; he received a cortisone injection to treat an ongoing TEAE of sciatica the day prior to the Week 36 visit.

Study CSL222_3001 (CT-AMT-061-02)
Study CSL222_3001 (CT-AMT-061-02) is an ongoing Phase 3 trial. The study sample size is constrained by the non-inferiority analysis of the primary endpoint, ABR.
Across Study CSL222_3001 (CT-AMT-061-02), 75 subjects were screened, 8 subjects were screen failures, and 67 subjects were enrolled. A total of 54 subjects with moderately severe or severe haemophilia B received a single IV dose of etranacogene dezaparvovec, 53 of whom received the planned dose of 2×10^{13} gc/kg, and 1 subject received approximately 10% of the planned dose. One subject died during long-term follow- up (post-dose Day 464) due to cardiogenic shock, which was considered unrelated to study treatment. One subject who received full treatment, but remained on routine prophylaxis, withdrew consent after 24 months post-dose, and will be followed for long-term safety through medical record review. The remaining 52 subjects continue to receive long-term follow-up.
The primary objective was to demonstrate the noninferiority of etranacogene dezaparvovec (when administered with the proposed dose of 2×10^{13} gc/kg) during the 52 weeks following establishment of stable FIX expression (Months 7 to 18) post-dose compared to standard of care routine FIX prophylaxis during the ≥ 6-month lead-in period, as measured by ABR. Secondary efficacy objectives include ABR assessment for superiority, endogenous FIX activity at 6, 12, and 18 months post-dose, annualised consumption and annualised infusion rate of FIX replacement therapy, and discontinuation of previous continuous routine prophylaxis.
Efficacy measurements include recording of bleeding episodes, FIX activity levels and FIX protein concentration, use of FIX replacement therapy, and PROs (EuroQol-5 dimensions-5 levels [EQ-5D-5L], International Physical Activity Questionnaire [iPAQ], Work Productivity and Activity Impairment Questionnaire [WPAI], Brief Pain Inventory [BPI] - Short Form, Haemophilia Activities List [HAL], and Haemophilia Quality of Life Questionnaire for Adults [Hem-A-QoL]), as well as an evaluation of joint health with trained personnel using the Haemophilia Joint Health Score (HJHS). Efficacy measurements for the optional sub-studies include Patient Reported Outcomes, Burdens, and Experiences (PROBE) questionnaires and musculoskeletal ultrasound.
It should be noted that the applicant has changed the primary efficacy endpoint during the ongoing study (protocol amendment 6).
The ABR (primary variable) for the ≥ 6-month lead-in period on routine FIX prophylaxis and for Months 7 to 18 post-dose was analysed using a repeated measures generalised estimating equations negative binomial regression model of the number of reported bleeding events, accounting for the paired design and the differential collection phases of the study. Treatment (i.e. period) was included as a categorical variable in the model. The primary endpoint for ABR remains those results obtained for the Month 18 data cut-off. The estimated ABR ratio, one-sided 97.5% Wald confidence interval (CI), and the corresponding p-value were determined.
The primary clinical efficacy endpoint was met. Treatment with AMT-061 was found to be non-inferior to standard of care routine FIX prophylaxis with regard to the ABR. The adjusted ABR ratios for Months 7 to 18 and for Months 7 to 24 of the post-treatment period to the ≥6-month lead-in period for the Full Analysis Set (FAS) were 0.36 (95% Wald CI: 0.20, 0.64) and 0.36 (95% Wald CI: 0.21, 0.63), respectively.
The mean adjusted ABR for all bleeding episodes was reduced following AMT-061 treatment and stable FIX expression, from a rate of 4.19 (95% CI: 3.22, 5.45) for the ≥6-month lead-in period to 1.51 (95% CI: 0.81, 2.82) for Months 7 to 18 of the post-treatment period (64% reduction [95% CI: 36%, 80%; p = 0.0002]). The adjusted ABR ratio for the Month 7 to 18 post-treatment period to lead-in period was 0.36 (95% Wald CI: 0.20, 0.64). As the upper limit of the Wald CI was less than 1.8, non-inferiority can be declared vs. the lead-in standard of care FIX prophylaxis. The reduction in ABR was maintained through to Month 24. The mean adjusted ABR for all bleeding episodes was 1.51 (95% CI: 0.83, 2.76) for Months 7 to 24 of the post-treatment period (64% reduction [95% CI: 37%, 79%; p = 0.0002 [not adjusted for multiplicity]) with an adjusted ABR ratio for the Month 7 to 24 post-treatment period to lead-in period of 0.36 (95% Wald CI: 0.21, 0.63).
During the ≥6-month lead-in period (cumulative 33.12 person-years of observation), the majority of subjects who later received treatment (40/54 [74.1%]) experienced bleeding episodes. A total of 136 bleeding episodes were reported for the lead-in period, including 118 FIX-treated bleeding episodes. The majority of bleeding episodes (118/136) were very mild to moderate in severity; 14 severe and 4

very severe bleeding episodes were reported in 10/54 (18.5%) subjects and 3/54 (5.6%) subjects, respectively. Traumatic and spontaneous bleeding episodes were reported in 29/54 (53.7%) and 24/54 (44.4%) subjects, respectively. The most common locations of bleeding episodes in the lead-in period were joints (59.3%) and muscles (31.5%). During Months 7 to 18 of the post-treatment period, following AMT-061 treatment and stable FIX expression (cumulative 49.78 person-years observed), the majority of treated subjects (34/54 [63.0%]) had zero bleeding episodes; bleeding episodes were reported in 20/54 (37.0%) subjects. During Months 7 to 18 of the post-treatment period, 54 bleeding episodes were reported, including 30 FIX-treated bleeding episodes. The majority of bleeding episodes (43/54) were very mild to moderate in severity; 7 severe and 2 very severe bleeding episodes were reported in 7/54 (13.0%) subjects and 2/54 (3.7%) subjects, respectively, and severity was missing for 2 episodes. Traumatic and spontaneous bleeding episodes were reported in 12/54 (22.2%) and 9/54 (16.7%) subjects, respectively. The most common locations of bleeding episodes during this post-treatment period were joint (20.4% of subjects) and surface (14.8% of subjects).
Sensitivity analyses demonstrated the robustness of the ABR results. For FIX-treated bleeding episodes, the adjusted mean ABR was 3.65 (95% CI: 2.82, 4.74) for the ≥6-month lead-in period and 0.84 (95% CI: 0.41, 1.73) for Months 7 to 18 of the post-treatment period (77% reduction [95% CI: 54%, 88%, p <0.0001), with an adjusted ABR ratio for the Month 7 to 18 post-treatment period to lead- in period of 0.23 (95% Wald CI: 0.12, 0.46). Compared to the ≥6-month lead-in period, the adjusted ABR for FIX-treated bleeding episodes was lower, at 0.99 (95% CI: 0.48, 2.03) for Months 7 to 24 of the post-treatment period (73% reduction [95% CI: 46%, 86%; p = 0.0001, not adjusted for multiplicity]) with an adjusted ABR ratio for the Month 7 to 24 post-treatment period to lead-in period of 0.27 (95% Wald CI: 0.14, 0.54). Similar ABR results were observed for the Months 7 to 18 post-treatment period and the Months 7 to 24 post-treatment period when the analysis was conducted with the PP population.

Summary of Type I Error-Controlled Primary and Secondary Endpoints After 18 Months Post-treatment (Full Analysis Set; Table 12, CSR CT-AMT-061-02 (CSL222_3001))

Endpoint	Point Estimate	95% CI	One-sided p-value	Statistical Significance
Primary Efficacy				
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period) for Non-inferiority	0.36	0.20, 0.64	NA	Yes
Secondary Efficacy				
Change From Baseline 1-stage (aPTT-based) FIX Activity (%) at 6 Months Post-treatment	36.00	31.47, 40.54	<0.0001	Yes
Change From Baseline 1-stage (aPTT-based) FIX (%) Activity at Year 1 Post-treatment	38.82	34.04, 43.60	<0.0001	Yes
Change From Baseline 1-stage (aPTT-based) FIX (%) Activity at Month 18 Post-treatment	34.31	29.52, 39.11	<0.0001	Yes
Mean Difference in Annualised Consumption of FIX Replacement Therapy Use (IU/kg/yr; Month 7 to 18 Post-treatment – Lead-in Period)	-3056.8	-3642.8, -2470.8	<0.0001	Yes
Adjusted Ratio for Annualised Infusion Rate of FIX Replacement Therapy (Month 7 to 18 Post-treatment: Lead-in Period)	0.03	0.01, 0.10	<0.0001	Yes
Odds Ratio 1-stage (aPTT-based) FIX Activity <12% of Normal (Month 6 to 18 Post-treatment: Lead-in Period)	0.036	0.014, 0.093	<0.0001	Yes
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period) for Superiority	0.36	0.20, 0.64	0.0002	Yes
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period), Spontaneous Bleeding Episodes	0.29	0.12, 0.71	0.0034	Yes
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period), Joint Bleeding Episodes	0.22	0.10, 0.46	<0.0001	Yes
LS Mean Difference in iPAQ Total Physical Activity Score (Post-treatment Period 1st Year – Lead-in Period)	-721.2	-1770.6, 328.3	0.9121	No
LS Mean Difference in EQ-5D-5L VAS (Post-treatment Period 1st Year – Lead-in Period)	0.1	-3.5, 3.8	0.4753	No

