EU Risk Management Plan

for

HEMGENIX (etranacogene dezaparvovec)

RMP version to be assessed as part of this application:

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QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

Abbreviations

Term / Abbreviation	Description
AAV	Adeno-associated virus
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aRMM	Additional risk minimisation measure
AST	Aspartate aminotransferase
ATHN	American Thrombosis and Hemostasis Network
BP	Blood Pressure
CI (95%)	Confidence interval (95%)
DAA	Direct Acting Agent
DNA	Deoxyribonucleic acid
DSUR	Development safety update report
DVT	Deep vein thrombosis
ED	Exposure day
EEA	European Economic Area
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
EU	European Union
FIX	Factor IX
gc	Genome copy
GLP	Good Laboratory Practice
HCC	Hepatocellular Carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hFIXco-Padua	gain-of-function Padua-variant of the human Factor IX
HIV	Human Immunodeficiency Virus
HIC	Intracranial Haemorrhage
IU	International Units
IV	Intravenous
LAM-PCR	Linear-amplification mediated polymerase chain reaction
LOD	Limit Of Detection

Term / Abbreviation	Description
LP1	Liver-specific promoter 1
NAb	Neutralizing antibody
NOAEL	No Observed Adverse Effect Level
NHP	Non-Human Primate
PWH	Persons With Hemophilia
rAAV	recombinant adeno-associated viral vector
(r)AAV5	(recombinant) adeno-associated virus 5
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TEE	Thromboembolic event
TIA	Transient ischemic attack
US	United States of America
VTE	Venous thromboembolism

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Part I: Product overview

Table Part I-1: Product Overview

Active substance (INN or common name)	AAV5-hFIXco-Padua (etranacogene dezaparvovec)
Pharmacotherapeutic group (ATC Code)	ATC Code: not yet assigned
Name of Marketing Authorization Applicant	CSL Behring GmbH
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	HEMGENIX®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Biotechnological, nucleic acid based, gene therapy medicinal product
	Summary of mode of action: Following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector Deoxyribonucleic acid (DNA) resides almost exclusively in episomal form. After 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 (FIX) procoagulant activity in patients with Hemophilia B, restoring the hemostatic potential.

	Important information about its composition: HEMGENIX, is a single-dose, gene therapy medicinal product intended for the long-term treatment of Hemophilia B via sustained restoration of FIX activity. It is comprised of a non-replicating, recombinant adeno-associated viral vector serotype 5 (rAAV5) with an expression cassette encoding a codon-optimized coding DNA sequence of the gain-of-function Padua-variant (R338L) of the human FIX (hFIXco-Padua) under the control of a liver-specific promoter 1 (LP1). HEMGENIX employs an AAV of serotype 5 and is manufactured using baculovirus technology. 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, containing a total of 1×10^{14} genome copies. This medicinal product contains 35.2 mg sodium per vial (3.52 mg/ml).
Hyperlink to the Product Information	HEMGENIX EUPI [link]
Indication(s) in the EEA	Current: Hemgenix is indicated for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors
	Proposed: Not applicable
Dosage in the EEA:	Current: Posology The recommended dose of etranacogene dezaparvovec is a single dose of 2×10^{13} gc/kg body weight corresponding to 2 mL/kg body weight, administered as an intravenous infusion after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. Etranacogene dezaparvovec can be administered only once.

	Method of administration Hemgenix is administered as a single-dose intravenous (IV) infusion after dilution of the required dose with sodium chloride 9 mg/mL (0.9%) solution for infusion. Etranacogene dezaparvovec must not be administered as an intravenous push or bolus. The diluted product should be administered at a constant infusion rate of 500 mL/hour (8 mL/min). In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped to ensure patient tolerability. 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 the infusion 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.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Pharmaceutical form: Concentrate for solution for infusion (sterile concentrate) Strength: 1 x 10^{13} genome copies /mL Appearance: Clear, colourless solution
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

(r)AAV5: (recombinant) adeno-associated virus 5, ATC: Anatomic Therapeutic Chemical Code, DNA: Deoxyribonucleic acid, FIX: Factor IX, gc: genome copy, hFIXco-Padua: gain-of-function Padua-variant of the human Factor IX, INN: International non-proprietary name, IV: intravenous, LP1: liver-specific promoter 1

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indications and target population

Hemgenix is indicated for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

Congenital Hemophilia B is an inherited X-chromosome linked bleeding disorder characterized by an increased bleeding tendency due to either a partial or complete deficiency of the essential blood coagulation factor, factor IX.

Incidence - Prevalence

According to the January 2021 Orphanet Report Series, the global birth prevalence / incidence of Hemophilia B is 1.665 per 100,000 individuals and the estimated European Union (EU) prevalence of Hemophilia B is 3 per 100,000 individuals (Orphanet, 2021).

World Federation of Hemophilia estimated prevalence at birth from the FranceCoag data to be 5 per 100,000 males. The birth prevalence of Hemophilia B is approximately 1 in 20,000 live male births worldwide. Prevalence is approximately 1 in 25,000 males in the United States of America (US) and EU (WFH, 2020).

Demographics of the population in the authorized indication and risk factors for the disease

Demographics

Hemophilia B is an X-chromosome linked recessive disorder; it is therefore more common in men (87%) than in women (5%) (unknown gender [6%]) (WFH, 2020). Most female carriers of hemophilia are asymptomatic, having a factor IX mutation on one X chromosome and one working copy of the factor IX gene on the other X chromosome. While hemophilia can occur in females, it is extremely rare; bleeding symptoms can occur in ~10% of female carriers (Scott, 2014). The disorder is lifelong (ie, occurs in all age groups) and is found in all ethnic groups.

Risk factors for the disease:

Hemophilia B is an X-chromosome linked disorder. Family history of hemophilia and carrier mother are the main risk factors. Generally, point mutations in the ‘coagulation factor IX’ gene (F9) can lead to severe Hemophilia B (Scott, 2014). Approximately two-thirds of

patients with hemophilia have a family history of bleeding. In the remaining one-third of patients, hemophilia results from spontaneous gene mutation. In such cases, 80% of mothers are carriers of a de novo mutated allele (Fauci et al, 2008).

The main existing treatment options:

Hemophilia B care is based on regular replacement therapy (prophylaxis) with hemostatic agents to prevent bleeding, or episodic therapy (also known as “on demand”) with a hemostatic agent after bleedings (WFH guideline, 2020).

There is no cure for Hemophilia B. The primary goals of Hemophilia B therapy are prevention of bleeding episodes, rapid and definitive treatment of bleeding episodes (breakthrough bleeds) that occur even while on a regular prophylactic regimen, and provision of adequate haemostasis during surgery and emergencies.

Currently, these goals are essentially met for patients with Hemophilia B through IV injections of recombinant or plasma-derived factor IX products, either at the time of a bleed (episodic) or by regular infusions (prophylaxis). Standard half-life factor IX products are administered as prophylaxis every other day to 3 times a week, while extended half-life recombinant FIX products allow less frequent dosing with routine infusions every 7, 10, or 14 days to prevent bleeding. Plasma and whole blood products are less effective than recombinant factor IX products since they contain lower concentrations of factor IX. They also convey risks of circulation overload, heart failure and viral contaminations. Recombinant factor IX products are widely accepted as the optimal treatment and are used in developed countries; fresh frozen plasma is the only product available in several developing countries.

Episodic therapy is highly effective at arresting hemorrhages. In patients with severe Hemophilia B, spontaneous bleeding episodes can be dramatically reduced when plasma factor IX activity levels are maintained continuously above 1% of normal (0.01 International Unit [IU]/mL) by prophylactic administration of factor IX protein. Since prophylaxis can reduce the risk of spontaneous bleeds and help reduce or prevent joint damage (Manco- Johnson et al, 2007; Valentino et al, 2015), it has become the standard of care in countries with access to adequate quantities of clotting factor concentrates. However, use of current prophylaxis products requires life-long, regular iv administration, an invasive and inconvenient process.

Natural history of the indicated condition in the population, including mortality and morbidity:

Hemophilia B manifests as profuse bleeding into joints and muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma. Recurrent joint bleeding can lead to chronic arthropathy, pain, and loss of function. Prophylaxis with factor IX replacement products in patients with Hemophilia B reduces the risk for spontaneous bleeds but does not eliminate them completely. Breakthrough bleedings particularly in the joints and muscles still occur in many patients on prophylaxis when factor IX activity levels are low. As few as only 1 or 2 bleeding episodes in a single joint, might potentially initiate the process of inflammation, leading to synovitis and chronic joint damage or hemophilic arthropathy (Dodd and Watts, 2012; Fischer and Hermans, 2013).

Chronic debilitating joint disease results from recurrent bleeding into the joint, synovial membrane inflammation, hypertrophy, cartilage damage, joint instability, subsequent atrophy of the muscles supporting the joint, and eventually, destructive arthritis. Chronic joint deformities that need to be managed by an orthopedic specialist may occur. Finally, joint replacement(s) may be needed.

Severe disease leads to spontaneous life-threatening bleeding episodes resulting in deaths and morbidity from chronic joint disease. When untreated, most individuals with severe Hemophilia B die from bleeding complications before 25 years of age. Even in the era of adequate factor replacement products, the hallmark of Hemophilia B is the lifelong propensity for bleeding (WFH, 2020).

The introduction of virus inactivation techniques in the preparation of plasma-derived concentrates in the 1980s, as well as the production of recombinant factors, greatly improved the safety of replacement therapy. Since then, the lifespan of hemophilia patients has progressively approached that of males in the general population, at least in high-income countries. A Dutch study followed 1066 patients from 2001 to 2018 and found that the median life expectancy of hemophilia patients was 77 years. While this is still lower than that of the general population, it has increased from the calculated lifespan of 70 years that was found in a similar study that followed patients from 1992 to 2001. This recent study also found the most common causes of death in hemophilia patients were intracranial bleeding and malignancies. Chronic liver disease, hepatocellular carcinoma, and acquired immunodeficiency syndrome were also causes of death related to Hemophilia but occurred less frequently (Hassan et al, 2020). The overall life expectancy in human immunodeficiency virus (HIV)-negative patients with severe Hemophilia A or B in the United Kingdom was 63

years, which is about 15 years lower than the general male population (Darby et al, 2007). With adequate prophylactic treatment, and without liver complications (e.g., HIV or Hepatitis C virus [HCV]), the life expectancy in patients with severe hemophilia can approach that of the general male population (Plug et al, 2004; Osooli et al, 2017). All-cause mortality rates in the hemophilia population due to coagulation defects and due to intracranial hemorrhage (HIC) are significantly increased compared to the general population.

Approximately 3 to 5% of patients with severe Hemophilia B develop alloantibody inhibitors that can neutralize native and administered FIX and render replacement ineffective. These inhibitors are usually immunoglobulin G (IgG) and often appear after approximately 10 infusions of FIX concentrate (Chitlur et al, 2009; Di Michele, 2011; Warrier, 1999). However, they may appear at any time in the patient's life. Inhibitor development is considered the most severe problem in hemophilia care today as it affects the efficacy of patient treatment, increases the risk of developing joint bleeds (Oladapo et al, 2018), increases the cost of hemophilia care, and leads to increased morbidity. Of note, inhibitor incidence in Hemophilia B is not well defined. Since Hemophilia B is a rare disease, it is difficult to obtain sufficient number of previously untreated patients (PUPs) to conduct large cohort and prospective studies focusing on the inhibitor incidence in Hemophilia B patients (Santoro et al, 2018). The incidence of FIX inhibitors has been reported to range between 1.5 and 5% of all patients with Hemophilia B (Di Michele, 2011; Annoni et al, 2013), with inhibitors rarely seen in mild or moderate disease. PedNet conducted a recent study to explore the incidence of inhibitor development in severe Hemophilia B patients followed up for up to 500 Exposure Days (ED). The cumulative inhibitor incidence was 9.3% (95% Confidence Interval [CI]: 4.4 to 14.1) at 75 ED, and 10.2% (95% CI: 5.1 to 15.3) at 500 ED (Male et al, 2020).