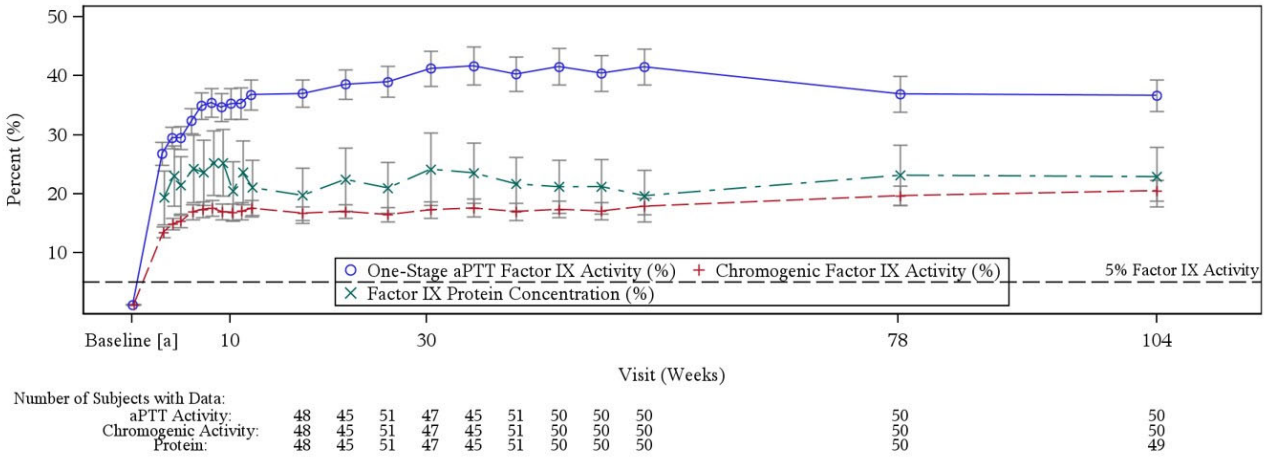
The adjusted ABR for all bleeding episodes decreased following AMT-061 treatment, from 4.19 (95% CI: 3.22, 5.45) for the ≥6-month lead-in period on standard of care routine FIX prophylaxis to 1.51 (95% CI: 0.81, 2.82) for Month 7 to 18 of the post-treatment period (64% reduction; [95% CI: 36%,80%, p = 0.0002]), and, similarly, to 1.51 (95% CI: 0.83, 2.76) for Month 7 to 24 of the post-treatment period (64% reduction; [95% CI: 37%, 79%, p = 0.0002; p-value not adjusted for multiplicity]).
ABR by subtype of bleeding episodes (spontaneous, joint, traumatic, and new and true), whether FIX-treated or not, was substantially reduced after AMT-061 treatment compared to the lead-in period. Spontaneous FIX-treated bleeding episodes were the only bleeding subtype that did not reach statistical significance for ABR in the Month 7 to 18 post-treatment period compared to the lead-in period, while total

reported spontaneous bleeding episodes (regardless of whether treated) did reach statistical significance. However, the reduction in both spontaneous and FIX-treated spontaneous bleeding episodes reached statistical significance (p-values not adjusted for multiplicity) for the Month 7 to 24 post-treatment period compared to the lead-in period.

Reductions in ABR were observed in most subgroups analysed; exceptions included subjects with a pre-existing anti-AAV5 NAb titre at baseline (N = 21; Month 7 to 18 rate ratio = 1.77; Month 7 to 24 rate ratio = 2.56). This higher ABR ratio in the anti-AAV5 NAb-positive subgroup was driven by a single subject with a pre-dose NAb titre of 3212.3. This subject did not respond to treatment with AMT-061 and was on prophylactic treatment, receiving 30 FIX injections during Months 7 to 18 and 1 reported FIX injection post-Month 18 prior to study discontinuation. Time within 5 half-lives of a FIX injection was removed from the time at risk, which resulted in approximately 1 day (1.09 days) at risk during Months 7 to 12, 7 to 18, and 7 to 24. During Months 7 to 18, this subject had 4 spontaneous and 1 unknown bleeds, resulting in an ABR of 1673.97. During Month 19 to 24, no new bleeding episodes occurred. When this subject was excluded from the analysis, superiority was reached with an adjusted rate ratio of 0.30 (95% CI 0.15, 0.62) for Month 7 to 18; the adjusted rate ratio was 0.39 (95% CI: 0.18, 0.82) for Month 7 to 24.

Clinically relevant and statistically significant increases in FIX activity were observed after administration of AMT-061. At Month 6, Month 12, Month 18, and Month 24 post-administration of AMT-061, the least squares (LS) mean change from baseline in FIX activity was 36.18% (95% CI: 31.41, 40.95; p <0.0001), 38.81% (95% CI: 34.01, 43.60; p <0.0001), 34.31% (95% CI: 29.52, 39.11; p <0.0001), and 34.13% (95% CI: 29.57, 38.69; p <0.0001 [not adjusted for multiplicity]), respectively. Treatment with AMT-061 was associated with lower odds of having FIX activity <12% of normal for Month 6 to 18 compared to the lead-in period (odds ratio: 0.027; 95% CI: 0.009, 0.080; p <0.0001), and for Month 6 to 24 compared to the lead-in period (odds ratio: 0.029; 95% CI: 0.010, 0.080; p <0.0001 [not adjusted for multiplicity]). No clinically meaningful differences were observed in the subgroup analyses.

Mean Uncontaminated Central Laboratory One-stage (aPTT-based) FIX Activity (%) and Mean FIX Protein Concentration (%) ± SE Over Time During the Post-Treatment Period (Full Analysis Set; Figure 5, CSR CT-AMT-061-02 (CSL222_3001))



The annualised consumption of FIX replacement therapy for the Month 7 to 18 and Month 7 to 24 post-treatment periods were significantly lower following treatment with AMT-061 as compared to standard of care during the lead-in period (mean difference: -248,825.0 IU/year [p <0.0001] and -248,392.6 IU/year [p <0.0001; not adjusted for multiplicity], respectively). In line with this, the annualised use (infusions/year) of FIX replacement therapy for the Month 7 to 18 and Month 7 to 24 post-treatment periods were significantly lower following AMT-061 administration (rate ratios [post-treatment/lead-in] of 0.03 [p <0.0001] and 0.04 [p <0.0001; not adjusted for multiplicity], respectively).

Following treatment with AMT-061, 52/54 (96.3%) subjects discontinued routine FIX prophylaxis and remained free of routine FIX prophylaxis from Day 21 through to Months 7 to 24.

Post-treatment mean FIX activity was numerically lower in subjects with pre-existing anti-AAV5 NAbs at baseline compared to those without pre-existing NAbs. There was no clinically meaningful correlation of pre-existing anti-AAV5 NAb titre with FIX activity at 24 months.
At dosing, 2 subjects had pre-existing target joints, which resolved during the post-treatment period. One subject had a new target joint that occurred during the post-treatment period (post-Month 7, on Day 381), and was not resolved at the time of the data cut-off for this report.
The percentage of subjects with 0 bleeding episodes increased following treatment with AMT-061 from 25.9% during the ≥6-month lead-in period to 63.0% and 50.0% during the Month 7 to 18 and Month 7 to 24 post-treatment periods. No statistically significant differences in iPAQ total physical activity scores were observed between the lead-in and post-treatment periods. A statistically significant increase in EQ-5D-5L VAS scores was not observed between the lead-in and first 12 months post- treatment; however, there was an improvement in the 12-24 month post-treatment period compared to the lead-in (LS mean increase: 2.8; p = 0.0244 [not adjusted for multiplicity]). Mean Haem-A-QoL total score improved, primarily due to improvements in the feeling, work and school, treatment burden, and future domains.
Statistically significant decreases in HJHS total scores (indicating improvement) were observed in the first and the second years post-AMT-061 treatment compared to the lead-in period, with LS mean decreases of -1.7 (p = 0.0196) and -2.1 (p = 0.0019) [p-values not adjusted for multiplicity], respectively.

6.4 Safety

At the time of data cut-off for this application, exposure to etranacogene dezaparvovec in Studies CSL222_2001 (CT-AMT-061-01) and CSL222_3001 (CT-AMT-061-02) ranged from ≥ 12 to < 48 months. Overall exposure was 1547.5 person-months.
All 57 subjects in the ISS Safety population were male. The mean (SD) age of subjects was 41.7 (± 15.42) years, and ages ranged from 19 to 75 years. Six subjects were aged > 65 years. Of the 52 subjects who self-reported race, 41 (78.8%) subjects identified as White, 3 (5.8%) subjects identified as Black or African American, 2 (3.8%) subjects identified as Asian, and 6 (11.5%) subjects identified as other.
No pertinent safety issue was identified in the nonclinical development of AMT-060 and etranacogene dezaparvovec that warranted specific investigation or particular monitoring in the clinical development program. To enable an in-depth assessment of patient safety, a comprehensive collection of relevant parameters for safety was defined in the protocol, including the definition of Adverse Events Qualifying for Special Notification, in line with regulatory guidance.
Study CSL222_2001 (CT-AMT-061-01) did not assess AEs reported before etranacogene dezaparvovec treatment as the study did not include a lead-in period.
In Studies CSL222_2001 (CT-AMT-061-01) and CSL222_3001 (CT-AMT-061-02), all 57 subjects treated with etranacogene dezaparvovec experienced at least 1 treatment-emergent adverse event (TEAE) during the post-treatment period. The System Organ Classes (SOCs) with the highest incidence of reported TEAEs were Infections and Infestations (73.7%), Musculoskeletal and Connective Tissue Disorders (68.4%), General Disorders and Administration Site Conditions (56.1%), Gastrointestinal Disorders (47.4%), Injury, Poisoning, and Procedural Complications (45.6%), Nervous System Disorders (43.9%), and Investigations (42.1%). The most frequently reported TEAEs by PT, irrespective of investigator causality assessment, were Arthralgia (36.8%), Headache (31.6%), Nasopharyngitis (26.3%), Fatigue (24.6%), and ALT Increased (21.1%).
Twelve subjects experienced 14 TEAEs of ALT Increased, and 9 subjects experienced 10 TEAEs of AST Increased.
Six (10.5%) subjects experienced 11 TEAEs in the Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) SOC. These included Adenoma Benign, Basal Cell Carcinoma (BCC), Benign Breast Neoplasm, Colon Adenoma, Gastrointestinal Neoplasm, Hepatocellular Carcinoma (HCC), Meningioma, Pancreatic Neuroendocrine Tumour, Prostate Cancer, and Skin Papilloma; all were assessed as not treatment-related by both the Investigator and Sponsor. The TEAEs of BCC, HCC, and Prostate Cancer were AEs Qualifying for Special Notification.
Thirty-nine (68.4%) subjects experienced 95 TEAEs that were assessed as treatment-related. Common treatment-related TEAEs by SOC were General Disorders and Administration Site

Conditions (19 [33.3%]), Investigations (13 [22.8%]), Nervous System Disorders (10 [17.5%]), and Gastrointestinal Disorders (8 [14.0%]). Common treatment-related TEAEs by PT were ALT Increased (9 [15.8%]), Headache (9 [15.8%]), Influenza-like Illness (7 [12.3%]), and AST Increased (5 [8.8%]). Most frequent treatment-related adverse events occurred either at, or in close temporal relationship to, treatment (i.e. infusion-related reactions or influenza-like illness) or were related to hepatic injury, presumably caused by an immune response to the vector, leading to increased ALT and/or AST values most often occurring within 3 months after treatment, with an earliest onset at Week 3. Of the 39 subjects who experienced treatment-related TEAEs, most had events that were rated as mild (27 [47.4%]) or moderate (11 [19.3%]) in severity. One subject (1.8%) experienced 2 events, ALT and AST Increased, that were rated as severe.
The incidence and distribution of TEAEs by SOC in the baseline anti-AAV5 NAb positive and negative subgroups were comparable. The 33 subjects who were seronegative for anti-AAV5 NAbs at baseline experienced 325 TEAEs; common TEAEs included Headache (36.4% of subjects), Arthralgia (33.3%), Fatigue (27.3%), ALT Increased (24.2%), Nasopharyngitis (24.2%), COVID-19 (21.2%), Toothache (18.2%), AST Increased (15.2%), Back Pain (15.2%), and Hypertension (15.2%). The 24 subjects who were seropositive for anti-AAV5 NAbs at baseline experienced 288 TEAEs; common TEAEs included Arthralgia (41.7%), Nasopharyngitis (29.2%), Headache (25.0%), Back Pain (25.0%), Pain in Extremity (25.0%), Blood Creatine Phosphokinase Increased (20.8%), Fatigue (20.8%), Influenza-like Illness (16.7%), Diarrhoea (16.7%), Nausea (16.7%), and Oropharyngeal Pain (16.7%). Of the 33 subjects who were seronegative for anti-AAV5 NAbs at baseline, 22 (66.7%) experienced 57 treatment-related TEAEs. The most frequently reported treatment-related TEAEs by PT that were experienced by subjects within this subject group included ALT Increased (18.2%), Headache (18.2%), AST Increased (12.1%), Dizziness (9.1%), Fatigue (9.1%), and Influenza-like Illness (9.1%). Of the 33 subjects who were seronegative for anti-AAV5 Nabs, 6 (18.2%) subjects experienced 6 treatment-emergent SAEs. No SAE by PT was reported in more than 1 subject, and no pattern in SAEs was notable.
In Study CSL222_3001 (CT-AMT-061-02) (Post-treatment Safety population), the TEAE profile was also comparable for subjects with an anti-AAV5 NAb titre < 1:3000, tested using the clinical trial assay (i.e. equivalent to subjects with an anti-AAV5 NAb titre of < 1:700 immediately before dosing or < 1:900 at any time during the ≥ 6-month lead-in period). No specific safety concern was identified for the subject (Subject 15-42-259) with a very high anti-AAV5 NAb titre of 1:3212, tested using the clinical trial assay.
A minority of 9 (16.7%) subjects used systemic corticosteroids for transaminase elevations in the post-treatment follow-up period of Study CSL222_3001 (CT-AMT-061-02). The mean corticosteroid treatment duration for those subjects was 79.8 days (range 51 to 130 days).
No treatment-related SAE was reported in Studies CSL222_2001 (CT-AMT-061-01) and CSL222_3001 (CT-AMT-061-02). Fifteen (26.3%) subjects experienced 18 treatment-emergent SAEs. Serious AEs with a PT of Blood Loss Anaemia were reported for 2 (3.5%) subjects; no other SAEs were reported in more than 1 subject. No trends were noted in SAEs based on age, race, ethnicity, or body mass.
In Study CSL222_3001 (CT-AMT-061-02), 1 case of HCC was reported in a male elderly subject with multiple risk factors for HCC, including hepatitis B and C, age > 50, alcohol use, fatty changes in the liver (steatosis), and family history of cancer. The HCC was identified on a routine abdominal ultrasound performed ~1 year after dosing with etranacogene dezaparvovec. The subject underwent an exploratory laparotomy with resection of 2 lesions in the liver. Etranacogene dezaparvovec is a non-replicating AAV5 vector that remains mainly episomal in the nucleus of transduced cells. A low frequency of random chromosomal integration of rAAV DNA has been observed during nonclinical investigation of the predecessor AMT-060 (Nonclinical Study NR-060-14-007) and is considered to present a theoretical risk for malignant transformation of cells due to insertional mutagenesis and activation, inactivation or alteration of host cell genes. Molecular and integration site analyses on the HCC tissue and adjacent liver tissue from the subject in Study CSL222_3001 (CT-AMT-061-02) were performed by an independent laboratory. Integration site (IS) analysis by 3‘LTR shearing extension primer tag selection/ligation-mediated polymerase chain reaction indicated that < 0.03% of the cells in the HCC and HCC-adjacent tissues had an adeno-associated virus (AAV) integration and did not indicate a dominant integration site in the HCC sample, as would be expected if the AAV vector had integrated, and led to clonal expansion of the tumour cells. Whole genome sequencing of the HCC showed mutations in a variety of genes that have been previously associated with HCC. Whole genome sequencing of the HCC-adjacent sample revealed a premalignant genetic signature similar to the HCC sample. This was also observed in RNA sequencing data that showed a pattern of gene

expression in the HCC-adjacent sample that is characteristic of a premalignant state rather than healthy liver tissue. Based on these results, it was concluded that the event was not a result of vector integration, and the event is assessed as unlikely related to etranacogene dezaparvovec administration. On 25 February 2022, the subject underwent a liver transplant and the Investigator confirmed that this would be considered the final resolution / treatment of the event.
One death was reported in Study CSL222_3001 (CT-AMT-061-02): A 75-year-old White male subject with a medical history of atrial enlargement, atrial fibrillation, and hypertension experienced a fatal event of cardiogenic shock associated with a urinary tract infection on post-dose Day 464. The Investigator considered the event of cardiogenic shock as severe in intensity and unrelated to study treatment. The Sponsor considered the event of cardiogenic shock as unrelated to study treatment.
Seven subjects had TEAEs Qualifying for Special Notification related to Investigational Product (IP) administration; i.e. Infusion Related Reaction (2 [3.5%]), Hypersensitivity (1 [1.8%]), Infusion Site Reaction (1 [1.8%]), Dizziness (2 [3.5%]), Eye Pruritus (1 [1.8%]), Flushing (1 [1.8%]), Headache (1 [1.8%]), Abdominal Pain Upper (1 [1.8%]), Urticaria (1 [1.8%]), Chest Discomfort (1 [1.8%]), and Pyrexia (1 [1.8%]). Three of the 7 subjects with infusion reactions related to IP administration required a dose interruption. Five of the 7 subjects were positive for anti-AAV5 NAbs at baseline. One subject in Study CSL222_3001 (CT-AMT-061-02) had a TEAE of Hypersensitivity, which qualified for Special Notification. The event occurred during administration of etranacogene dezaparvovec and resulted in discontinuation of treatment and receipt of a partial dose (approximately 10%). The discontinuation of treatment in this subject occurred under the oversight and at the direction of a sub-investigator. A subsequent process review led to a protocol amendment that incorporated guidance for trial sites on how to respond to infusion reactions. It is noted that, after implementation of the amendment, no further treatment discontinuations occurred.
Administration of etranacogene dezaparvovec was associated with a small (< 3 mmHg) transient decrease in mean systolic blood pressure within 3 hours post-dose.

6.5 Final clinical benefit-risk assessment

Taken together, there is clinical benefit of etranacogene dezaparvovec in being a less burdensome treatment suggested by the QoL (not adjusted for multiplicity, exploratory endpoints).
The 2 clinical studies with etranacogene dezaparvovec, supported by Phase 1/2 Study CT-AMT-060-01, showed a clinically relevant reduction in all types of bleeding, sustained FIX expression and activity resulting in a statistically significant reduction in FIX consumption, and superior management of haemophilia B in patients with a severe bleeding phenotype.
As the sample size is too small to detect rare or uncommon adverse events and the long-term experience with etranacogene dezaparvovec is limited to approx. 24 months, there are still uncertainties regarding the safety of etranacogene dezaparvovec.
Etranacogene dezaparvovec shows a favourable benefit-risk balance for male adults with haemophilia B who have a severe bleeding phenotype, as indicated by current or historical repeated spontaneous bleeding episodes (which may include joint or life-threatening haemorrhage), established joint damage due to haemarthrosis, and / or the current use of FIX continuous prophylaxis, and a pre-existing anti-AAV5 NAb antibody titre < 1:900, based on the validated neutralising AAV5 antibody assay with an extended measuring range (equivalent to <1:700 based on the previous clinical study assay).

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Hemgenix was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Hemgenix®

Composition

Active substances

Etranacogene dezaparvovec is a gene therapy medicinal product that employs a non-replicating, recombinant adeno-associated viral vector serotype 5 (AAV5) containing a codon-optimized coding DNA sequence for the human coagulation Factor IX variant R338L (hFIXco-Padua) under the control of a liver-specific promoter (LP1).

Etranacogene dezaparvovec is produced using recombinant baculovirus technology.

Contains genetically modified adeno-associated virus-based vector serotype 5 (AAV5).

Excipients

Sucrose, polysorbate-20, potassium chloride, potassium dihydrogen phosphate (less than 1 mmol or 39 mg potassium per vial), sodium chloride, disodium phosphate (corresponding to ≤ 1.53 mmol or 35.2 mg sodium per vial), hydrochloric acid, water for injections.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.
Etranacogene dezaparvovec is a clear, colourless solution.
After dilution, etranacogene dezaparvovec should be a clear, colourless solution.

Each mL of etranacogene dezaparvovec contains a nominal concentration of 1×10^{13} genome copies (gc).

Each vial contains an extractable volume of not less than 10 mL of concentrate for solution for infusion.

The total number of vials in each pack corresponds to the dosing requirement for the individual patient, depending on the patient`s body weight (see sections “Dosage/Administration” and section “Packs”).

Indications/Uses

Etranacogene dezaparvovec is an adeno-associated virus vector-based gene therapy indicated for treatment of male adults with severe/moderately severe Haemophilia B (congenital Factor IX deficiency) and with a preexisting neutralising adeno-associated viral vector serotype 5 (AAV5) antibody titre below 1:900 to reduce the frequency of bleeding episodes and the need for Factor IX replacement therapy who:

- currently use Factor IX prophylaxis therapy,
- or have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.

Dosage/Administration

Etranacogene dezaparvovec must be prescribed and administered in a clinical treatment centre by a healthcare professional with experience in treating Haemophilia B.

Patient selection

For patient selection, baseline testing is required. This includes examinations of:

- Preexisting neutralising adeno-associated viral vector serotype 5 (AAV5) antibody titre (see section Indications/Uses, section Dosage/Administration, section Warnings and Precautions and section Clinical Efficacy). A validated assay for neutralising AAV5 antibodies approved for etranacogene dezaparvovec should be used.
- Factor IX inhibitor presence.
  In case of a positive test result for human Factor IX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive etranacogene dezaparvovec.
- Liver health, including:
  - Enzyme testing (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin). It is recommended that the ALT test is repeated at least once prior to etranacogene dezaparvovec administration to establish patient's ALT baseline.
  - Hepatic ultrasound and elastography.

  In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consideration of a consultation with hepatologist is recommended to assess eligibility for etranacogene dezaparvovec (see section Dosage/Administration and section Warnings and Precautions).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Posology

For single-dose intravenous infusion only.