The burden of Hemophilia is high for the individual patient, their families and for society. Patients may not be able to participate in certain activities (e.g, contact sports), and may encounter long-term impairments in mobility and functional status leading to absence from school or work. Issues may surface with social participation and peer integration, particularly when children are growing up. Hemophilia patients are less likely to proceed into full-time employment and occupational disability is more frequent (Fischer and Hermans, 2013). Living with Hemophilia can have a substantial effect on mental wellbeing, with anxiety and depression having an increased prevalence in persons with Hemophilia (PWH), compared to the general population (Al-Huniti et al, 2020). A systematic literature review revealed the significant economic burden associated with Hemophilia B in the US and the substantial costs and health resources utilized by Hemophilia B patients (Li et al, 2019).

Treatment adherence is a key challenge at 2 transition points: when young people with hemophilia switch to self-infusion, and again when they move away from home and assume the full responsibility of self-care. Adherence to prophylaxis has been found to be suboptimal in many adolescents (13 to 17 years of age) and young adults (18 to 30 years of age) with Hemophilia. In general, the main barriers to adherence to prophylaxis include high perceived burden of treatment, no or low burden of bleeds and symptoms, venous access difficulties, and viewing prophylaxis as complicated and time-consuming (WFH, 2020).

Important co-morbidities:

Consequences of bleeding:

Hemophilia is characterized by increased bleeding into joints and muscles (Dunn, 2011; Plug, 2004). Repeated bleeding into joints may result in physical disability owing to hemophilic arthritis (Aledort, 1994).

Although prophylaxis in hemophilia started in the pediatric population, its use in adults is now well established. Prophylaxis has the dual benefit of reducing the risk of joint bleeds as well as intracerebral hemorrhage. HIC remains a significant contributor to morbidity and mortality in patients with both severe and non-severe hemophilia (Payne et al, 2017). The aging PWH who have not been treated with routine prophylaxis since birth will likely experience physical disability due to hemophilic arthropathy, chronic pain and reduced muscle bulk, all of which will contribute to abnormal gait and predisposition to falls (Sammels et al, 2014).

Osteoarthritis is becoming more of an issue especially in combination with hemophilic arthropathy. Joint replacements especially of the knee, elbow and ankle are now routinely performed in the larger Hemophilia centers in patients with mean ages in their 30's to 40's; as patients with Hemophilia live longer and are operated at a relatively young age, redo and revision joint surgery is more often encountered (Beeton et al, 2000; Silva and Luck, 2005; Rodriguez-Merchan, 2007; Goddard et al, 2010; Song et al, 2018).

Chu et al, 2018 performed a longitudinal population-based study using Taiwan's National Health Insurance Research Database to compare the incidence of comorbidities and their risk factors among 411 workers with those in an age- and sex-matched general population (n=1600). Compared with the general population, workers with hemophilia were found to have higher risks for hemorrhagic stroke, arthritis/arthropathy, and knee or hip replacement

after multivariate adjustment, with hazard ratios (95% CI) of 4.60 (2.81 to 7.53), 4.03 (3.34 to 4.87), and 1.29 (1.10 to 1.41), respectively.

Age-related comorbidities:

Modern treatments, as well as general improvements in health care and living standards, are constantly changing the demography of Hemophilia. The life expectancy of Hemophilia B patients is steadily approaching that of the general population (Canaro, 2015). Comorbidities that trend with age, such as high cholesterol, high blood pressure, and obesity are affecting the older hemophilia population. Such issues predispose these individuals to chronic diseases such as cardiovascular disease and chronic kidney disease. The older hemophilia population faces additional complications, such as joint arthropathy and complications related to HIV and HCV infection, which impact the incidence of cancer and liver disease in this population. For patients with severe hemophilia in particular, adequate management of comorbidities is frequently compromised by the increased risk of hemorrhage. As the demographic shift continues, hemophilia care centers can expect to encounter more patients with greater levels of complexity (Berntorp, 2015).

Cardiovascular diseases:

It has been suggested in the literature that cardiovascular-related mortality may be reduced in patients with hemophilia, due to a protective effect resulting from the disease (Biere-Rafi et al, 2010; Darby et al, 2007). However, data are often conflicting and with the hemophilia population aging, it is now recognized that many risk factors, such as hypertension and overweight, occur quite frequently in PWH (Kempton et al, 2021).

A large cross-sectional study from the United Kingdom and the Netherlands found that the prevalence of hypertension (defined as blood pressure [BP] > 140/80 mmHg and/or use of antihypertensive medication) was higher in a cohort of older Hemophilia patients (≥ 30 yr) compared with a healthy age-matched male population (49 vs. 40%). Moreover, the prevalence increased with age, rising from 53% in patients aged 50 to 59 years to > 80% in patients aged 60 years or older, and was higher in patients with severe Hemophilia than in those with mild or moderate disease (Fransen van de Putte, 2012). Furthermore, the data demonstrated that the risk of atherosclerotic cardiovascular disease was greater using the QRISK 2 score (an online assessment tool for estimating the 10-year risk of having a cardiovascular event, in people who do not already have heart disease) in men with Hemophilia over the age of 40 compared to the general population (8.9 vs. 6.7%).

These data are mirrored by a study from the United States (US) in which hypertension prevalence in adult hemophilia patients (≥ 18 yr) was compared with that of a nationally representative sample provided by the National Health and Nutrition Examination Survey. The results showed that the prevalence of hypertension was greater in hemophilia patients compared to the general population (49.1 vs. 31.7%), increased with age, and was higher in patients with moderate or severe hemophilia than in those with mild disease (von Drygalski, 2013).

Another cross-sectional study covered a 5-year period and included PWH aged ≥ 35 years who were cared for at a single hemophilia treatment center in the United States. Medical records were extensively reviewed to collect the information about cardiovascular events. The study cohort comprised 185 PWH (102 Hemophilia A and 83 Hemophilia B). Lifetime prevalence of a cardiovascular event was 19.5% (36/185, 95% CI 13.8 to 25.2%). Compared with US non-Hispanic White males, PWH had about twice the prevalence of coronary artery disease, stroke and myocardial infarction (Sharathkumar et al, 2011).

In individuals without hemophilia, hypertension is a significant risk factor for HIC, with the risk doubling for each increase of 20 mmHg in systolic BP or 10 mmHg in diastolic BP (Kim et al, 2005; Lewington et al, 2002; Song et al, 2004). In hemophilia patients, the rate of HIC is approximately 20 to 50 times higher than that in the general population (Giroud et al, 1991; Ljung, 2008; Nilsson et al, 1992; Fransen van de Putte, 2012), and hemophilia patients with HIC have a high rate of comorbid hypertension (Zanon et al, 2012). High blood pressure, in turn, is a risk factor for atherosclerosis and cardiovascular disease (Roger et al, 2011) as well as erectile dysfunction (Feldman et al, 1994).

Viral infections

Most PWH who have been treated with coagulation factor concentrates prior to the introduction of viral inactivation in 1985 are likely to have been infected with HIV and/or HCV. All PWH with HIV are generally now on antiretroviral therapy, which is highly effective in suppressing viral replication, so essentially HIV is a chronic disease. HIV patients are at increased risk of cardiovascular disease, and risk factor control should always be addressed (Shah et al, 2018).

An increasing number of adults with Hemophilia and HCV have in recent years been treated with oral direct acting agent (DAA) treatments for HCV eradication, replacing historical use of interferon (Walsh et al, 2020). Two studies conducted by the American Thrombosis and Hemostasis network (ATHN-5 and ATHN-6) studied 226 patients to evaluate HCV outcomes

after eradication, including with DAAs. This represents the largest collection of patients with bleeding disorders infected by HCV and shows a similar distribution of HCV genotypes in people with bleeding disorders, compared to the population of people with HCV infection who were exposed to potential infection via other risks factors such as the use of illicit intravenous drugs, chronic dialysis, unprotected sexual contact, or being incarcerated. Over 97% of participants in ATHN 5 demonstrated sustained response at 12 weeks after the end of DAA therapy, a reliable indicator of cure, and less than 1% of participants in ATHN 6 discontinued DAA therapy early due to adverse reactions. (Walsh et al, 2020).

Hepatocellular carcinoma (HCC) is by far the most prevalent form of primary liver cancer, representing 90% of liver cancers worldwide (D'Souza et al, 2020). HCC development has been strongly linked to Hepatitis B virus (HBV) and HCV infections and is associated with approximately 80% of HCC cases (El-Serag, 2012). Most cases of HCV-related and HBV-related HCC occur among patients with advanced fibrosis or cirrhosis, with the 5-year cumulative risk of developing HCC for cirrhotic patients ranging between 5 and 30% (El-Serag, 2012). However, HCC occurs in up to 20% of patients with a non-cirrhotic liver (Desai et al, 2019; Trevisani et al, 2010).

Osteoporosis and fracture risk:

Worldwide, osteoporosis is associated with more than 8.9 million fractures each year (Johnell and Kanis, 2006). As reported by the National Health and Nutrition Examination Survey, the prevalence of osteoporosis in men is 5.7% among those over the age of 65 years (Looker and Frenk, 2015). In contrast, cross-sectional studies of men with hemophilia over the age of 50 years have reported the prevalence of osteoporosis to be significantly higher in all disease severities (44% severe, 25% moderate, and 39% mild) (Kempton et al, 2014). Meta-analyses of studies in both paediatric and adult populations have found consistently lower bone mineral density in PWH (Iorio et al, 2010; Paschou et al, 2014).

Fracture is the main consequence of osteoporosis and can contribute to chronic pain and disability which is already a significant concern for PWH. Major osteoporotic fractures are those that occur in the hip, spine, forearm, or shoulder either spontaneously or from a fall at a standing height. These are considered fragility or low-trauma fractures. The exact risk of fracture in PWH and with low bone mineral density or osteoporosis is unclear. There are several reports that estimate that, when compared to the general population, PWH have a higher risk of fracture (Gay et al, 2015). In one study, the prevalence of hip or vertebral fracture in men aged 50 to 54 years was 16 to18% and significantly higher than estimates of

the general population (0.1%) of the same age and from the same geographic region (Okamoto et al, 2019).

Part II: Module SII - Non-clinical part of the safety specification

Preclinical studies were initiated with a gene therapy product employing a non-replicating recombinant adeno-associated virus serotype 5 expressing the wild type of the human coagulation factor IX via a codon optimized transgene cassette (AAV5-hFIX; AMT-060; CSL220). Etranacogene dezaparvovec (AAV5-hFIXco-Padua; AMT-061; CSL222) was subsequently developed from AAV5-hFIX by introduction of a 2 nucleotide change in the transgene for human FIX, generating thereby the naturally occurring Padua variant of FIX (R338L), which exhibits significantly augmented activity.

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Single-dose toxicity: Toxicity studies with vector biodistribution investigations have been performed in four Good Laboratory Practice (GLP) compliant single dose studies: two biodistribution and safety studies with a 180-day observation period in cynomolgus macaques with AAV5-hFIX/CSL220 (NR-060-14-010) and etranacogene dezaparvovec (AAV5-hFIXco-Padua/CSL222; NR-061-17-001), and two biodistribution and safety studies in C57Bl/6 mice with CSL220 (NR-060-14-002) and CSL222 (NR-061-18-002). • The cynomolgus macaque studies showed a comparable safety profile for CSL220 and etranacogene dezaparvovec. • The overall no-observed-adverse-effect-level (NOAEL) for CSL222 was 9.0 × 10^13 gc/kg. • Vector DNA integration into the host genome was studied in liver samples from the CSL220 GLP studies and indicated no potential carcinogenic risk of the product. The safety of CSL220 and CSL222 formulated with and without the addition of polysorbate 20 was evaluated in wild-type male mice (NR-061-18-002). • The addition of the polysorbate 20 to the formulation had no effect on the safety profile of CSL220 and CSL222 in wild-type mice. • In terms of potential toxicity, no target organ toxicities were identified for both products. • Microthrombi in lungs were observed upon necropsy in 1 out of 10 mice only at the highest dose cohorts ($9x10^{13}$gc/kg) for both CSL220 and CSL222 in NR-061-18-002. At these highest doses tested, the FIX	Etranacogene dezaparvovec (CSL222) is identical to CSL220 (AMT-060), with exception of a 2 nucleotide change in the coding region of the therapeutic transgene, generating the gain-of-function Padua variant (R338L) of FIX. These studies did not raise concerns for etranacogene dezaparvovec in relation to human safety at the intended doses.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
activity levels were grossly supraphysiological (~2000% and 500% for CSL222 and CSL220, resp.) Microthrombi were not observed at lower doses and also were not detected in the NR-060-14-002 study that employed an even higher max dose of CSL220 ($2.3x10^{14}$gc/kg).	
Repeated-dose toxicity: • Repeated dose toxicity studies were not performed as CSL220 and CSL222 will be administered only once. In view of this intended clinical administration, no repeated dose toxicity studies were required as per the 2018 Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014).	Not applicable as CSL220 and CSL222 are administered only once.
Genotoxicity (mutagenicity): • In line with the 2018 Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014) standard genotoxicity studies, as applied to a conventional chemical drug, were not performed. • Vector DNA integration site analysis performed on the host genome of liver samples from the CSL220 GLP study (NR-060-14-007) indicated no potential carcinogenic risk. (See Single dose toxicity studies section, above).	The risk of any consequence due to insertional mutagenesis associated genotoxicity is considered negligible for CSL220 due to only marginal integration levels of the vector DNA into the host genome. These findings are considered applicable to CSL222 as well due to the nearly identical (2 nucleotide difference) vector DNA sequence.
Carcinogenicity: • Linear - amplification mediated polymerase chain reaction (LAM-PCR) plus high throughput sequencing was conducted on DNA extracted from the livers of both mouse and cynomolgus macaques after administration of CSL220 at various doses. • Both episomal (concatemeric) and integrated forms of CSL220 DNA were retrieved but the sequences were present almost exclusively as non-integrated episomal forms. • The retrieved integrants were randomly distributed throughout the host genome. No specific clustering was seen in cynomolgus macaque genome, while some level of clustering around active genes was seen in the mouse. • There were no findings of in vivo clone selection in the animals.	The observed marginal integration level and associated integration profile of CSL220 are deemed applicable CSL222 as well. Altogether the findings do not indicate a risk of CSL222 to contribute to malignant transformation and do not raise specific carcinogenicity concerns for use in humans.

AAV5: adeno-associated virus 5, DNA: Deoxyribonucleic acid, gc: genome copy, GLP: good laboratory practice, (h)FIX: (human) Factor IX, hFIXco-Padua: gain-of-function Padua-variant of the human Factor IX, LAM-PCR: Linear-amplification mediated polymerase chain reaction,
NOAEL: no-observed-adverse-effect-level

Safety pharmacology

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
GLP safety study in cynomolgus macaques (NR-060-14-010): A single dose GLP toxicity study with IV injection of CSL220 in male cynomolgus macaques was performed, with assessments performed across a 26-week period. The objectives of this study were to determine the potential toxicity of a single infusion of four doses ranging from 5×10^{11} gc/kg to 9.3×10^{13} gc/kg of CSL220, to evaluate the potential reversibility of any findings over a 6-month period, and to provide data to support the use of CSL220 vector in humans. In addition, biodistribution of the vector DNA was determined in target and off-target tissues. The animals were between 31 and 42 months of age at the time of dosing. • There were no unscheduled deaths and no clinical signs related to treatment with CSL220. • Cardiology, biochemistry, immunological, and inflammatory marker parameters were all unaffected by treatment with CSL220. • There were no macroscopic or microscopic tissue findings that could be attributed to the administration of CSL220; therefore, it was concluded that a single IV infusion of CSL220 at levels between 5×10^{11} gc/kg and 9.3×10^{13} gc/kg was well tolerated in the cynomolgus macaque. • There was no evidence of any significant toxicological finding, and no target organ effects were observed. **GLP study in cynomolgus macaques (NR-061-17-001):** Liver enzymes were transiently increased during first week after dosing with CSL222 or CSL220 in cynomolgus monkeys.	It is understood that transaminitis may be reflective of immune mediated liver injury, that could depress transgene maintenance and consequent FIX-Padua expression. In non-clinical studies of CSL222 only transient mild increases in liver enzymes were observed in cynomolgus monkeys. Effects on other major vital physiological functions are not anticipated.

AAV5: adeno-associated virus 5, DNA: Deoxyribonucleic acid, gc: genome copy, GLP: good laboratory practice, (h)FIX: (human) Factor IX, IV: intravenous

Other toxicity-related information or data

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Irritancy and Sensitization: Local tolerance at the injection site has been assessed as part of the GLP general toxicity studies. • No injection site reactions were reported.	No concerns in relation to human safety were raised.
Immunogenicity: **GLP safety study in cynomolgous macaques (NR-061-17-001):** An ascending dose study of CSL222 ($5x10^{11}$, $5x10^{12}$, $2.5x10^{13}$, $9x10^{13}$ gc/kg) was conducted in cynomolgus macaques, with a single comparator dose ($5x10^{12}$ gc/kg) of CSL220 to bridge observations between the predecessor product CSL220 and CSL222. • There were no mortalities nor severe clinical findings related to treatment. • All animals treated with either CSL220 or CSL222 developed high titer antibodies against AAV5 capsid proteins post product infusion. • Six non-human primates (NHP) from 4 different groups developed antibodies against human FIX, a finding that was attributed to cross species antigenicity of human versus NHP FIX. • Animals displayed only mild (~2x control) and transient liver enzyme elevations in the first week post product infusion. • At a comparable dose of $5x10^{12}$ gc/kg of either CSL220 or CSL222 similar levels of vector DNA in plasma, vector DNA biodistribution, transgene mRNA as well as protein expression was observed. • Baseline corrected FIX activity of etranacogene dezaparvovec-infused NHPs was approximately 6.5 times that of CSL220 treated NHP at equal dose, in line with expected results of the gain-of-function Padua variant of FIX utilized in CSL222 compared to the wild-type hFIX employed in CSL220. • Due to the lack of observed adverse events (AEs) the NOAEL was set at the highest dose studied ($9x10^{13}$ gc/kg).	Transient liver enzyme elevations observed in non-clinical studies, is an expected risk following administration of CSL222 in humans (for details, please see Section SVII.3.1)

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
GLP safety study in C57Bl/6 mice (NR-060-14-002): • The only notable finding in this study was observed on Day 8, which was increased spleen weight in the highest dose group associated with a mild transient increase in the number and size of germinal centers in the spleen that had resolved by Day 28 of the study. • These effects were also present to a lesser extent in animals receiving the highest dose in combination with prednisone at Day 8 post-administration. • This finding is considered a reaction to the injection of viral proteins and the subsequent immune reaction towards the capsid proteins as supported by its transient character. **GLP safety study in cynomolgus macaques (NR-060-14-010):** A single dose GLP toxicity study with IV injection of CSL220 in male cynomolgus macaques was performed, with assessments performed across a 26-week period. • Cardiology, biochemistry, immunological, and inflammatory marker parameters were all unaffected by treatment with CSL220.	
Teratogenicity and fetotoxicity: Small amounts of AAV vector DNA have been observed in previous non-clinical studies in blood, urine, saliva, nasal secretions, feces, and semen. • In a non-clinical paternal germline transmission study in mice (NR-060-14-001), no vector DNA transmission to the offspring occurred at a dose level 10 × the clinical dose. • Specifically, while vector DNA was present in sperm, it was not detectable in the uterus and placenta of the females and in the offspring. • There were no effects of treatment on maternal behavior, body weights, food consumption, mating performance, fertility indices, pregnancy performance, external fetal abnormalities, and fetal weights.	No concerns in relation to human safety were raised.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Supraphysiologic levels of FIX and associated thrombosis: • In NHPs treated with etranacogene dezaparvovec (NR-061-17-001), total FIX clotting activity (one stage aPTT) reached average activity levels at the high dosed group (9 x 10^{13} gc/kg) of near 500% of normal human levels. • There was no evidence for an increase in the thrombosis markers Thrombin-antithrombin or D-Dimer. There were no thrombogenic events recorded in this preclinical study.	High percentages like the ones observed in non-clinical studies are not expected in humans due to a lower administered dose. The proposed clinical dose of etranacogene dezaparvovec is only 25% of that used in the highest dose group of NHPs. Therefore, no concerns in relation to human safety were raised.

AAV5: adeno-associated virus 5, AE: adverse event, DNA: Deoxyribonucleic acid, gc: genome copy, GLP: good laboratory practice, (h)FIX: (human) Factor IX, IV: intravenous, NHP: Non-human primate, NOAEL: no-observed-adverse-effect-level, TEAE: Treatment-emergent adverse event, aPTT: Activated partial thromboplastin time

In summary, the pharmacology studies demonstrated a strong correlation between dose and human factor IX expression levels and confirmed the biological activity of the expressed human factor IX protein. The studies confirmed that both CSL220 (AAV5-hFIX) and CSL222 (AAV5-hFIXco-Padua) induce expression of functional human factor IX protein.

Biodistribution studies in animals have shown the preferential distribution and persistence of the vector DNA in the liver, with broad distribution to other organs at a lower level, for CSL220 and CSL222. Due to the liver-specific promoter used, factor IX mRNA and protein expression was limited to the liver.

The paternal germline transmission/reproduction study revealed no effect on reproduction upon CSL220 treatment.

The comparable dosing of CSL222 and CSL220 in the NHP study also permitted quantitative assessment of the hFIX-Padua variant's specific activity relative to the wild-type hFIX. Factor IX activity, at a dose of 5×10^{12} gc/kg, is approximately 6-times higher per unit protein expressed for CSL222 (Padua variant) as compared to CSL220 (wild type). At the higher dose of 2.5×10^{13} gc/kg (close to the dose of 2×10^{13} gc/kg that is being administered in the clinical studies with CSL222), the factor IX activity:protein ratio (specific activity) was between 7 and 9. These results are similar to the increase in specific activity reported for the FIX-Padua protein compared with "wild-type" factor IX protein, in animal models (Crudele et al, 2015; Monahan et al, 2015).

The toxicity study in cynomolgus macaques with etranacogene dezaparvovec demonstrated that a single IV infusion in the dose range of 5×10^{11} gc/kg to 9×10^{13} gc/kg was well tolerated by cynomolgus macaques. Based on this study, the proposed no-observed-adverse-effect-level (NOAEL) for CSL222 is 9×10^{13} gc/kg, which is 4.5-times above the dose of 2×10^{13} gc/kg, employed in the phase 3 clinical trial.

The formulation bridging study in mice showed that biodistribution, factor IX expression, and safety were comparable for CSL220 and CSL222 at equal dose and not influenced by the addition of polysorbate 20 to the formulation.

Part II: Module SIII - Clinical trial exposure

The clinical development program for etranacogene dezaparvovec comprises 4 studies:

- CSL220_1001 (CT-AMT-060-01): A phase 1/2, open-label, uncontrolled, single-dose, dose-ascending, multi-center trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) administered to adult patients with severe or moderately severe Hemophilia B.
- CSL220_1002 (CT-AMT-060-04): A phase 1/2b extension study assessing the long-term safety and efficacy of an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) previously administered to adult patients with severe or moderately severe Hemophilia B during the CT-AMT-060-01 phase 1/2 study.
- CSL222_2001 (CT-AMT-061-01): A phase 2b, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIX-Padua) administered to adult subjects with severe or moderately severe Hemophilia B.
- CSL222_3001 (CT-AMT-061-02): A phase 3, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIX-Padua) administered to adult subjects with severe or moderately severe Hemophilia B.

Taking into consideration the mechanism of action of etranacogene dezaparvovec (continued transgene expression), the duration of exposure is defined as the time on study from treatment date to the minimum of end-of-study visit date, early termination date, or data cutoff date. Person-months is the total number of months contributed to each exposure duration interval. A summary of clinical trial exposure to CSL220 and CSL222 for all 4 studies (cumulative exposure) in person time is presented in Table SIII-1. Overall exposure by age and gender is presented in Table SIII-2, by dose in Table SIII-3, and by ethnic origin in Table SIII-4.