The dose of etranacogene dezaparvovec is a single dose of 2×10^{13} genome copies (gc) per kilogram (kg) of body weight (bw) or 2.0 mL/kg bw, administered as an intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline) (see section “Dosage/Administration” and section “Instructions for handling”).

The dose should be calculated as follows:

Etranacogene dezaparvovec dose (in mL) = **patient body weight** (in kilogram) $\times$ **2**

Etranacogene dezaparvovec can be administered **only once.**

Monitoring post-administration

After administration of etranacogene dezaparvovec, regular monitoring is required. This includes examinations of:

- Liver enzymes to monitor for liver enzyme elevations which may indicate immune-mediated liver hepatotoxicity (see section “Warnings and precautions”). Monitor ALT levels by testing weekly for at least 3 months following administration of etranacogene dezaparvovec (see section “Dosage/Administration” and section “Warnings and precautions”). After 3 months, it is recommended to test ALT every 3 months in the first year post-treatment and every 6 months in the second year post-treatment, with subsequent yearly testing for at least 5 years to routinely assess liver function.
- Factor IX activity (e.g. weekly for at least 3 months) (see section “Dosage/Administration” and section “Warnings and precautions”).
    - Monitor patients regularly for their Factor IX activity in particular when exogenous Factor IX is administered.
    - The use of different assay reagents may have impact on the test results, therefore the same assay and reagents should be used to monitor patients over time.
    - Use of exogenous Factor IX concentrates before and after etranacogene dezaparvovec administration may impede assessment of endogenous, etranacogene dezaparvovec-derived Factor IX activity.
- Perform regular alpha-fetoprotein (AFP) level testing and abdominal ultrasound (e.g. annually) in patients with preexisting risk factors for hepatocellular carcinoma (see section “Warnings and precautions”).

- Monitor patients for human Factor IX inhibitors. Post-dose testing should be performed if plasma Factor IX activity levels are not achieved, decrease or if bleeding is not controlled or returns.

Corticosteroid regimen

An immune response to the adeno-associated viral vector serotype 5 (AAV5) capsid proteins will occur after etranacogene dezaparvovec administration (see section “Undesirable effects”). This may lead to elevations in liver transaminases (transaminitis) (see sections “Warnings and precautions” and section “Undesirable effects”). In case of elevated ALT levels above the normal limits or to double of the patient’s baseline value within the first 3 months post-dose, a corticosteroid treatment should be considered to dampen the immune response, e.g. starting with oral 60 mg/day prednisolone or prednisone (see below). Corticosteroid tapering should be commenced, once the ALT levels are below the upper limit of normal levels.

Table 1. Recommended prednisolone treatment applied in clinical studies with etranacogene dezaparvovec:

Timeline	**[$]Prednisolone oral dose (mg/day)**
Week 1	60
Week 2	40
Week 3	30
Week 4	30
Maintenance dose until ALT level returns to baseline level	20
Taper dose after baseline level has been reached	Reduce daily dose by 5 mg/week

[$]Medications equivalent to prednisolone may also be used. A combined immunosuppressant regimen or the use of other products can also be considered in case of prednisolone treatment failure or contraindication.

Discontinuation of continuous routine prophylaxis with exogenous human Factor IX

It may take several weeks before improved haemostatic control becomes apparent after etranacogene dezaparvovec infusion (see section “Pharmacokinetics” and section “Clinical Efficacy”). Therefore, continued haemostatic support with exogenous human Factor IX may be required during the first weeks after etranacogene dezaparvovec administration to provide sufficient Factor IX coverage for the initial days post-treatment. Monitoring of the Factor IX activity (e.g. weekly for at least 3 months) is recommended post-dose to follow patient`s response to etranacogene dezaparvovec.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified organisms. Personal protective equipment including gloves, safety goggles, protective clothing and masks should be worn while preparing or administering etranacogene dezaparvovec (see section “Instructions for handling”).

For instructions on preparation, handling, measures to take in case of accidental exposure to and disposal of the medicinal product, see section “Instructions for handling”.

Special patient groups

Patients with hepatic disorders

A dose adjustment in patients with hepatic disorders should not be considered (see section “Warnings and precautions”).
The safety and efficacy of etranacogene dezaparvovec in patients with advanced hepatic impairment, including cirrhosis, advanced liver fibrosis (e.g. suggestive of or equal to METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) Stage 3 disease or a liver elastography (FibroScan) score of ≥9 kPa), or uncontrolled Hepatitis B and C, has not been studied (see section “Pharmacokinetics”).

Patients with renal disorders

In the pivotal Phase 3 study, 8 of the 54 enrolled patients were renally impaired. Seven patients had mild, and 1 patient had moderate renal impairment (see section “Clinical Efficacy”). All 8 patients with renal impairment responded to etranacogene dezaparvovec treatment.
A dose adjustment should not be considered.
The safety and efficacy of etranacogene dezaparvovec in patients with severe renal impairment and end-stage renal disease has not been studied (see “Pharmacokinetic properties”).

Elderly patients

Clinical studies with etranacogene dezaparvovec included 6 elderly patients with Haemophilia B aged 68 to 75 years at time of enrollment. No meaningful differences in the safety and efficacy of etranacogene dezaparvovec were observed in these patients compared to patients aged 18 to 65 years and no dose adjustment should be considered (see section “Pharmacokinetic properties”).

Children and adolescents

The safety and efficacy of etranacogene dezaparvovec in children below 18 years of age has not been studied. No data are available.

Preexisting neutralising adeno-associated viral vector serotype 5 (AAV5) antibodies

In the clinical studies with etranacogene dezaparvovec, patients with preexisting neutralising AAV5 antibody titre up to 1:678 at baseline, based on the clinical trial assay (equivalent to 1:898 titre based on the validated neutralising AAV5 antibody assay with an extended measuring range), responded to the treatment (see section “Clinical Efficacy”).
A dose adjustment should not be considered.

Safety and efficacy of etranacogene dezaparvovec in patients with preexisting neutralising AAV5 antibody titres above 1:678, based on the clinical trial assay (equivalent to 1:898 titre based on the validated neutralising AAV5 antibody assay with an extended measuring range), have not been established. In a patient with a 1:3212 titre of preexisting neutralising AAV5 antibodies at screening (using the clinical trial assay), no response to treatment was observed.

Mode of administration
For intravenous use.

Etranacogene dezaparvovec is administered as a single intravenous infusion after dilution of the required dose with 0.9% normal saline:

- For patients <120 kg bw, the total dose of etranacogene dezaparvovec should be diluted with 500 mL - 0.9% normal saline infusion bag.
- For patients ≥120 kg bw, the total dose of etranacogene dezaparvovec should be diluted with two 500 mL - 0.9% normal saline infusion bags by dividing the etranacogene dezaparvovec dose equally between the two 500 mL infusion bags.

The diluted product should be administered at a constant infusion rate of 500 mL/hour (8 mL/min).

Etranacogen dezaparvovec **must not** be administered as an intravenous push or bolus.

- In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped to ensure patient tolerability (see section “Warnings and precautions”). If the infusion is stopped, it may be restarted at a slower rate when the infusion reaction is resolved.
- If the infusion rate needs to be reduced, or stopped and restarted, the etranacogene dezaparvovec solution should be infused within the shelf life of diluted etranacogene dezaparvovec, i.e., within 24 hours after the dose preparation (see section “Shelf life after opening”).

For instructions on dilution of the product before administration, see section “Instructions for handling”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

Infusion Reactions
Infusion reactions, including hypersensitivity reactions, are possible (see section “Undesirable effects”).
Patients should be closely monitored for infusion reactions throughout the infusion period and for at least 3 hours after end of infusion.
The recommended infusion rates provided in section “Dosage/Administration” should be closely adhered to ensure patient tolerability.
Suspicion of an infusion reaction (see section “Undesirable effects”) requires slowing or stopping of the infusion. Based on clinical judgement, additional treatment with e.g. a corticosteroid or antihistamine may be considered for management of an infusion reaction.

Hepatotoxicity
Intravenous administration of a liver-directed adeno-associated viral (AAV) vector may potentially lead to liver transaminase elevations (transaminitis). Transaminitis, particularly when observed in the first 3 months after etranacogene dezaparvovec administration, is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the AAV-vector based gene therapy.

To mitigate the risk of potential hepatotoxicity, transaminases should be closely monitored, e.g. once per week for at least 3 months after etranacogene dezaparvovec administration. A course of corticosteroid taper should be considered in the event of alanine aminotransferase (ALT) increase to above the upper limit of normal or to double the patient’s baseline levels (see section “Dosage/Administration”), along with human Factor IX activity examinations.

To assist in the interpretation of test results in case of ALT increases, monitoring of ALT may be accompanied by monitoring of aspartate aminotransferase (AST) and creatine phosphokinase (CPK) to help rule out alternative causes for ALT elevations, including potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise. Retesting of ALT levels within 24 to 48 hours should be also considered.

In clinical studies with etranacogene dezaparvovec, transient, asymptomatic and predominantly mild elevations in liver transaminases were observed, most often in the first 3 months after etranacogene dezaparvovec administration. These transaminase elevations resolved either spontaneously or with administration of a corticosteroid taper to normal levels after a period of up to several weeks (see section “Undesirable effects”).

Follow-up monitoring of transaminases (see section “Dosage/Administration”) in all patients who developed liver enzyme elevations is recommended on a regular basis until liver enzymes return to baseline.

It is recommended that patients treated with Hemgenix should be advised to avoid, if possible, concomitant use of hepatotoxic medication or potential hepatotoxic agents (including potentially hepatotoxic herbal products, nutritional supplements, and alcohol) due to the risk of potential loss or decrease in efficacy and more serious hepatic reactions.

Immune-mediated neutralisation of the adeno-associated viral vector serotype 5 (AAV5) vector capsid
In AAV-vector based gene therapies, preexisting neutralising AAV antibodies may impede transgene expression at desired therapeutic levels.

In the clinical studies with etranacogene dezaparvovec, the patient sub-group with detectable preexisting neutralising AAV5 antibodies up to titres of 1:678, based on the clinical trial assay (equivalent to 1:898 titre based on the validated neutralising AAV5 antibody assay with an extended measuring range), showed mean Factor IX activity that was numerically lower compared to that patient sub-group without detectable preexisting neutralising AAV5 antibodies. However, both patient groups, with and without detectable preexisting neutralising AAV5 antibodies, demonstrated an improved haemostatic protection compared to the standard of care Factor IX prophylaxis (see section “Clinical Efficacy”).

Patients are recommended to be assessed for the titre of preexisting neutralising AAV5 antibodies before treatment with etranacogene dezaparvovec. In 1 patient with a preexisting neutralising AAV5 antibody titre of 1:3212 (using the clinical trial assay), no Factor IX expression was observed and recommencing of exogenous Factor IX prophylaxis was needed (see section “Clinical Efficacy”).