Table SIII-1: Duration of exposure

Cumulative for all indications (person time)				
	CSL222 (AAV5-hFIXco-Padua; etranacogene dezaparvovec)		CSL220 (AAV5-hFIX)	
Duration of exposure	**Patients**	**Person time (Months)**	**Patients**	**Person time (Months)**
1 m	0	0	0	0
1 to <3 m	0	0	0	0
3 to <6 m	0	0	0	0
6 to <12 m	0	0	0	0
12 to <18 m*	3	50.6	0	0
18 to <24 m	47	958.7	0	0
24 to <36 m	7	197.2	0	0
36 to <48 m	0	0	0	0
48 to <60 m	0	0	8	474.8
≥60 m	0	0	2	120.4
Total	**57**	**1206.5**	**10**	**595.2**

*One subject died prior to 18 months. A protocol defined visit window of ± 2 weeks surrounding each scheduled visit results in 2 subjects exposure calculating to 17.7 months (instead of 18 months).m: month

Table SIII-2: Age group and gender

Age group	CSL222 (AAV5-hFIXco-Padua; etranacogene dezaparvovec)		CSL220 (AAV5-hFIX)	
	Patients	**Person time (Months)**	**Patients**	**Person time (Months)**
Infants and toddlers (<2 years)	0	0	0	0
Children (2 to 11 years)	0	0	0	0
Adolescents (12 to 17 years)	0	0	0	0
Adults (18 to 49 years)	41	871.0	6	356.9
Adults (50-64 years)	9	189.4	1	60.2
Elderly people	7	146.1	3	178.2
65-74 years	6	130.9	3	178.2
>75 years	1	15.2	0	0
Total	**57**	**1206.5**	**10**	**595.2**

Table SIII-3: Dose

Dose of exposure	CSL222 (AAV5-hFIXco-Padua; etranacogene dezaparvovec)		CSL220 (AAV5-hFIX)	
	Patients	**Person time (Months)**	**Patients**	**Person time (Months)**
5×10^{12} gc/kg	0	N/A	5	298.1
2×10^{13} gc/kg	57*	1206.5	5	297.1
Total	**57***	**1206.5**	**10**	**595.2**

*Includes one subject administered a partial (~10%) dose, N/A: not applicable

Table SIII-4 Ethnicity

Ethnicity	CSL222 (AAV5-hFIXco-Padua; etranacogene dezaparvovec)		CSL220 (AAV5-hFIX)	
	Patients	**Person time (Months)**	**Patients**	**Person time (Months)**
Hispanic or Latino	4	79.8	0	0
Not Hispanic or Latino	48	1030.7	10	595.2
Total	**52***	**1110.5**	**10**	**595.2**

*Five (5) subjects' values of ethnicity and race are not provided due to local privacy regulations.

Table SIII-5 Race

Race	CSL222 (AAV5-hFIXco-Padua; etranacogene dezaparvovec)		CSL220 (AAV5-hFIX)	
	Patients	**Person time (Months)**	**Patients**	**Person time (Months)**
White	41	857.4	9	534.9
Non-White	11	253.1	1	60.3
Total	**52***	**1110.5**	**10**	**595.2**

*Five (5) subjects' values of ethnicity and race are not provided due to local privacy regulations.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Criteria	Reasons for exclusion	Is it considered to be included as missing information ?	Rationale for not including as missing information
History of positive Factor IX inhibitor test	Patients with active FIX inhibitors have risk of anaphylaxis, severe allergic reactions and nephrotic syndrome	No	Patients with a history of FIX inhibitors will not be treated with etranacogene dezaparvovec (Hemgenix Summary of Product Characteristics [SmPC]).
Positive FIX inhibitors test at Screening (measured by the local laboratory)	Patients with active FIX inhibitors have risk of anaphylaxis, severe allergic reactions and nephrotic syndrome	No	Prior to treatment, baseline testing for the FIX inhibitors should be performed in each patient. Patients will only be considered eligible for treatment with etranacogene dezaparvovec when they test negative for FIX inhibitors (Hemgenix SmPC).
Screening laboratory values (measured by the central laboratory): • Alanine aminotransferase (ALT) > 2 times upper normal limit • Aspartate aminotransferase (AST) > 2 times upper normal limit • Total bilirubin > 2 times upper normal limit • Alkaline phosphatase (ALP) > 2 times upper normal limit	Reason for this exclusion was to have as normal liver function as possible to allow for optimal liver-directed gene therapy in a clinical trial setting.	Yes (Use in patients with severe hepatic impairment)	Not applicable.
Screening laboratory values (measured by the central laboratory): • Creatinine > 1.5 times upper normal limit	No additional risk or modification of dosing anticipated with renal disease but excluded for purposes of clinical trial.	No	Specific to conduct of clinical trial only; no specific risk related to use of etranacogene dezaparvovec in patients with increased creatine > 1.5 times ULN is expected

Criteria	Reasons for exclusion	Is it considered to be included as missing information ?	Rationale for not including as missing information
Positive HIV serological test at Screening, not controlled with anti-viral therapy as shown by CD4+ counts ≤ 200 per µL or by a viral load of >200 copies per mL (measured by the central laboratory)	Avoid exposing immunocompromised subjects (low CD4+ count) to an experimental product.	No	Patients with active infections, either acute or uncontrolled chronic, will not be treated with etranacogene dezaparvovec (Hemgenix SmPC).
Active infection with Hepatitis B or C virus as reflected by Hepatitis B surface Antigen (HBsAg), Hepatitis B extracellular Antigen (HBeAg), Hepatitis B Virus DeoxyriboNucleic Acid (HBV DNA) or Hepatitis C Virus RiboNucleic Acid (HCV RNA) positivity, respectively, at screening (measured by the central laboratory).	To avoid exposing subjects with potentially highly compromised hepatic function to an experimental product.	Yes (Use in patients with severe hepatic impairment)	Not applicable.
History of Hepatitis B or C exposure, currently controlled by antiviral therapy	To avoid exposing subjects with potentially highly compromised hepatic function to an investigational product.	No	Specific to conduct of clinical trial only; not anticipated to be used in patients who are not stable on antiviral treatment or who are currently undergoing HCV eradication.
Any coagulation disorder other than Hemophilia B	Gene therapy directed at replacing missing gene (factor IX)	No	Etranacogene dezaparvovec is only indicated for the treatment of adult patients with Hemophilia B (congenital Factor IX deficiency) (Hemgenix SmPC). Therefore, use in patients with other coagulation disorders is not anticipated.
Thrombocytopenia, defined as a platelet count below 50×10^9 / L, at Screening (measured by the central laboratory)	Potential interference to measure safety and efficacy of etranacogene dezaparvovec.	No	Etranacogene dezaparvovec is only indicated for the treatment of adult patients with Hemophilia B (congenital Factor IX deficiency) (Hemgenix SmPC). Therefore, use in patients with other coagulation disorders is not anticipated.

Criteria	Reasons for exclusion	Is it considered to be included as missing information ?	Rationale for not including as missing information
Planned surgery for the initial 6 months after Investigational medicinal product (IMP) administration in this trial	Potential for inadequate hemostasis during surgery and interference to measure efficacy of etranacogene dezaparvovec.	No	Specific to conduct of clinical trial only.
Previous arterial or venous thrombotic event (e.g., acute myocardial infarction, cerebrovascular disease and venous thrombosis)	Potential interference to measure safety of etranacogene dezaparvovec.	No	Specific to conduct of clinical trial only; Loss of any cardiovascular protective effect from normalizing FIX levels is offset by the ability to more completely address pharmacotherapy of underlying cardiovascular risk.
Active severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease, alcoholism, drug dependency or any other psychological disorder evaluated by the investigator to interfere with adherence to the protocol procedures or with the degree of tolerance to the IMP.	Potential interference to measure safety and efficacy of etranacogene dezaparvovec.	No	Specific to conduct of clinical trial only. Of note, patients with active infections, either acute or uncontrolled chronic, will not be treated with etranacogene dezaparvovec (Hemgenix SmPC).

Criteria	Reasons for exclusion	Is it considered to be included as missing information ?	Rationale for not including as missing information
Known significant medical condition that may significantly impact the intended transduction of the vector and/or expression and activity of the protein, including but not limited to: a. Disseminated intravascular coagulation b. Accelerated fibrinolysis c. Advanced liver fibrosis (suggestive of or equal to METAVIR Stage 3 disease, e.g., a FibroScan™ score of ≥9 kPa is considered equivalent)	Potential interference to measure safety and efficacy of etranacogene dezaparvovec.	No (a, b) Yes (c) (Use in patients with severe hepatic impairment)	a, b: Specific to conduct of clinical trial only. c: Patients with advanced hepatic fibrosis will not be treated with etranacogene dezaparvovec (Hemgenix SmPC).
Known history of an allergic reaction or anaphylaxis to FIX products	Patients with historical anaphylaxis have risk of anaphylaxis, severe allergic reactions and nephrotic syndrome upon re-exposure to FIX	No	Use in patients with historical inhibitors with anaphylaxis currently receiving FIX prophylaxis at standard doses is thought to be no different than the trial population.
Known uncontrolled allergic conditions or allergy/hypersensitivity to any component of the IMP excipients	Potential serious adverse reactions	No	Hypersensitivity to etranacogene dezaparvovec or excipients will be contraindicated.
Receipt of an experimental agent within 60 days prior to Visit 1	Avoid possible interactions with other experimental drugs that would confound results in etranacogene dezaparvovec studies	No	Specific to conduct of clinical trial only.
Current participation or anticipated participation within one year after IMP administration in this trial in any other interventional clinical trial involving drugs or devices.	Avoid possible interactions with other experimental drugs that would confound results in etranacogene dezaparvovec studies	No	Specific to conduct of clinical trial only.

Criteria	Reasons for exclusion	Is it considered to be included as missing information ?	Rationale for not including as missing information
Known history of allergy to corticosteroids	Use of corticosteroids may be required to address transient elevations in liver function tests	No	Use is not anticipated in patients unable to receive steroids
Known medical condition that would require chronic administration of steroids	Avoid possible interactions that would confound results in etranacogene dezaparvovec studies	No	Specific to conduct of clinical trial only.

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, FIX: Factor IX, HBsAg: Hepatitis B Surface Antigen, HIV: human immunodeficiency virus, IMP: Investigational medicinal product, ULN: upper limit of normal

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

Given the rarity of the disease, the small Hemophilia B patient population and the even smaller sizes of the cohorts, extrapolation of data on captured adverse events (AEs) and serious adverse events in order to provide a meaningful perspective on the nature and frequency of these incidents is of limited value.

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.3-1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pediatric patients	Have not been included in the initial clinical trials. Of note, etranacogene dezaparvovec is only indicated for the treatment of adult patients with Hemophilia B (congenital Factor IX deficiency) (Hemgenix SmPC). Therefore, use in the paediatric population is not anticipated.
Women including Pregnant women and Breastfeeding women	Have not been included in the initial clinical trials. Hemophilia B is extremely rare in women (approximately 5%) (WFH, 2020) suggesting that some women who carry the mutation are symptomatic and require treatment.
	Two female partners of two subjects who participated in the CT-AMT-060-01 phase 1 study experienced paternal exposure before pregnancy. • The outcome of the first pregnancy was a male baby. No further information on the child was provided. • The outcome of the second pregnancy was a female baby. The mother was informed on the subject's Hemophilia B status and the requirement to test the child for her FIX percentage in due course. No additional information was provided.
	There are no data regarding etranacogene dezaparvovec use in women. • It is not known whether this medicinal product can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Etranacogene dezaparvovec should not be used during pregnancy (Hemgenix SmPC). • It is unknown whether etranacogene dezaparvovec is excreted in human milk. A risk to the newborns/infants cannot be excluded. Etranacogene dezaparvovec should not be used during breast feeding (Hemgenix SmPC).

Type of special population	Exposure
Immunocompromised subjects	Patients with HIV not controlled with anti-viral therapy, HBV, and HCV infection if they were currently receiving antiviral therapy and/or positive for any of HBsAg, HBV DNA or HCV RNA were excluded from clinical studies with etranacogene dezaparvovec. Patients with underlying chronic well controlled medical history of these conditions were included in clinical studies.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with severe hepatic impairment were not included in clinical development. Two patients with moderate hepatic impairment and seven patients with mild hepatic impairment were included in CSL222_3001 (CT-ATM061-02) trial.
Patients with renal impairment	Patients with severe renal impairment were not included in clinical development. There were 7 subjects with mild renal impairment and 1 patient with moderate renal impairment.
Patients with cardiovascular impairment	Patients with uncontrolled cardiovascular disease were excluded from clinical development. Cardiovascular function was not reported.
Patients with mild/moderate Hemophilia with severe bleeding phenotype	Patients with FIX activity > 2% were not included in clinical studies.
Population with different ethnic origin	Included in the clinical development program. See Table SIII.4.
Subpopulations carrying relevant genetic polymorphisms	All subjects included in these gene therapy clinical trials had an X-linked recessive disorder (Hemophilia B). Genetic abnormalities in the factor IX gene are reported in the clinical study reports. No other genetic polymorphisms were characterized.
Patients with previous gene therapy treatment	Not included in the clinical development program Due to the potential interference to assess efficacy and safety of etranacogene dezaparvovec, subjects who had received a previous gene therapy product were excluded from clinical trials with etranacogene dezaparvovec.

DNA: deoxyribonucleic acid, FIX: Factor IX, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: human immunodeficiency virus, HBsAg: Hepatitis B Surface Antigen, RNA: ribonucleic acid

Part II: Module SV – Post-authorization experience

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Etranacogene dezaparvovec is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use. Therefore, no potential for misuse for illegal purposes is anticipated.

Specific risks of advanced therapy medicinal product

Hemophilia B is caused by a partial or complete deficiency in the coagulation protein FIX and is currently treated by life-long IV injections of recombinant or plasma-derived FIX products. Etranacogene dezaparvovec is intended to be used as a one-time intravenous IV infusion in the treatment of Hemophilia B patients who currently use Factor IX prophylaxis therapy or have current or historical life-threatening hemorrhage or repeated, serious spontaneous bleeding episodes. Treatment with etranacogene dezaparvovec is intended to result in stable expression of hFIX-Padua, a natural occurring gain-of function variant of wild type FIX, in the liver which is the main site of FIX synthesis.

The etranacogene dezaparvovec vector genome is packaged within adeno-associated virus 5 (AAV5) derived capsids. The vector genome of etranacogene dezaparvovec consists of a codon optimized Padua derivative of the human FIX (hFIX-Padua) gene under control of the liver-specific human LP1 promoter. Additionally, the expression cassette contains SV40 intron and SV40 poly A sequences for optimal expression and is flanked by intact inverted terminal repeats from AAV2. Characteristics of etranacogene dezaparvovec which may cause adverse effects to patients and third parties are evaluated during the environmental risk assessment (ERA) and are summarized below.

Etranacogene dezaparvovec is produced in expresSF+ insect cells with the help of a Baculovirus Expression Vector System. The potential risk posed by the used recombinant baculoviruses is negligible since baculoviruses have a limited host range and are not able to replicate in mammalian cells. In addition, the recombinant baculoviruses are removed from the drug substance and its absence is assured by release testing. As a consequence of the manufacturing platform, low levels of short baculovirus DNA and expresSF+ cell DNA fragments can be present, which, in theory, might lead to a limited expression of small peptides. Due to the size and origin of these fragments and the shedding profile of etranacogene dezaparvovec, the risk of this adverse effect to human health and the

environment is considered negligible. This has been confirmed in previous applications of recombinant adeno-associated viral vectors (rAAVs), which did not reveal any harmful effects that could possibly be related to residual baculovirus or expresSF+ insect cell DNA impurities.

In theory, unintended exposure of third parties, like health care professionals and close contacts, to etranacogene dezaparvovec might cause an immune response to the particles or expression of hFIX-Padua. The potential risk caused by an immune response to etranacogene dezaparvovec particles is considered negligible since it is highly unlikely that third parties will be exposed to and infected by infectious particles. Additionally, the consequence of this immune response will be similar to that of a wild type AAV and is considered negligible.

The probability that unintended exposure to etranacogene dezaparvovec will result in expression of hFIX-Padua is considered extremely low. Although the expression of hFIX-Padua might, in theory, be able to dysregulate coagulation, the likelihood that this will occur is, in view of the applied dose and the extreme overexpression needed, considered negligible. Consequently, the risk of both potential adverse effects to human health are considered negligible.

Etranacogene dezaparvovec lacks all virus protein encoding sequences, which makes etranacogene dezaparvovec replication deficient. Nonetheless, scenarios in which etranacogene dezaparvovec can replicate in vivo, or even revert to a replication competent AAV either during manufacturing or post-administration, are theoretically conceivable. The risk of possible generation of replication competent AAV during manufacturing is considered negligible due to the design of the manufacturing system and the fact that absence of replication competent AAV is assured by release testing. Post administration, replication of etranacogene dezaparvovec would require a simultaneous infection of one-and-the-same cell with etranacogene dezaparvovec, wild type AAV and a helper virus. The likelihood that these requirements are met is considered highly unlikely and in the case of complementation will lead to the new formation of replication deficient etranacogene dezaparvovec particles. Therefore, risk of complementation is considered negligible. The likelihood that also (non)homologous recombination events between etranacogene dezaparvovec and wild type AAV will occur is considered negligible. The risk of the generation of replication competent rAAV due to this (non) homologous recombination is considered negligible. In addition, etranacogene dezaparvovec might be, in theory, eligible for homologous recombination with a SV40-like virus. The potential risk posed by this recombination event is considered negligible as it is highly unlikely that SV40 sequences will be present in the patient and share

sufficient homology with etranacogene dezaparvovec and that the recombination will actually materialize and form infectious virus particles.

Insertional mutagenesis is a generally recognized safety concern of vector-based gene therapies. In theory, random integration of rAAV DNA into the host genome might lead to insertional mutagenesis that in worst-case can contribute to the development of malignancy. The potential risk of random integration of etranacogene dezaparvovec in unintended subjects is considered negligible due to the fact that rAAVs remain mainly episomal and due to the fact that it is considered highly unlikely that unintended individuals will be exposed to infectious etranacogene dezaparvovec particles. In addition, non-clinical studies and data from the subject who experienced HCC (CSL222_3001 /CT-AMT-061-02; see Section SVII.3) did not reveal integration at sites that raised any concern with carcinogenicity.

Paternal germline transmission studies in mice employing a dose 10 times that recommended for human Hemophilia B patients did not show any transmission of vector DNA to mated females or their offspring. Furthermore, a neutralizing humoral immune response directed against the AAV5 vector capsid will develop in all immune competent Hemophilia B patients. This immune response will penetrate into the seminal fluid compartment and render vector particles non-transmissible. All subjects in clinical trials of Hemgenix have developed such an immune response within 2-3 weeks post vector infusion. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. In conjunction with the recommended barrier contraception period of 1 year after vector infusion this renders any risk of inadvertent germline transmission negligible.

In addition to potential adverse effects to (un)intended individuals, also the potential adverse effects are assessed that etranacogene dezaparvovec might pose to the environment. In this respect, the potential adverse effects related to the exposure of etranacogene dezaparvovec to animals and plants, the potential adverse effects on the dynamics of populations of species in the receiving environment and the genetic diversity of each of these populations, the potential adverse effects facilitating the dissemination of infectious diseases, the potential adverse effects compromising prophylactic or therapeutic medical or veterinary treatment and the potential adverse effects on the biogeochemistry are evaluated. The risk of these potential adverse effects related to the proposed release of etranacogene dezaparvovec to the environment are all assessed as negligible.

Standard precautions to mitigate spillage and/or aerosol formation of the genetically modified organism will be applied during the preparation and administration of etranacogene

dezaparvovec. In view of the ERA outcome, no additional management measures are required.

Taken together, no immediate and/or delayed effects on human health are expected for persons working with etranacogene dezaparvovec or coming into contact with or in the vicinity of the genetically modified organism as it is released. Likewise, no effects on the environment are to be expected. The likelihood that etranacogene dezaparvovec becomes persistent and invasive in natural habitats is considered negligible. The host range of etranacogene dezaparvovec will be limited just like that of wild-type AAV and etranacogene dezaparvovec has been rendered non replicating, which provide in addition selective disadvantage. In the unlikely event that infectious particles are shed, the chance of subsequent spread into the environment is therefore considered negligible. In conclusion, under the prerequisite of applying the ERA related inclusion criteria for risk mitigation, the overall risk of the marketing of etranacogene dezaparvovec to human health and the environment is considered negligible.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. Known or potential risks that require no further characterization or are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the routine risk minimization measures are sufficient for the safe use of the product:

    - **Nausea:** Four ADRs were reported in the CSL222 (AMT-061) clinical studies, which were non serious and mild. They occurred 4 to 6 days after administration and lasted 4 to 6 days. Nausea is listed in Hemgenix summary of product characteristics (SmPC). Routine pharmacovigilance is sufficient to monitor this risk.
    - **Fatigue:** Four ADRs were reported in the CSL222 (AMT-061) clinical studies, which were non serious and mild. They occurred on the day of administration to 13 days later and lasted 3 to 72 days (duration was not reported for 1 of the events). Fatigue is listed in Hemgenix SmPC. Routine pharmacovigilance is sufficient to monitor this risk.
    - **Malaise:** Two ADRs were reported in the CSL222 (AMT-061) clinical studies, which were non serious and mild. They occurred 2 to 10 days after administration and lasted 5 to 6 days. Malaise is listed in Hemgenix SmPC. Routine pharmacovigilance is sufficient to monitor this risk.
    - **Dizziness:** Four ADRs were reported in the CSL222 (AMT-061) clinical studies, which were non-serious and either mild (n=3) or moderate (n=1). They occurred on day 1 to 8 after administration and lasted 1 to 5 days. Only for the moderate event, the administration was interrupted. Dizziness is listed in Hemgenix SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

- **Headache:** Ten ADRs were reported in the CSL222 (AMT-061) clinical studies, which were non-serious and either mild (n=8) or moderate (n=2). They occurred on day 1 to 10 after administration and lasted 1 to 11 days. Headache is listed in Hemgenix SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Hepatotoxicity

Risk-benefit impact:

The most prevalent hypothesis for the underlying mechanism of hepatotoxicity is a cytotoxic T cell-mediated immune response against the vector capsid sequences displayed on vector-transduced hepatocytes with resultant loss of transduced cells and consequent constraint on transgene expression (Manno et al, 2006; Mingozzi et al, 2007; Arruda and Doshi, 2020).

In the non-clinical study NR-061-17-001, liver enzymes were transiently, and mildly (~2x control) increased during first week after dosing with etranacogene dezaparvovec (AAV5-hFIXco-Padua) or AAV5-hFIX in cynomolgus monkeys.

Review of data from the CSL222 (AMT-061) clinical program revealed that serum transaminase elevations occurred most often in the first 1 to 2 months following administration, with asymptomatic ALT elevation being the most common treatment related AE.

Published results of clinical trials show that IV administration of a liver directed AAV vector may lead to transaminase elevations which in general respond promptly and normalize after administration of corticosteroids, or resolve without any treatment (Rangarajan et al, 2017; Nathwani et al, 2011; Nathwani et al, 2014 and Nathwani et al, 2018; George, 2017; Manno et al, 2006).