Hepatocellular carcinogenicity
Etranacogene dezaparvovec is composed of a non-replicating AAV5 vector whose DNA was demonstrated to maintain largely in episomal form with only a few random human DNA integration

events recorded. Although rare, vector integration into human genome may potentially result in insertional mutagenesis that can conceivably contribute to the development of malignancy.
No etranacogene dezaparvovec-associated clonal expansion or carcinogenicity was observed in preclinical or clinical studies to date (see section “Preclinical Data” and section “Clinical Efficacy”).
It is recommended that patients with preexisting risk factors for hepatocellular carcinoma (such as hepatic cirrhosis, advanced hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) receive regular abdominal ultrasound screenings and are regularly monitored (e.g. annually) for alpha-fetoprotein (AFP) elevations in the 5 years following administration (see section “Dosage/Administration”).

Shedding
Temporary shedding of etranacogene dezaparvovec vector DNA will occur in blood and semen of patients receiving etranacogene dezaparvovec (see section “Pharmacokinetics”). Due to the non-infectious and non-replicating nature of the shed vector DNA fragments, the risk of an adverse effect to human health upon accidental exposure and the environmental risks are considered negligible. Patients needs to be instructed for use of barrier contraception for a minimum of 6 months after treatment with etranacogene dezaparvovec.

Blood, organ, tissue and cell donation
Patients treated with etranacogene dezaparvovec should not donate blood, or organs, tissues and cells for transplantation to minimize the risk of exposure to non-target individuals.

Caregivers should be advised on the proper handling of waste material generated from contaminated medicinal ancillaries during etranacogene dezaparvovec use (see section “Instructions for handling”).

Sodium and potassium content
This medicinal product contains ≤ 1.53 mmol (35.2 mg) sodium per vial, corresponding to 1.8 % of the WHO for an adult recommended daily intake of 2 g.

This medicinal product contains potassium, but less than 1 mmol (39 mg) of potassium per vial, i.e. it is almost "potassium-free”.

Interactions

No interaction studies have been performed.

Pregnancy, lactation

There are no data regarding etranacogene dezaparvovec use in women.

Fertility

No clinical studies have been performed to evaluate the effects of etranacogene dezaparvovec on impairment of human fertility.

Effects on male fertility have been evaluated in animal studies with mice. No adverse impact on the fertility was observed (see section “Preclinical Data”).

Effects on ability to drive and use machines

Etranacogene dezaparvovec has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section “Undesirable effects” may temporarily affect the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions in clinical studies related to etranacogene dezaparvovec were alanine aminotransferase (ALT) elevations (10/57 patients (17.5%)), headache (9/57 patients (15.8%)), influenza-like illness (8/57 patients (14%)) and aspartate aminotransferase (AST) elevations (5/57 patients (8.8%)). No serious adverse reactions were reported.

List of adverse reactions

The following table shows the overview of adverse drug reactions (ADRs) from clinical studies with etranacogene dezaparvovec, categorized according the MedDRA System Organ Class (SOC), Preferred Term Level and frequency per patient. From a total of N=57 patients treated with etranacogene dezaparvovec (n=3 patients from a Phase 2b and n=54 patients from a Phase 3 clinical study), the identified ADRs are listed based on the following convention for frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing frequency.

Table 2. Adverse drug reactions (ADRs) obtained from clinical studies with etranacogene dezaparvovec

MedDRA System Organ Class (SOC)	Adverse Reaction (Preferred Term)	Patients number (%)	Frequency per patient
Nervous system disorders	Headache	9 (15.8%)	Very common
	Dizziness	2 (3.5%)	Common
Gastrointestinal disorders	Nausea	4 (7.0%)	Common
General disorders and administration site conditions	Influenza-like illness	8 (14.0%)	Very common
	Malaise	2 (3.5%)	Common
	Fatigue	4 (7.0%)	Common
Investigations	Alanine aminotransferase increased	10 (17.5%)	Very common
	Aspartate aminotransferase increased	5 (8.8%)	Common
	Blood creatine phosphokinase increased	4 (7.0%)	Common
	Blood bilirubin increased	1 (1.8%)	Common
Injury, poisoning and procedural complications	Infusion related reaction (Hypersensitivity, Infusion site reaction, Dizziness, Eye pruritus, Flushing, Abdominal pain upper, Urticaria, Chest discomfort, Pyrexia)	7 (12.0%*)	Very common*

*Individual symptoms occurred in 1 or 2 subjects (incidence 1.8 to 3.5%) within 24 hours post-dose.

Description of specific adverse reactions and additional information

Infusion related reactions

In the clinical studies with etranacogene dezaparvovec, infusion-related reactions of mild to moderate severity have been observed. The infusions were temporarily interrupted in 3 patients and resumed at a slower infusion rate after treatment with antihistamines and/or corticosteroids. In 1 patient infusion was stopped and not resumed (see section “Properties/Effects”).

Immune-mediated transaminitis

In the clinical studies, ALT increased occurred in 10 out of 57 patients. The onset of ALT elevations ranged from day 22 to 78 post-dose. Nine out of 10 patients with ALT elevations received a tapered course of corticosteroid. Four of the 10 patients with an ALT elevation had also an AST elevation. The mean duration of corticosteroid treatment for the elevated ALT was 79.8 days. All treatment-emergent ALT increased were non-serious and resolved within 3 to 127 days.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are no clinical study data regarding overdose with etranacogene dezaparvovec.

Properties/Effects

ATC code

B02BD16

Mechanism of action

Etranacogene dezaparvovec is a gene therapy designed to introduce a copy of the human Factor IX gene into hepatocytes to address the root cause of the Haemophilia B disease. Etranacogene dezaparvovec consists of a codon-optimized coding DNA sequence of the gain-of-function Padua variant of the human Factor IX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5) (see section “Composition“).
Following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form. Subsequent to transduction, etranacogene dezaparvovec directs long-term liver-specific expression of Factor IX-Padua protein. As a result, etranacogene dezaparvovec partially or completely ameliorates the deficiency of circulating Factor IX procoagulant activity of patients suffering from Haemophilia B, restoring the haemostatic potential and limiting bleeding episodes and the need for exogenous Factor IX treatment.

Pharmacodynamics

Not applicable

Clinical efficacy

The safety and efficacy of etranacogene dezaparvovec was evaluated in 2 prospective, open-label, single-dose, single-arm studies, a Phase 2b study performed in the US (CT-AMT-061-01) and a Phase 3 multi-national study performed in US, UK and EU (CT-AMT-061-02). Both studies enrolled adult male patients (body weight (bw) range: 58 to 169 kg) with moderately severe or severe Haemophilia B (N=3 in Phase 2b and N=54 in Phase 3), who received a single intravenous dose of 2×10^{13} genome copies (gc)/kilogram (kg) bw of etranacogene dezaparvovec and entered a follow-up period of 5 years.

Phase 2b study (CT-AMT-061-01)

In the ongoing Phase 2b study, all 3 enrolled patients, aged 43 to 50 years at enrolment, with moderately severe and severe Haemophilia B received a single intravenous dose of etranacogene dezaparvovec. All 3 patients completed 3 years of follow-up post-administration, and will continue follow-up to a total of 5 years post-dose.

The key efficacy endpoint of the Phase 2b study was to explore the endogenous human Factor IX activity at 6 weeks and 18 months after etranacogene dezaparvovec administration. Further efficacy endpoints included the reduction of bleeding episodes, annualized bleeding rate (ABR) and the need for exogenous Factor IX replacement therapy.

All 3 patients demonstrated clinically relevant increases in Factor IX activity and discontinued their routine Factor IX replacement prophylaxis within 1 to 4 days after etranacogene dezaparvovec administration. The Factor IX activity increased to a mean (±SD) of 30.6% (±6.97%) (range: 23.9% to 37.8%) of normal at week 6 post-dose. The Factor IX activity increased to 40.8%, 44.2%, and 50.0% of normal at 52 weeks, 24 months and 30 months, respectively, as measured by one-stage (aPTT-based) assay.

The endogenous Factor IX activity level continued to be elevated at 3 years post-dose at 32.3% and 41.5% in the 2 subjects with available uncontaminated samples (see section “Pharmacokinetics”).

A sustained reduction in bleeding episodes was demonstrated at 3-year follow-up. The patients had 1, 3, or 5 bleeding episodes in the year before enrolment. Two of the 3 patients did not experience any bleeding episodes after treatment with etranacogene dezaparvovec. Over 3 years after treatment, 1 patient experienced 1 traumatic and 1 spontaneous, mild bleed (muscle bleeds, same lower leg), each requiring a single dose of exogenous Factor IX replacement. The mean ABR for the 3 patients, calculated as the total number of bleeding episodes divided by the time at risk in years, was 0.22 over the period of 3 years of follow-up. The mean ABRs for spontaneous and traumatic bleeding episodes over 3 years were both 0.11.

All 3 patients were positive for preexisting neutralising antibodies to AAV5 capsid protein (titre range: 1:19.5 to 1:33.0 at baseline) with no clinically evident effect on liver transaminase elevations or treatment efficacy. After etranacogene dezaparvovec administration, neutralising antibody titres to AAV5 capsid protein increased to >36,450 (upper limit of quantification) in all 3 patients by week 2 and remained >36,450 through year 3.

Transient, mild increases in alanine aminotransferase (ALT) levels were reported in 2 patients who did not receive treatment with corticosteroids, and the ALT increases were not associated with loss of Factor IX activity. All 3 patients had a prior Hepatitis C infection and 2 patients had a controlled HIV infection.

None of the 3 patients showed evidence of neutralising inhibitors to etranacogene dezaparvovec-derived Factor IX over 3 years post-dose.

Phase 3 study (CT-AMT-061-02)

In the ongoing pivotal Phase 3 study, a total of N=54 patients aged 19 to 75 at enrolment (n=47 ≥18 and < 65 years; n=7 ≥ 65 years) with moderately severe or severe Haemophilia B completed a ≥6-month observational lead-in period with standard of care routine Factor IX prophylaxis after which patients received a single intravenous dose of etranacogene dezaparvovec. Post-treatment follow-up visits occurred regularly, with 53/54 patients completing at least 18 months of follow-up. One patient with numerous cardiovascular and urologic risk factors, aged 75 at screening, died of urosepsis and cardiogenic shock at month 15 post-dose (at age 77 years), an event confirmed not treatment-related. The remaining 53/54 patients continue follow-up for a total of 5 years post-dose. Of these, 1 patient received a partial dose (10%) of etranacogene dezaparvovec due to an infusion related reaction during infusion.