Decreased FIX activity has been reported in the literature along with ALT elevation, following infusion of AAV vector and this may have an impact on the benefit-risk balance of the product. Asymptomatic transient elevation in transaminases that resolved without treatment was reported in a study investigating the single infusion of rAAV–human FIX vector to adult males with severe (< 1% FIX activity) Hemophilia B. These events were

accompanied by declining FIX levels (Manno et al, 2006). ALT elevations with reduced FIX levels were also observed in patients receiving a single IV infusion of a novel serotype 8 pseudo-typed, self-complementary AAV (AAV8) vector expressing a codon-optimized FIX transgene. All patients received a tapering dose of prednisone, which resulted in the resolution of hepatocellular toxicity events and the preservation of transgenic FIX expression (Nathwani et al, 2014).

Important Identified Risk 2: Infusion reactions (including hypersensitivity)

Risk-benefit impact:

In the clinical studies with etranacogene dezaparvovec, infusion-related reactions of mild to moderate severity have been observed in 7/57 subjects.

From the scientific literature, so far limited side effects after intravenous infusion of AAV-based gene therapy have been reported, however mild infusion related complaints were reported (Leebeek and Miesbach, 2021).

Based on the limited exposure data and the potential impact on the benefit-risk profile of Hemgenix in case only a partial infusion can be administered, infusion reactions including hypersensitivity were classified as an important identified risk.

Important Potential Risk 1: Risk of malignancy in relation to vector integration in the DNA of body cells

Risk-benefit impact:

Regulatory guidelines on gene therapy recognize the need for long-term follow-up when vectors with the capacity of integration or latency are administered to patients. Chromosomal integration of vectors is considered to present a risk for malignant transformation of cells due to insertional mutagenesis and activation, inactivation, or alteration of host cell genes. Therefore, viral vectors mediating transfer of their genetic material into the cell nucleus are considered to have a high risk for delayed adverse reactions (CHMP, 2009).

Although the rAAV genome remains mainly episomal in the nucleus of transduced cells, a low frequency of random integration has been reported (Smith, 2008). Random integration of rAAV DNA into the host genome might lead to insertional mutagenesis, which can, in worst case, contribute to malignant transformation. Analyses of the integration in the performed non- clinical studies, and the subject who developed hepatocellular carcinoma (HCC) in the CSL222_3001 (CT-AMT-061-02) study did not reveal integration at sites that would raise

any concern with respect to carcinogenicity. Thus, while the likelihood of insertional mutagenesis contributing to the development of malignancy is considered very low, the potential consequence of such event would be severe. Of note: no malignancy linked to an rAAV based gene therapy has been seen in any of the more than 250 clinical trials of rAAV vectors thus far (Sabatino et al, 2022, White paper of the ASGCT Working group on AAV integration).

One case of HCC was observed in the CSL222_3001 (CT-AMT-061-02) clinical study in an elderly subject with multiple risk factors (HCV, HBV, age > 50, alcohol use, family history of cancer). Comprehensive integration site analysis and whole genome sequencing of the tumor and adjacent liver by an independent laboratory revealed no evidence to support a relationship between treatment with etranacogene dezaparvovec and the development of the tumor; mutations commonly associated with HCCs were found in the tumor with pre-malignant changes seen in the adjacent tissue. Based upon established risk factors for HCC and the lack of a genetic association in the evaluation of this patient, the event was considered unlikely related to AAV5-based gene therapy.

Important Potential Risk 2: Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid

Risk-benefit impact:

Pre-existing neutralizing antibodies (NAbs) against the viral vector are thought to be able to preclude efficient liver transduction (Mingozzi and High, 2011) and hence significantly reduce efficacy (Falese et al, 2017; Li et al, 2012).

Product failure due to immune-mediated neutralization of the AAV5 vector capsid could lead to a decrease in circulating FIX activity levels, exposing the patient to risk of breakthrough bleeds and subsequent sequelae.

Twenty-four out of the 57 subjects included in the clinical development program of etranacogene dezaparvovec were positive for anti AAV5 NAbs (titer ≥ 1:7) at baseline. One subject with a screening NAb titer of 3212 did not respond to treatment with etranacogene dezaparvovec. The second highest titer at baseline reported in the AMT-061 clinical development program was 678 in a subject that responded to the treatment.

From literature, one study was identified, in which serum samples were taken from healthy volunteers in France in order to characterize the humoral immune response to the AAV capsid, including AAV5. The prevalence of anti-AAV5 total IgG antibody was 40%, which

was lower compared to anti-AAV1 (67%) and anti-AAV2 (72%). Additionally, neutralizing factor seroprevalence for AAV5 was low (3.2%) and all individuals who were seropositive for AAV5 presented low titers (1:20) (Boutin et al, 2010).

Important Potential Risk 3: Thromboembolic events

Risk-benefit impact:

The plausible mechanism for thrombogenicity is a supraphysiologic factor IX expression with corresponding higher (than normal) factor IX activity. In addition, it is postulated that Hemophilia B patients are at reduced risk of thromboembolic events due to inborn deficiency in the clotting cascade. Alleviating symptoms of Hemophilia B by restoring Factor IX activity may counterweight the reduced potential risk of thromboembolism and set it to the level as observed in the general population with non-hemophilic Factor IX levels (Sood et al, 2018; Kamphuisen et al, 2014).

In the literature an association between FIX activity, particularly increased levels of FIX, and venous thromboembolism (VTE) is described (Wang et al, 2020; Heikal et al, 2013; Lavigne et al, 2003; Weltermann et al, 2003).

In CSL222_3001 (CT-AMT-061-02), 4 Treatment emergent adverse events (TEAEs) in 3 subjects were identified as potentially relating to a thromboembolic event and reported as Preferred Terms of Angina pectoris (2 events) and Peripheral arterial occlusive disease and Transient ischemic attack (TIA) (1 event, each). No thromboembolic events were identified in Study CSL222_2001 (CT-AMT-061-01). Three of the 4 TEAEs were assessed by the Investigator as not related to etranacogene dezaparvovec and 1 serious TEAE of TIA occurred 229 days after dosing with etranacogene dezaparvovec; the causality was unlikely related taking into consideration most likely alternative cause of pre-existing advanced cardiac and cerebrovascular disease.

Endogenous FIX activity achieved clinically relevant levels in the majority (52/54) of subjects, with no subject showing supraphysiologic FIX activity, however, based on the limited exposure data and the potential impact on the benefit-risk profile of Hemgenix, thromboembolic events were classified as an important potential risk.

Important Potential Risk 4: Germline transmission

Risk-benefit impact:

Several (non)clinical studies, and scientific literature indicates that transduction competent rAAV particles are not present in semen following IV administration for longer than 4 days post infusion (Schuettrumpf et al, 2006; Fonck et al, 2022; Arruda et al, 2001; Favaro et al, 2009; Jakob et al, 2005; Nathwani et al, 2011). Vector DNA is only temporarily detectable in semen and mainly available in the seminal fluid instead of the cellular fraction of semen. Moreover, non-replicating rAAV vectors show a very low integration potential, minimizing the likelihood of stable transduction of germline cells. Additionally, and in line with the above constraints, no paternal germline transmission was observed in the performed nonclinical study (NR-060-14-001). Similarly, studies using other AAV serotype-based vectors have not shown germline transmission via the male line and maternal-fetal transmission (Salmon et al, 2014). Of note, it is recommended that patients use barrier contraception for 1 year following Hemgenix administration (Hemgenix SmPC). Therefore, the potential risk to human health of germ-line transmission of CSL222 (AMT-061) is considered negligible.

Important Potential Risk 5: Transmission to third parties (horizontal transmission)

Risk-benefit impact:

Based on results of shedding and clearance tests in pre-clinical and clinical studies, it is assumed that quantitative polymerase chain reaction (qPCR)-detectable etranacogene dezaparvovec DNA fragments may be present in patients' body fluids and excreta for several weeks after administration. However, these fragments will not necessarily represent infectious vector particles.

The scientific literature supports that the shedding is most likely fragmented vector DNA and that this does not equate transduction competent virus particles. No adverse event has been reported referring to "Transmission to third parties (horizontal transmission)" in the clinical studies with etranacogene dezaparvovec. The environmental risk assessment has outlined that infectious AAV particles are restricted to the plasma compartment and are cleared from the circulation during the first 3 days after vector administration (Favre, 2001). After this period, it is considered that all infectious particles have infected test-subject's cells or have been rendered non-infectious through other mechanisms (e.g., degradation by test-subject effector mechanisms, development of an opsonizing inhibitory humoral immune response against AAV5 capsid).

The risk of infectious particles shedding and further transmission to of third parties remains theoretical.

Important Potential Risk 6: Development of FIX inhibitors

Risk-benefit impact:

The formation of inhibitory antibodies against coagulation factors is a major complication of factor replacement therapy. No subjects developed inhibitors in the clinical development program of etranacogene dezaparvovec. Additionally, no FIX alloantibody inhibitor formation was seen in clinical trials reported in literature, where patients were exposed to human factor IX or human factor IX- Padua gene transfer and where the expressed levels of factor IX were measurable (Manno et al, 2003; Manno et al, 2006; Nathwani et al, 2011; Nathwani et al, 2014; Nathwani et al, 2018 and George, 2017). The risk of FIX inhibitor formation following gene the administration of Hemgenix remains theoretical.

Missing information 1: Use in patients with severe hepatic impairment

Risk-benefit impact:

Subjects with ALT > 2 times upper normal limit, AST > 2 times upper normal limit, total bilirubin > 2 times upper normal limit and ALP > 2 times upper normal limit were excluded from participation in clinical trials. Two subjects with moderate hepatic impairment and seven subjects with mild hepatic impairment as per NCI Organ Dysfunction Working Group classification were included in the CSL222_3001 (AMT-CT-061-02) study. The use of etranacogene dezaparvovec in subjects with severe hepatic impairment, has not been evaluated. Etranacogene dezaparvovec is a liver-directed gene therapy and therefore patients with pre-existing severe hepatic impairment may experience more severe hepatic function AEs and potential negative effect on efficacy.

Missing information 2: Long-term effect

Risk-benefit impact:

The need for long-term follow-up is communicated by regulatory guidelines, which recognize the potential risk of declining treatment efficacy over time (CHMP, 2009).

Declined levels of FIX have been observed in clinical trial results published in the literature, likely due to the cytotoxic T cell-mediated immune response against the vector capsid

sequences displayed on hepatocytes (Manno et al, 2006; Mingozzi et al, 2007; Arruda and Doshi, 2020).

The clinical evidence supporting the long-term effects of etranacogene dezaparvovec is limited to the 2 ongoing clinical studies (CSL222_2001/CT-AMT-061-01 [N=3] and CSL222_3001/CT-AMT-061-02 [N=54]) that will be completed after 5 years of post-infusion follow-up.

The number of patients in etranacogene dezaparvovec clinical studies followed up for > 24 months is limited and long-term safety and durability of etranacogene dezaparvovec are not characterized.

Missing information 3: Use in female patients

Risk-benefit impact:

Female patients constitute only a small proportion of Hemophilia B patients. The disease is extremely rare in women (approximately 5%) (WFH, 2020), however some women who carry the mutation are symptomatic and require treatment.

Female patients were not included in the initial clinical trials. There is no clinical data regarding administration of etranacogene dezaparvovec to female subjects. It is not known whether this medicinal product can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Etranacogene dezaparvovec should not be used during pregnancy. It is unknown whether etranacogene dezaparvovec is excreted in human milk. A risk to the newborns/infants cannot be excluded. Hemgenix should not be used during breast feeding (Hemgenix SmPC).

Considering the potential impact of the one-time non-reversible nature of the treatment and lack of information on the use in the female population, use of etranacogene dezaparvovec in female patients is considered missing information.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable for the initial RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk 1: Hepatotoxicity

Potential mechanisms:

The most plausible mechanism underlying the liver effects of etranacogene dezaparvovec is a cytotoxic T cell-mediated immune response against the vector capsid sequences displayed on hepatocytes with resultant loss of transduced cells and consequent constraint on transgene expression (Manno et al, 2006; Mingozzi et al, 2007; Arruda and Doshi, 2020). On the other hand, liver function abnormalities were also reported without a measurable immunological cytotoxic T-cell response in the peripheral blood, as determined by enzyme-linked immunospot assays. It should be noted though, that this assay is not well standardized and has several limitations (Leebeek and Miesbach, 2021).