The primary efficacy endpoint for the Phase 3 study was to assess the ABR reduction between month 7 to 18 post-dose after establishment of stable Factor IX expression by month 6, compared to the observational lead-in period. For this purpose, all bleeding episodes, regardless of investigator assessment, were considered. The efficacy results showed superiority of etranacogene dezaparvovec to continuous routine Factor IX prophylaxis. The ABR for all types of bleeds after stable Factor IX expression decreased in the Full Analysis Set (FAS; N=54) from a mean of 4.19 for the lead-in period to a mean of 1.51 (1-sided p = 0.0002) in the months 7-18 post-dose (see Table 3). These results demonstrated an overall ABR reduction by 64% (95% Confidence Interval (CI): 36%, 80%, 1-sided p = 0.0002) from the lead-in to the post-treatment period.

Severe or very severe bleeding episodes were reported during the lead-in period in 18.5% and 5.6% of patients, respectively, and decreased during month 7-18 to 13% and 3.7% of patients for severe and very severe bleeds, respectively. The ABRs by subtype of bleeding episodes were significantly reduced after etranacogene dezaparvovec treatment compared to the lead-in period, i.e., for spontaneous from 1.52 to 0.44 (p = 0.0034), for joint from 2.35 to 0.51 (p<0.0001), or for traumatic bleeding episodes from 2.09 to 0.62 (p<0.0001).

Table 3. Total bleeding events and ABRs

Number	≥6-month Lead-in period FAS (N=54)	7-18 months Post-dose FAS (N=54)	≥6-month Lead-in period (N=53[***])	7-18 months Post-Dose (N=53[***])
Patients with bleeds	40 (74.1%)	20 (37.0%)	40 (75.5%)	19 (35.8%)
Patients with zero bleeds	14 (25.9%)	34 (63.0%)	13 (24.5%)	34 (64.2%)
Any bleeds	136	54	136	49
Mean adjusted[*] ABR** (95% CI) for any bleeds	4.19 (3.22, 5.45)	1.51 (0.81, 2.82)	3.89 (2.93, 5.16)	1.07 (0.63, 1.82)
ABR[**] ratio (post-dose / lead-in)	-	0.36	-	0.28
2-sided 95% Wald CI		(0.20, 0.64)		(0.17, 0.43)
1-sided p-value[****]		p = 0.0002		p< 0.0001

Abbreviations: ABR = annualized bleeding rate; FAS = Full Analysis Set including all 54 patients dosed; CI = confidence interval

[*]Adjusted: Adjusted ABR and comparison of ABR between lead-in and post-treatment period was estimated from statistical modelling (i.e., from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.)

[**]The ABR was measured from month 7 to 18 after etranacogene dezaparvovec infusion, ensuring this period represented steady-state Factor IX expression from the transgene.

[***]The population data includes all patients dosed except for one patient with the preexisting neutralising AAV5-antibody titre of 1: 3212 (using the clinical trial assay) who did not respond to treatment, i.e., did not show Factor IX expression and activity post-dose.

[****]1-sided p-value ≤0.025 for post-treatment/lead-in <1 was regarded as statistically significant.

The study also demonstrated superiority of etranacogene dezaparvovec at 18-months post-dose over the standard of care routine Factor IX prophylaxis in the lead-in period. The ABR for Factor IX-treated bleeding episodes during the month 7 to 18 post-treatment period was reduced by 77% (95% CI: 54%, 88%, 1-sided p <0.0001) in comparison to lead-in period (see Table 4).

Table 4. ABRs for Factor IX-treated bleeding episodes

	≥6-Month Lead-in period FAS (N=54)	7-18 Months Post-dose FAS (N=54)
Mean adjusted ABR (95% CI) for any bleeds	3.65 (2.82, 4.74)	0.84 (0.41, 1.73)
ABR ratio (Post-dose/ Lead-in) 2-sided 95% Wald CI 1-sided p-value	-	0.23 (0.12, 0.46) p<0.0001
Mean adjusted ABR (95% CI) for joint bleeds	2.13 (1.58, 2.88)	0.44 (0.19, 1.00)
Joint bleed ABR ratio (Post-dose / Lead-in) 2-sided 95% Wald CI 1-sided p-value	-	0.20 (0.09, 0.45) p<0.0001
Mean adjusted ABR (95% CI) for spontaneous bleeds	1.34 (0.87, 2.06)	0.45 (0.15, 1.39)
Spontaneous bleed ABR ratio (Post-dose / Lead-in) 2-sided 95% Wald CI 1-sided p-value	-	0.34 (0.11, 1.00) p-value = 0.0254

Abbreviations: ABR = Annualized Bleeding Rate; FAS = Full Analysis Set including all 54 subjects dosed; CI = Confidence Interval

After single-dose of etranacogene dezaparvovec, clinically relevant increases in Factor IX activity were observed (see Table 5). At 6 months, 12, 18 and 24 months post-dose, patients achieved a mean (±SD) uncontaminated[#] Factor IX activity levels, as measured by the one-stage (aPTT-based) assay, of 38.95% (± 18.72) (range: 8.2 to 97.1), 41.48% (± 21.71) (range: 5.9 to 113.0), 36.90% (±21.40) (range: 4.5 to 122.9), and 36.66 (± 18.96) (range: 4.7 to 99.2) of normal, respectively. Factor IX activity below 12% of normal was observed only in 3 patients at 24 months post-dose.

Table 5. Factor IX activity at 6, 12, 18 and 24 months (FAS; one-stage (aPTT-based) assay)

	Baseline[ð] (N=54)[#]	6 months post-dose (N=51[#])	12 months post-dose (N=50[#])	18 months post-dose (N=50[#])	24 months post-dose[ŋ] (N=50[#])
Mean % (SD)	1.19 (0.39)	38.95 (18.72)	41.48 (21.71)	36.90 (21.40)	36.66 (18.96)
Median % (min, max)	1.0 (1.0, 2.0)	37.30 (8.2, 97.1)	39.90 (5.9, 113.0)	33.55 (4.5, 122.9)	33.85 (4.7, 99.2)
Change from baseline LS mean (SE)[ϕ] 95% CI 1-sided p-value[§]	n.a.	36.18 (2.432) 31.41, 40.95 p<0.0001	38.81 (2.442) 34.01, 43.60 p<0.0001	34.31 (2.444) 29.52, 39.11 p<0.0001	34.13 (2.325) 29.57, 38.69 p<0.0001

Abbreviations: aPTT = activated Partial Thromboplastin Time; CI = confidence interval; FAS = Full Analysis Set including all 54 patients dosed; LS = least squares; max = maximum; min = minimum; n.a. = not applicable; SD = standard deviation; SE = standard error.

[ð]Baseline: baseline Factor IX activity was imputed based on subject's historical Haemophilia B severity documented on a case report form. If the subject had documented severe Factor IX deficiency (Factor IX plasma level <1%), their baseline

Factor IX activity level was imputed as 1%. If the subject had documented moderately severe Factor IX deficiency (Factor IX plasma level ≥1% and ≤2%,) their baseline Factor IX activity level was imputed as 2%.
[#]Uncontaminated: the blood samples collected within 5 half-lives of exogenous Factor IX use were excluded. Both the date and time of exogenous Factor IX use and blood sampling were considered in determining contamination. Patients with zero uncontaminated central laboratory post-treatment values had their change from baseline assigned to zero for this analysis, and had their post-baseline values set equal to their baseline value. Baseline Factor IX was imputed based on patients' historical Haemophilia B severity documented on the case report form. The FAS included 1 patient who received only 10% of the planned dose, 1 patient who died at month 15 post-dose due to unrelated concomitant disease, 1 patient who did not respond to treatment and 1 patient with contamination with exogenous Factor IX. Accordingly, the population data included 54 to 50 patients with uncontaminated sampling.
[ϕ]Least Squares Mean (SE) mean from repeated measures linear mixed model with visit as a categorical covariate.
[§]1-sided p-value ≤0.025 for post-treatment above baseline was regarded as statistically significant.
[η]For month 24, data was based on an ad-hoc analysis and the p-value was not adjusted for multiplicity.

Neutralising AAV5 capsid antibodies were present in 21/54 (38.9%) patients at baseline. At 18 months post-dose, mean Factor IX activity was 31.14% and 39.87% for patients with and without preexisting neutralising AAV5 antibodies, respectively, with LS mean increases from baseline of 26.83% (95% CI: 19.24, 34.41; 1-sided p <0.0001) and 38.72% (95% CI: 32.49, 44.95; 1-sided p <0.0001), respectively. While overall numerically lower mean Factor IX activity was observed in patients with preexisting AAV5 antibodies, no clinically meaningful correlation between an individual antibody titre of preexisting neutralising AAV5 antibodies with their Factor IX activity at 18 months post-dose was identified. Factor IX activity increase was observed up to a titre of 1:678, based on the clinical trial assay (equivalent to 1:898 titre based on the validated neutralising AAV5 antibody assay with an extended measuring range), at 18 months post-dose (see Table 6). In 1 patient (1/54) with a titre of 1:3212 for preexisting neutralising AAV5 antibodies at screening (using the clinical trial assay) no response to etranacogene dezaparvovec treatment was observed, with no Factor IX expression and activity.

Table 6. Endogenous Factor IX activity levels (%) post-dose and preexisting neutralising AAV5 antibodies (FAS; one-stage (aPTT-based) assay)

				Change from Baseline		
	Number of patient	**Mean (%) (SD)**	**Median (%) (Min, Max)**	**Least Squares (LS) mean (SE)[†]**	**95% CI**	**1-sided p-value to baseline**
With neutralising AAV5 antibodies						
Baseline	21	1.24 (0.44)	1.00 (1.0, 2.0)	n.a.	n.a.	n.a.
Month 6	18	35.91 (19.02)	36.60 (8.2, 90.4)	30.79 (3.827)	23.26, 38.32	<0.0001
Month 12	18	35.54 (17.84)	39.95 (8.5, 73.6)	31.59 (3.847)	24.02, 39.16	<0.0001
Month 18	17	31.14 (13.75)	32.00 (10.3, 57.9)	26.83 (3.854)	19.24, 34.41	<0.0001
Month 24	17	32.98 (18.51)	33.50 (9.1, 88.3)	28.35 (3.928)	20.62, 36.08	<0.0001
Without neutralising AAV5 antibodies						
Baseline	33	1.15 (0.36)	1.00 (1.0, 2.0)	n.a.	n.a.	n.a.
Month 6	33	40.61 (18.64)	37.30 (8.4, 97.1)	39.46 (3.172)	33.23, 45.69	<0.0001

				Change from Baseline		
	Number of patient	Mean (%) (SD)	Median (%) (Min, Max)	Least Squares (LS) mean (SE)†	95% CI	1-sided p-value to baseline
Month 12	32	44.82 (23.21)	38.65 (5.9, 113.0)	43.07 (3.176)	36.83, 49.31	<0.0001
Month 18	33	39.87 (24.08)	35.00 (4.5, 122.9)	38.72 (3.172)	32.49, 44.95	<0.0001
Month 24	33	38.55 (19.19)	35.40 (4.7, 99.2)	37.40 (2.933)	31.64, 43.16	<0.0001

Abbreviations: FAS = Full Analysis Set including all 54 patients dosed; aPTT = activated partial thromboplastin time; CI = confidence interval; LS = least square; Max = maximum; Min = minimum; n.a. = not applicable; SD = standard deviation; SE = standard error.
†Least squares mean (SE) from repeated measures linear mixed model with visit as a categorical covariate.

All patients were on prophylactic Factor IX replacement therapy prior to dosing with etranacogene dezaparvovec. The consumption of Factor IX replacement therapy was significantly lower between month 7 and 18 following treatment with etranacogene dezaparvovec compared to standard of care routine Factor IX prophylaxis during the lead-in period, with a mean Factor IX consumption decrease by 248,825 IU / year / patient (96.69%,1-sided p <0.0001). Between month 7 to 24 following treatment with etranacogene dezaparvovec a mean Factor IX consumption decrease by 248.392.6 IU/year/patient (96.52%; 1-sided p < 0.0001) was observed. From day 21 through to months 7 to 24, 52 of 54 (96.3%) treated patients remained free of continuous routine Factor IX prophylaxis.

The Phase 3 study evaluated health related quality of life using the validated Haemophilia specific Haemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL). The Hem-A-QoL questionnaire included an overall total score as well as ten separate domain scores. Hem-A-QoL scores ranged from 0 to 100 with lower scores reflecting better quality of life. Etranacogene dezaparvovec treatment showed an improvement compared to the lead-in period in the Hem-A-QoL mean total/score post-dose at the month 12 assessment. The domains that contributed most to this improvement included ‘Feelings’, ‘Work/School’, ‘Treatments’, and ‘Future’. The 12 month Hem-A-Qol score data are shown in Table 7:

Table 7. Change in Haemophilia B quality of life questionnaire for adults (Hem-A-QoL) score with etranacogene dezaparvovec treatment versus lead-in period (FAS)

Total Hem-A-QoL Score* with a Least Square (LS) mean (SE) Difference from lead-in period to 12 months post-dose 95% CI 1-sided p-value** percent improvement compared to lead-in period	-5.50 (0.972) -7.42, -3.58 p<0.0001 21.5%
Difference in mean Feelings score (SE) **95% CI** 1-sided p-value** percent improvement compared to lead-in period **‘Feelings’** reflected current emotions associated with having Haemophilia B.	-9.42 (1.938) -13.26,-5.59 p<0.0001 45.7%

Difference in mean Work/School score (SE) 95% CI 1-sided p-value** percent improvement compared to lead-in period **'Work/School'** reflected how well patients have thought they perform those responsibilities.	-4.99 (1.825) -8.61, -1.38 p=0.0036 28.8%
Difference in mean Treatment score (SE) 95% CI 1-sided p-value** percent improvement compared to lead-in period **'Treatment'** reflected how burdened patients are by their Haemophilia B treatments.	-14.48 (1.789) -18.42, -11.34 p<0.0001 59.0%
Difference in mean Future score (SE) **95% CI** 1-sided p-value** percent improvement compared to lead-in period **'Future'** reflected concerns about how Haemophilia B will affect patient`s life plans.	-5.02 (1.736) -8.45, -1.58 p = 0.0023 16.2%

Abbreviations: Hem-A-QoL = Hemophilia Quality of Life Questionnaire for Adults; FAS = Full Analysis Set including all 54 patients dosed; LS = Least square; SE = Standard error; CI = Confidence Interval
*The analyses were not adjusted for multiplicity.
**1-sided p-value ≤0.025 for the post-treatment versus lead-in period was considered statistically significant. The nominal p-values were not adjusted for multiplicity.

Elderly patients

Clinical studies with etranacogene dezaparvovec included 6 elderly patients with Haemophilia B aged 68 to 75 years at time of enrolment. No meaningful differences in the safety and efficacy of etranacogene dezaparvovec were observed in these patients compared to patients aged 18 to 65 years.

Paediatrics

Etranacogene dezaparvovec has not been studied in children below 18 years of age. No data are available.

Pharmacokinetics

Factor IX activity and Factor IX protein

Clinically relevant and statistically significant increases in Factor IX activity were observed after administration of etranacogene dezaparvovec (see section "Clinical Efficacy").

In the Phase 3 study, following a single dose of etranacogene dezaparvovec, the mean Factor IX activity levels, as measured by one-stage (activated Partial Thromboplastin Time (aPTT)-based) testing, gradually increased, and patients achieved a mean (± SD) uncontaminated[a] Factor IX activity levels of 38.95% (± 18.72), 41.48% (± 21.71), 36.90% (± 21.40 and 36.66% (±18.96) of normal,

respectively, at 6, 12, 18 and 24 months ([a]uncontaminated: excluding measurements within 5 half-lives of Factor IX replacement therapy).
The time to onset of Factor IX protein expression post-dose was detectable by first uncontaminated measurement at week 3, as measured in Phase 3 study (or at week 1 as measured in Phase 2b study; see section “Clinical Efficacy”). In general, although more variable, Factor IX protein kinetic profile during the post-treatment period followed a trend similar to Factor IX activity.
Durability analysis of post-dose Factor IX activity, performed using a linear mixed-effects repeated measures model for change in the Phase 3 study, showed stable Factor IX levels from 6 months up to 24 months (see section “Clinical Efficacy”). Durability analysis of post-dose Factor IX activity for etranacogene dezaparvovec predecessor, the rAAV5-hFIX gene therapy encoding wild type human Factor IX used in preceding clinical and preclinical studies, revealed that the post-dose Factor IX levels were stable from 6 months up to 5 years when compared with the month 6 (see section “Preclinical Data”).

Absorption

Not specified

Distribution

The etranacogene dezaparvovec-derived Factor IX protein produced in the liver is expected to undergo similar distribution pathways as the endogenous native Factor IX protein in people without Factor IX deficiency.

Metabolism

The etranacogene dezaparvovec-derived Factor IX protein produced in the liver is expected to undergo similar catabolic pathways as the endogenous native Factor IX protein in people without Factor IX deficiency.

Elimination

The etranacogene dezaparvovec-derived Factor IX protein produced in the liver is expected to undergo similar elimination pathways as the endogenous native Factor IX protein in people without Factor IX deficiency.

Etranacogene dezaparvovec vector DNA shedding

The pharmacokinetics of vector DNA shedding in blood and semen following etranacogene dezaparvovec administration was characterized in Phase 2b and Phase 3 studies.

The pharmacokinetics of shedding following Hemgenix administration was characterised using a sensitive polymerase chain reaction (PCR) assay to detect vector DNA sequences in blood and

semen samples. This assay is sensitive to transgene DNA, including fragments of degraded DNA. It does not indicate whether DNA is present in the vector capsid, in cells or in the fluid phase of the matrix (e.g. blood plasma, seminal fluid), or whether intact vector is present.

In the Phase 2b study (N=3), clearance of vector DNA from semen and blood, as confirmed by 3 subsequent measurements below limit of detection (LOD), was achieved in 2/3 patients after 3 years post-dose. The earliest absence of vector DNA was achieved at 26.1 weeks post-dose in semen (mean 26.21; range: 26.1 to 26.3 weeks) and 31.1 weeks post-dose in blood (mean 54.71; range: 31.1 to 78.3 weeks). One of 3 patients had positive blood testing results at 3 years post-dose.

In the Phase 3 study, the time of observed maximum levels of vector DNA ranged between 4 to 7 hours in blood and between weeks 5 and 27 in semen after etranacogene dezaparvovec administration (N=54 patients). The earliest absence of vector DNA in blood (i.e. confirmed with 3 subsequent measurements below LOD of vector DNA) was observed by week 17 (1/54; 1.9% of patients). A total of 56% (30/54) of patients reached absence of vector DNA from blood by month 24. The earliest absence of vector DNA in semen was observed by week 6 (1/54; 1.9% of patients). A total of 69% (37/54) of patients reached absence of vector DNA from semen by month 24. Several subjects did not return the required number of blood and semen samples to assess the shedding status as per the definition. Considering shedding results obtained from the final 2 available consecutive samples, a total of 40/54 (74%) and 47/54 (87%) patients were identified to have reached absence of vector DNA from blood and semen, respectively, at 24 months post-dose.
The median time to absence of vector DNA was 52.3 weeks in blood and 45.8 weeks in semen at 24 months post-dose.

Hepatic impairment

In the Phase 3 study, patients with varying degree of baseline liver steatosis, specifically the degree of hepatic steatosis with the Controlled Attenuation Parameter (CAP) score of ≥S2 (≥260 decibels/m) versus <S2 (<260 decibels/m) were compared. Patients with (CAP) scores of ≥S2 (≥260 decibels/m; n=12; range: 262 to 400)), <S2 (<260 decibels/m; n=28; range: 100 to 259) and missing score (n=14) showed no clinically relevant different Factor IX activity levels between the groups following etranacogene dezaparvovec administration.
Patients with advanced liver impairment and advanced fibrosis (elastography of e.g. ≥9 kPA, or suggestive of or equal to METAVIR Stage 3 disease) were not studied (see section “Dosage/Administration”).

Renal impairment

In the Phase 3 study, patients with mild renal impairment (creatinine clearance (CLcr) = 60 to 89 mL/min defined by Cockcroft-Gault equation, n=7) were observed to have numerically higher Factor IX activity (up to 37% relative difference) compared to those with normal renal function (CLcr ≥90 mL/min; n=45) across different time points following etranacogene dezaparvovec administration. One patient with moderate renal impairment (CLcr = 30 to 59 mL/min) in this study had similar Factor IX activity as patients with normal renal function.
Etranacogene dezaparvovec was not studied in patients with severe renal impairment (CLcr = 15 to 29 mL/min) or end-stage renal disease (CLcr< 15 mL/min) (see section “Dosage/Administration”).

Paediatric population

Etranacogene dezaparvovec has not been studied in children below 18 years of age. No data are available.