Evidence source(s) and strength of evidence:

In the majority mild and transient transaminitis events were observed in the preclinical studies and during the clinical development program of etranacogene dezaparvovec.

Furthermore, liver function abnormalities have been reported in clinical trials results published in the literature and investigating IV administration of a liver directed AAV vector (Rangarajan et al, 2017; Nathwani et al, 2011; Nathawani et al, 2014; Nathawani et al, 2018; George, 2017; Manno et al, 2006).

Characterization of the risk:

Fourteen TEAEs of Alanine aminotransferase increased in 12 subjects were reported in the CSL222(AMT-061) clinical studies (2 events in CSL222_2001/CT-AMT-061-01 and 12 events in CSL222_3001 /CT-AMT-061-02). Seven of these events were mild, 6 were moderate and 1 was severe. Nine subjects (experiencing 10 out of 14 events) were treated with steroids, including prednisone, prednisolone, and methylprednisolone. The outcome was reported as recovered/resolved for 13 events and recovering/resolving for the remaining event. FIX activity was preserved within a clinically meaningful range in all the subjects.

Additionally, 9 TEAEs of Aspartate aminotransferase increased in 8 subjects were reported in the CSL222 clinical studies (1 subject in CSL222_2001/CT-AMT-061-01 and 8 in CSL222_3001/CT-AMT-061-02). Seven events were of mild intensity, and the remaining 2 were moderate and severe, respectively. Eight out of 9 events were accompanied by events of Alanine aminotransferase increased (see above) and for the remaining transient event, a concomitant event of Blood creatine phosphokinase increased was reported and no other related events. The outcome was reported as recovered/resolved for 8 events and recovered/resolved with sequelae for the remaining event. Three events were not related, 2 events were possibly related, and 4 events were related to the treatment.

Lastly, 1 TEAE of Transaminases increased (ALT and AST elevation) was reported in the CSL222_2001/CT-AMT-061-01 study. The event was non-serious, of mild intensity and assessed as not related. No treatment was administered for this event and the outcome was reported as recovered/resolved.

Risk factors and risk groups:

Common causative/risk factors for hepatotoxicity include:

- Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver
- Drug-drug interactions
- Alcohol abuse in patients with cirrhotic liver changes
- Concomitant use of hepatotoxic medications

Preventability:

To mitigate the risk of potential hepatotoxicity, transaminases should be closely monitored, e.g, once per week for 3 months after etranacogene dezaparvovec administration. A course of corticosteroid taper should be considered in the event of ALT increase to above the upper limit of normal or to double the patient's baseline levels, along with human FIX activity examinations.

Information on this safety concern is provided in the patient card, health care professional guide and patient guide (See Section V.2 and Annex 6).

Impact on the risk-benefit balance of the product:

Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.

Public health impact:

The impact on public health is expected to be negligible. Liver enzyme elevations can be managed by appropriate monitoring of liver function tests and implementation of corticosteroid taper.

Important Identified Risk 2: Infusion reactions (including hypersensitivity)

Potential mechanisms:

Administration of AAV vectors will induce innate immune response, followed by adaptive immune responses leading to the development of neutralizing antibodies in all individuals, which will be present long-term (Leebeek and Miesbach, 2021). Subjects with pre-existing anti-AAV5 antibodies may be at greater risk for infusion-related reactions (Gorovits et al, 2021).

Evidence source(s) and strength of evidence:

Mild to moderate infusion-related reactions were observed the clinical studies with etranacogene dezaparvovec.

In the scientific literature, a small number of infusion-related reactions after intravenous infusion of AAV5-based gene therapy has been reported. These events were successfully mitigated by slowing or pausing the infusion and administering medications such as antihistamines, antipyretics, or glucocorticoids (Ozelo et al, 2022).

Characterization of the risk:

In the CSL222 (AMT-061) clinical studies, 7/57 subjects (12.3%) experienced in total 13 infusion-related reactions (all subjects were included in CSL222_3001/CT-AMT-061-02). The Preferred Terms reported included Infusion related reaction (2), Dizziness (2), Abdominal pain upper, Chest discomfort, Eye pruritus, Flushing, Headache, Hypersensitivity, Infusion site reaction, Pyrexia, Urticaria. All 13 events were non serious and either mild (n=9) or moderate (n=4). Most events (n=11) resolved on the same day.

In 3 out of 7 subjects, administration was temporarily interrupted and restarted at a slower infusion rate following treatment with antihistamines and/or corticosteroids. In 1 additional subject, administration was discontinued, and the subject received a partial dose (~10%).

The rate of infusion related reactions was higher in patients with preexisting neutralizing anti-AAV5 antibodies at baseline (8,8%; 5/57 patients) compared to patients without (3,5%; 2/57 patients). However, the small number of subjects is not sufficient to confirm such an association.

Risk factors and risk groups:

No specific risk factors are known. However, patients with high levels of preexisting neutralizing antibodies against AAV5 might be more likely to experience infusion reactions.

Preventability:

Etranacogene dezaparvovec should be administered in a setting where personnel and equipment are immediately available to treat infusion related reactions. The diluted product should be administered at a constant infusion rate of 500 mL/hour (8 mL/min).

Patients should be closely monitored for infusion reactions throughout the infusion period and at least for 3 hours after end of infusion. The recommended infusion rate should be closely adhered to ensure patient tolerability. Suspicion of an infusion reaction requires slowing or stopping of the infusion. Based on clinical judgement, treatment with e.g., a corticosteroid or antihistamine may be considered for management of an infusion reaction (Hemgenix SmPC).

Impact on the risk-benefit balance of the product:

The infusion-related reactions in the clinical studies have all been of mild to moderate severity. Subjects with pre-existing anti-AAV antibodies may be at greater risk for infusion-related reactions emanating from AAV antibody-mediated immune complex formation and complement activation. However, the small number of subjects in the clinical studies and the limited information in scientific literature is not sufficient to prove such an association.

Public health impact:

The impact on public health is considered negligible. The infusion can be temporarily interrupted and resumed at a slower infusion rate upon treatment with antihistamines and/or corticosteroids.

Important Potential Risk 1: Risk of malignancy in relation to vector integration in the DNA of body cells

Potential mechanisms:

In contrast to wild type AAV, rAAV vector genomes do not undergo site-specific integration into the host genome and remain mainly as episomal structures within the nucleus of transduced cells. However, random integration events are observed with a low frequency of 0.1 to 1% of all transduction events (Smith, 2008). Apart from the frequency of integration, the occurrence of insertional mutagenesis depends upon the site of integration. Exceptionally, insertional mutagenesis could conceivably contribute to the development of tumor formation.

Evidence source(s) and strength of evidence:

Chromosomal integration of vectors is considered to present a risk for malignant transformation of cells due to insertional mutagenesis and activation, inactivation, or alteration of host cell genes. Therefore, viral vectors mediating transfer of their genetic material into the cell nucleus present a risk for delayed adverse reactions (CHMP, 2009).

One case of hepatocellular carcinoma was observed in the CSL222 clinical development program in an elderly subject with multiple risk factors (HCV, HBV, age > 50, alcohol use, family history of cancer). The event was considered as unlikely related to the etranacogene dezaparvovec treatment upon review of detailed genetic and insertion site analysis.

Characterization of the risk:

Etranacogene dezaparvovec is a non-replicating recombinant AAV5 vector that remains largely non-integrating upon transduction of target cells. Nonclinical and clinical studies showed a low level of random integration events and did not reveal integration at sites that raised any concern of carcinogenicity and thus is not expected to cause development of cancer.

No undisputed model has been described to assess oncogenicity by insertional mutagenesis. rAAV mediated insertional mutagenesis was assessed using linear amplification

PCR (LAM-PCR) plus 454-pyrosequencing. This assay was performed in collaboration with the German Cancer Research Center using AAV1-lipoprotein lipase in mice and lipoprotein lipase deficiency-patients muscle tissue (Kaeppel et al, 2013) and with AAV5-porphobilinogen deaminase in nonhuman primate liver tissue (Pañeda et al, 2013). This assay has produced consistent results in animal models and in tissue of patients. In summary, integration site analyses of liver following IV administration of rAAV did show a measurable but low level of integration, but no signs for malignant transformation was seen.

Similarly, liver tissue samples from the GLP toxicity studies with AAV5-hFIX, the predecessor of etranacogene dezaparvovec (AAV5-hFIXco-Padua), in mice and Cynomolgus macaques were used for integration analysis. The retrieved vector sequences were almost exclusively non-integrated episomal forms. In NHP, the low amount of retrieved integrants were randomly distributed throughout the host genome with no preferred integration in genes associated with mediation of malignant transformation. In mice, low amounts of integrants were retrieved with some integration site clustering in active genes such as Alb, Tc39c, Esp38, and Lrrc4c.

Although not generally accepted as validated model, the performed analyses of integration by LAM-PCR technology did not give any indication of genotoxicity. Accordingly, the likelihood of oncogenicity by insertional mutagenesis is considered highly unlikely, although it cannot be excluded completely.

In CSL222_3001/CT-AMT-061-02, 1 event 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. This was identified on a routine abdominal ultrasound performed ~1 year after dosing with etranacogene dezaparvovec. The subject underwent an exploratory laparotomy with resection of the smaller of 2 lesions in the liver. Results from a histological analysis of the lesion were consistent with HCC. Molecular and integration site analyses were performed on the HCC tissue from the liver lesion and adjacent liver tissue by an independent laboratory and reviewed by external experts. Integration site analysis by 3‘LTR shearing extension primer tag selection/ligation-mediated polymerase chain reaction (S-EPTS/LM-PCR) (Schmidt and Bajaj, 2001) indicated that < 0.03% of the cells in the HCC and HCC-adjacent tissues had an AAV integration and did not indicate a dominant IS in the HCC sample, as would be expected if the AAV vector had integrated and led to clonal expansion of the tumor 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 ribonucleic acid 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 was assessed as unlikely related to etranacogene dezaparvovec administration.

Hepatocellular carcinoma (HCC) is a major global public health problem due to the rising incidence and high mortality in both developing and developed countries. To mitigate this important worldwide health care challenge, it is critical to detect the cancer early. Early detection allows the application of curative treatments. The epidemiology and risk factors for HCC are well known and vary with geographic region. The prevention strategy of Hepatitis B vaccination results in a decline in Hepatitis B. The European Centre for Disease Prevention and Control reported a rate of 8.9 cases of hepatitis C per 100 000 population (excluding 3 countries which only reported acute cases and 2 countries that reported no data). From 2010-2019, the overall number of cases diagnosed and reported across the 23 EU/EEA Member States that reported data consistently over this time, excluding those who only reported acute cases, showed year-to-year fluctuations with no clear long term trend (ECDC, 2021; Dhanasekaran et al, 2012). New antiviral therapies and surveillance are available that can lead to improved outcomes by decreasing the likelihood of future HCC and/or diagnosing HCC earlier. Early diagnosis of HCC is critical since the clinical outcome depends to a large extent on the ability to identify this cancer early. Resection and transplantation remain the cornerstones of curative therapy for HCC but several advances in the treatment of unresectable HCC are beginning to expand the therapeutic armamentarium (Dhanasekaran et al, 2012).

The prevalence of HCC among PWH A or B was reported in 5 articles and ranged from 0.007% (Ghosh and Shetty, 2012) to 6.9% (Miesbach et al, 2009). The lowest prevalence estimates of 0.007% was based on a study using questionnaires to ascertain individuals' HCC status, and only 1 out of 13,470 individuals included in the cohort reported HCC. The study with the largest prevalence estimates of 6.9% was based on a small cohort of 29 individuals with Hemophilia A, only 2 of which were found to have HCC. The second lowest prevalence estimate of 0.69% (Kessler et al, 2016) was based on a study of individuals with acquired hemophilia only, as opposed to congenital Hemophilia, where only 1 case of liver carcinoma was captured. If these studies are excluded, the prevalence of HCC among PWH A or B ranged between 0.79% (Thalappillil et al, 2019) to 1.7% (Fransen van der Putte, 2012). Two studies reported the cumulative incidence of HCC among PWH to be 1.6% (HuangYC, 2015)

and 1.12% (Biron-Andreani et al, 2014). Lastly, 1 study reported an HCC prevalence estimate of 0.74% among people with Hemophilia B specifically (Thalappillil et al, 2019).