Preclinical data

Preclinical studies were initiated with a gene therapy product employing the recombinant adeno-associated virus serotype 5 (rAAV5) expressing the wild type human coagulation factor IX (rAAV5-hFIX). Etranacogene dezaparvovec (rAAV5-hFIX-Padua) was subsequently developed from rAAV5-hFIX by introduction of a 2 nucleotide change in the transgene for human Factor IX, generating the naturally occurring Padua variant of Factor IX, which exhibits significantly augmented activity (see section “Clinical Efficacy”).
Etranacogene dezaparvovec and its predecessor were intravenously administered to mice and nonhuman primates (NHP) to determine the biodistribution and potential toxicity. Dose-dependent preferential distribution to the liver was confirmed for both vectors and their transgene expression. Both products were well tolerated and not associated with adverse effects during a 3 or 6-month follow up period, respectively. The No Observed-Adverse-Effect-Level (NOAEL) was set at the highest dose tested in NHPs of 9×10^{13} genome copies (gc)/kilogram (kg) bodyweight (bw), which is approximately 5-fold above the recommended human etranacogene dezaparvovec dose of 2×10^{13} gc/kg bw.

Genotoxicity

Genotoxic and reproductive risks were evaluated with the rAAV5-hFIX. The integration site analysis in host genomic DNA was performed on liver tissue from mice and NHP injected with rAAV5-hFIX up to a dose of 2.3×10^{14} gc/kg bw, corresponding to approximately 10-fold the clinical dose in human. The retrieved rAAV5-hFIX vector DNA sequences represented almost exclusively episomal forms that

were non-integrated into the host DNA. The remaining low level of integrated rAAV5-hFIX DNA was distributed throughout the host genome with no preferred integration in genes associated with mediation of malignant transformation in human.

Reproductive toxicity

The risk of germline transmission after administration of 2.3 x 10^{14} gc/kg bw rAAV5-hFIX, i.e., a dose approximately 10-fold higher than recommended for human, was assessed in mice. The rAAV5-hFIX administration resulted in detectable vector DNA in the reproductive organs and sperm of male animals. However, following mating of these mice with naïve female animals at 6 days after administration, the rAAV5-hFIX vector DNA was not detected in the female reproductive tissues nor in the offspring, indicating no paternal germline transmission.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, with the exception of 0.9% normal saline solution used for etranacogene dezaparvovec dilution prior to administration (see section “Instructions for handling”).

The compatibility of etranacogene dezaparvovec was established for intravenous infusion lines with integrated in-line 0.2 µm filters made out of polyethersulfone (PES).

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Once diluted with 0.9% normal saline (see section “Instructions for handling”), etranacogene dezaparvovec can be stored at +15 to +25°C in the infusion bag protected from light. However, the administration of etranacogene dezaparvovec dose to the patient should be completed within 24 hours after the dose preparation.
The stability after dilution was established for Polyethylene/Polypropylene (PE/PP) copolymer, Polyvinyl chloride (PVC)-free infusion bags with 0.9% normal saline.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.

Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.
For storage conditions after dilution of the medicinal product, see section “Shelf life after opening”.

Instructions for handling

Handling of etranacogene dezaparvovec
Personal protective equipment, including gloves, safety goggles, protective clothing and masks, should be worn while handling and administering etranacogene dezaparvovec.

Before preparation of etranacogene dezaparvovec for administration

1. Etranacogene dezaparvovec does not contain preservatives. Use aseptic techniques during the preparation and administration of etranacogene dezaparvovec. Use a new needle/vial adapter and syringe for each etranacogene dezaparvovec vial.
2. Use etranacogene dezaparvovec vial(s) only once (single-use vial(s)).
3. Verify the required dose of etranacogene dezaparvovec based on the patient’s body weight. The total number of vials in each finished pack corresponds to the dosing requirement for each individual patient based on the body weight.

Required supplies and materials for preparation

- Normal saline infusion bag(s) of 500 mL (1 or 2 based on the patient`s body weight) (see section “Shelf life after opening”)
- Label(s) for the infusion bag(s) of 500 mL
- IV Infusion line/drip chamber primed with 0.9% normal saline
- Infusion bag connector(s)
- 20 mL or larger luer-lock syringe(s)
- 20 G needles or vial adaptors
- 70% isopropyl alcohol
- Sharps disposal container

Preparation

4. Etranacogene dezaparvovec must be diluted with 0.9% normal saline solution prior to administration.
   ► Prior to dilution, withdraw the volume of the calculated etranacogene dezaparvovec dose (in mL) from the 500 mL infusion bag(s) with 0.9% normal saline solution (see section “Shelf life

after opening"). The volume of 0.9% normal saline to be removed from the infusion bag(s) will vary based on the patient body weight (see Table 9).

- For patients <120 kilogram (kg) bodyweight (bw), dilute etranacogene dezaparvovec in one 500 mL-0.9% normal saline solution infusion bag.
- For patients ≥120 kg bw, dilute etranacogene dezaparvovec with two 500 mL-0.9% normal saline solution infusion bags by dividing the total dose of etranacogene dezaparvovec equally between two 500 mL infusion bags.

Table 8. Preparation of 0.9 percent normal saline infusion bags

Patient body weight	Number of 500 mL 0.9% normal saline infusion bag(s) required	Volume of 0.9% normal saline to withdraw
Less than 120 kg body weight	1	Equal to the total Hemgenix dose (in mL) from one bag
Equal to or more than 120 kg body weight	2	Equal to the total Hemgenix dose (in mL). Remove half of the dose equivalent volume from each of the two infusion bags.

► Remove the amount of 0.9% normal saline with a luer lock syringe at the mixing adapter site of the applicable connector.

Injection of Hemgenix to the infusion bags

5. Add the volume of the required etranacogene dezaparvovec dose to the infusion bag(s) to bring the total volume in each infusion bag back to 500 mL.
6. Do not add etranacogene dezaparvovec into the airspace of the infusion bag during diluting.
7. Gently invert the infusion bag(s) at least 3 times to mix the solution and ensure even distribution of the diluted product.
8. To avoid foaming:
   ► **Do not** shake the etranacogene dezaparvovec vial(s) or the prepared infusion bag(s).
   ► **Do not** use filter needles during preparation of etranacogene dezaparvovec.
9. To reduce the risk of spillage and/or aerosol formation, the infusion bag(s) should be connected to an infusion tubing prefilled with sterile 0.9% normal saline solution.
10. The infusion tubing prefilled with sterile 0.9% normal saline solution should be connected to the main intravenous infusion line which has been primed with sterile 0.9% normal saline solution prior to use.
11. Use only 0.9% normal saline solution since the stability of etranacogene dezaparvovec has not been determined with other solutions and diluents.

Administration of etranacogene dezaparvovec

Required supplies and materials for administration

- Winged intravenous needle or catheter set
- Infusion pump
- 0.2 µm in-line filter
- Antiseptic skin preps
- 70% isopropyl alcohol wipes
- Gauze and tape, or transparent dressing
- Sharps disposal container
- Virucidal agent to treat spill/spill kit

12. Do not infuse the diluted etranacogene dezaparvovec solution in the same intravenous line with any other products.
13. **Do not** use a central line or port.
14. Diluted etranacogene dezaparvovec should be visually inspected prior to administration. The diluted etranacogene dezaparvovec should be a clear, colourless solution. If particulates, cloudiness or discoloration are visible in the infusion bag, do not use etranacogene dezaparvovec.
15. Use the product after dilution as soon as possible. You **must not** exceed the storage time of the diluted product beyond that provided section “Shelf life after opening”.
16. Use an integrated (in-line) 0.2 µm filter made out of polyethersulfone (PES) (see section “Incompatibilities”).
17. The diluted etranacogene dezaparvovec solution must be administered into a peripheral vein by a separate intravenous infusion line through a peripheral venous catheter.
18. Etranacogene dezaparvovec solution should be infused closely following the infusion rate(s) provided in section “Dosage/Administration”. The administered should be completed within ≤24 hours after the dose preparation (see section “Dosage/Administration”).
19. After the entire content of the infusion bag(s) is infused, the infusion line must be flushed at the same infusion rate with 0.9% normal saline solution to ensure all etranacogene dezaparvovec is delivered.

Measures to take in case of accidental exposure

Accidental exposure to etranacogene dezaparvovec should be avoided.
Local guidelines on handling of material that have been in contact with the Genetically Modified Organism (GMO) should be followed in case of accidental exposure. Work surfaces and materials which have potentially been in contact with etranacogene dezaparvovec must be decontaminated with appropriate disinfectant.

- In case of accidental exposure to eyes, immediately flush eyes with water for at least 15 minutes. **Do not** use alcohol solution.
- In case of accidental needle stick exposure, encourage bleeding of the wound and wash injection area well with soap and water.
- In case of accidental exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. **Do not** use alcohol solution.
- In case of accidental inhalation, move the person into fresh air.
- In case of accidental oral exposure, abundantly rinse mouth with water.
- In each case, obtain subsequently medical attention.

Disposal
Etranacogene dezaparvovec contains a GMO. Unused medicinal product and all materials (solid and liquid waste) that have been in contact with the GMO should be handled and disposed of as potentially infectious waste in a container dedicated to GMO, autoclaved and destroyed in accordance with local biosafety guidelines.

Non-disposable materials should be cleaned with a disinfectant with viricidal activity e.g. a chlorine releasing disinfectant like hypochlorite containing 0.1% available chlorine (1000 ppm) after usage and then autoclaved, if possible. Contact surfaces should be disinfected with a similar disinfectant.

Authorisation number

68780 (Swissmedic)

Packs

1 carton with 11 - 48 vials (each vial = 10 mL) adjusted to the patient's body weight [A].
The total number of vials in each finished pack, corresponds to the dosing requirement for an individual patient depending on the body weight (see Table 9), and is provided on the package.

Table 9. Multi-Vial Kits Configurations

Patient body weight in kilogram (kg)	Total vial number	Total volume of etranacogene dezaparvovec in mL
51 - 55	11	110
56 - 60	12	120
61 - 65	13	130
66 - 70	14	140
71 - 75	15	150
76 - 80	16	160
81 - 85	17	170
86 - 90	18	180
91 - 95	19	190
96 - 100	20	200
101 - 105	21	210
106 - 110	22	220
111 - 115	23	230
116 - 120	24	240
121 - 125	25	250
126 - 130	26	260
131 - 135	27	270
136 - 140	28	280
141 - 145	29	290
146 - 150	30	300
151 - 155	31	310
156 - 160	32	320
161 - 165	33	330
166 - 170	34	340
171 - 175	35	350
176 - 180	36	360
181 - 185	37	370
186 - 190	38	380
191 - 195	39	390
196 - 200	40	400
201 - 205	41	410
206 - 210	42	420
211 - 215	43	430
216 - 220	44	440

221 - 225	45	450
226 - 230	46	460
231 - 235	47	470
236 - 240	48	480

Marketing authorisation holder

CSL Behring AG, Berne

Date of revision of the text

December 2023