Five studies reported the prevalence or incidence of HCC among PWH A or B who were also infected with HCV or HBV. The prevalence of HCC among PWH and HCV was reported in 3 studies and ranged from 2.1% (Thalappillil et al, 2019) to 4.6% (Khan et al, 2013), and the cumulative incidence reported in 2 studies ranged from 1.4% (Santagostino et al, 2003) to 2.5% (Fransen van de Putte et al, 2014). One study reported a cumulative incidence of HCC of 0.36% (Santagostino et al, 2003) among PWH B specifically and HCV. Only 1 study reported the prevalence of HCC among PWH and HBV, which was estimated to be 1.3% (Thalappillil et al, 2019).

Given this targeted literature review, the overall prevalence of HCC ranges from 0.79 to 1.7% in PWH. HCV and HBV are known risk factors for the risk of developing HCC. In patients with HCV infection, the prevalence of HCC ranges from 2.1 to 4.6% and only one study found the prevalence of HCC among individuals that had HBV (1.3%).

Risk factors and risk groups:

The following have been described as risk factors for the development of HCC (Llovet et al, 2021):

- Infection with Hepatitis B and/or Hepatitis C
- Chronic alcohol consumption
- Advanced fibrosis
- Cirrhosis
- Non-alcoholic steatohepatitis (NASH), associated with diabetes mellitus, or obesity
- Non-alcoholic fatty liver disease
- Advanced age
- Male gender

Preventability:

It is recommended that patients with preexisting risk factors for hepatocellular carcinoma (such as hepatic cirrhosis, hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) undergo regular liver ultrasound screenings and are regularly monitored

(eg, annually) for alpha fetoprotein elevations for at least 5 years following administration, especially those with preexisting risk factors for hepatocellular carcinoma (such as hepatic cirrhosis, hepatic fibrosis, Hepatitis C or B disease, non-alcoholic fatty liver disease) (Hemgenix SmPC).

Information on this safety concern is provided in the patient card, health care professional guide and patient guide (See Section V.2 and Annex 6).

Impact on the risk-benefit balance of the product:

Although the rAAV vector genome mainly remains episomal in the nucleus of the transduced cells, a small fraction will randomly integrate in the host genome leading to the risk of insertional mutagenesis. In the worst case, insertional mutagenesis can contribute to the development of tumor formation and negatively affect the benefit risk balance of the product. Routine screening of patients with pre-existing risk factors for HCC will ensure the early identification and treatment of tumor formation.

Public health impact:

Negligible due to the rarity of Hemophilia B patients and HCC.

Important Potential Risk 2: Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid

Potential mechanisms:

Pre-existing neutralizing antibodies (NAbs) against AAV are widely distributed in the general population (Leebeek and Miesbach, 2021). High levels of pre-existing neutralizing antibodies are thought to be able to preclude efficient liver transduction through an immune response (Leebeek and Miesbach, 2021; Mingozzi and High, 2011) and hence significantly reduce efficacy.

Product failure due to immune-mediated neutralization of the AAV5 vector capsid could lead to a decrease in circulating FIX activity levels exposing the patient to risk of breakthrough bleeds and subsequent sequelae.

Evidence source(s) and strength of evidence:

The CSL222 clinical studies suggest that although AAV5 neutralizing antibodies were prevalent in humans, the absolute levels at which they were present may not have been

adequate to significantly impact the infused dose of etranacogene dezaparvovec in the majority of patients.

All patients receiving Hemgenix will develop NAbs against AAV5 in the weeks after administration. However, by that time the vector DNA will have been delivered to the nucleus of the cell where it will direct transgene expression. As such, production of hFIX-Padua is not expected to be impacted by the generation of the anti-capsid humoral immune response.

Characterization of the risk:

In the CSL222 (AMT-061) studies, 24 out of 57 (45.6%) subjects were positive for NAbs to AAV5 (≥ limit of detection (LOD); titer=7). In CT-AMT-061-01, all 3 subjects were positive for NAbs to AAV5 at baseline and in CSL222_3001 (CT-AMT-061-02), baseline levels of NAbs to AAV5 were < LOD for 33 out of 54 (61.2%) subjects and ≥ LOD for 21 out of 54 (38.8%) subjects.

In the CSL222_3001 (CT-AMT-061-02) study, one subject with a baseline anti-AAV5 NAb titer of 3212 had no safety findings but did not demonstrate FIX expression following treatment and needed to continue FIX prophylactic treatment. The second highest titer at baseline reported in the CSL222 clinical development program was 678 in a subject that responded to the treatment. Additionally, all subjects with lower titers also responded to the treatment.

Breakthrough bleeding particularly in the joints and muscles still occur in many patients on prophylaxis when FIX activity levels are low. As few as only one or two bleeding episodes in a single joint might potentially initiate the process of inflammation, leading to synovitis and chronic joint damage or hemophilic arthropathy (Dodd and Watts, 2012; Fischer and Hermans, 2013).

Chronic debilitating joint disease results from recurrent bleeding into the joint, synovial membrane inflammation, hypertrophy, cartilage damage, joint instability, subsequent atrophy of the muscles supporting the joint, and, eventually, destructive arthritis. Chronic joint deformities that need to be managed by an orthopedic specialist may occur. Furthermore, joint replacement(s) may be needed.

Risk factors and risk groups:

There is a lack of data in patients with neutralizing anti-AAV5 antibodies above 1:678. Therefore, these patients could be considered at higher risk, due to the limited clinical experience.

Preventability:

Before administration of Hemgenix, baseline testing for preexisting neutralizing anti-AAV-5 antibody titer is required (Hemgenix SmPC). Potential events of bleeding will be closely monitored to better understand the association between baseline preexisting neutralizing anti-AAV-5 antibodies and bleeding events/lack of effect.

Impact on the risk-benefit balance of the product:

Product failure due to immune-mediated neutralization of the AAV5 vector capsid could lead to a decrease in circulating FIX activity levels and subsequent sequelae, such as bleeding events and need for FIX prophylaxis treatment.

Public health impact:

The impact on public health is considered negligible as patients can revert to prophylaxis therapy in case of insufficient FIX activity expressed by the transgene.

Important Potential Risk 3: Thromboembolic events

Potential mechanisms:

The plausible mechanism for thrombogenicity is a supraphysiologic FIX expression with corresponding higher (than normal) FIX activity. It should be noted that FIX activity will be restored in Hemophilia B patients treated with etranacogene dezaparvovec. Therefore, these individuals will no longer be “protected” from thromboembolic events due to their hemophilic state, but instead have the similar risk of developing such events, compared to the general population.

Evidence source(s) and strength of evidence:

Thromboembolism (e.g., pulmonary embolism, venous thrombosis, and arterial thrombosis) has occurred when using Factor IX-containing concentrate.

One event of pulmonary thrombi was observed in the pre-clinical studies of etranacogene dezaparvovec. Additionally, in the clinical development program of etranacogene dezaparvovec, four events potentially relating to a thromboembolic episode were reported.

Characterization of the risk:

In the toxicology investigations of etranacogene dezaparvovec the microscopic evaluations revealed minimal pulmonary thrombi for one animal (out of 10) from each of the 5×10^{13} gc/kg AAV5-hFIX-Padua + polysorbate 20 and 5×10^{13} gc/kg AAV5-Hfix-polysorbate 20 treatment groups.

In Study CSL222_3001(CT-AMT-061-02), 4 TEAEs in 3 elderly subjects were identified as potentially relating to a thromboembolic event and reported as Preferred Terms of Angina pectoris (2 events), Peripheral arterial occlusive disease and Transient ischemic attack (TIA) (1 event, each). No thromboembolic events were identified in Study CT-AMT-061-01. Three of the 4 TEAEs were assessed by the Investigator as not related to etranacogene dezaparvovec and 1 serious TEAE of TIA occurred 229 days after dosing with etranacogene dezaparvovec; the causality was unlikely related taking into consideration most likely alternative cause of pre-existing advanced cardiac and cerebrovascular disease.

The highest expression seen to date in clinical trials (124%) is within the normal range. Further, once patients have achieved FIX activity levels in the non-hemophilic range (>40%) and particularly when steady-state levels are within the middle of the normal range (50-200%), it will be unlikely that they receive any additional exogenous FIX administration. Of note, the Padua mutation is currently not associated with increased risk of thrombosis at factor IX activity levels within the normal range and has not been identified in populations of subjects with VTE. FIX activity of up to 551% have been reported in relatives of the original reported subject with thrombophilia (Simioni et al, 2009) without associated thrombosis.

One of the patients with a high expression of FIX (>200 IU/dL) participating in the phase 1 B-AMAZE study (using FLT180a, a AAVS3 capsid carrying a FIX variant with a gain of function mutation), developed a thrombotic occlusion of AV-fistula for which anticoagulant treatment was started (Chowdary et al, 2020).

It has been suggested that heightened levels of FIX are associated with the increased risk of thromboembolic events (TEEs), including VTE, pulmonary embolism (PE), and arterial embolism. After a semi-structured, qualitative review of the current literature, various conclusions about this potential association could be made. One case-control study

(Wang et al, 2020) found that among elderly patients (mean age 78.7 years) with VTE there was an increased risk of VTE in individuals with FIX levels in the highest quartile (>132 IU/dL) compared to FIX levels in the lowest quartile (<104 IU/dL), with an OR of 2.4 (95% CI: 1.1, 5.2). Another retrospective study investigated the association between FIX and VTE (Heikal et al, 2013) among younger individuals under the age of 65 and found that 26.3% of individuals with VTE had elevated FIX activity (upper limit of normal FIX activity defined as the 95th percentile of the values found in healthy controls), which was significantly greater compared to the reference group of healthy controls without VTE (OR=6.8; 95% CI: 1.18, 39.07). Similar results were found in an analysis of 18 individuals (Lavigne et al, 2003) with the outcome of VTE who came from families in which high levels of coagulation factors were inherited as a genetic trait (FVIII, FIX, FIX). Of these 18 individuals who experienced VTE (median age of 32 years), 13 individuals had elevated levels of coagulation factors. Compared to the reference group of family members without elevated factor levels, high levels of the three factors were associated with the occurrence of VTE (OR=41; 95% CI: 4.9-353). Finally, a prospective study followed 546 patients with a first episode of spontaneous VTE, to investigate the association between heightened FIX levels and recurrent VTE (Weltermann et al, 2003). In this cohort of individuals with a mean age of 48 years, 66 people out of 546 (12%) experienced a recurrent VTE, including deep vein thrombosis (DVT) and PE (44 had DVT only; 22 had PE (with or without DVT). Patients with recurrent VTE had higher levels of FIX compared to those without recurrent VTE (133 IU/dL vs. 123 IU/dL, respectively). And according to a time to event Kaplan-Meier analysis, patients with FIX levels ≥138 IU/dL had a higher risk of recurrence compared to those with FIX levels <138 IU/dL (p-value<0.001).

On the other hand, one case-control study (Chougule et al, 2016) showed no difference in FIX levels comparing 101 individuals with VTE and 86 controls without VTE (OR=0.85, 95% CI: 0.27, 2.65). Importantly, no studies in our semi-structured search investigated the association between FIX and TEEs specifically among individuals with Hemophilia B. We see from this literature search that the majority of studies demonstrated an association between FIX activity, particularly heightened levels of FIX, and VTE.

Risk factors and risk groups:

Risks factors in the targeted population are the same in the general population and include (Geerts et al, 2008; Previtali et al, 2011):

Venous thrombosis risks

- Pregnancy
- Hormone replacement therapy
- Surgery
- Immobilization
- Trauma
- Cancer

Arterial thrombosis risks

- Smoking
- Hypertension
- Hypercholesterolemia
- Peripheral vascular disease
- Diabetes
- Obesity

Preventability:

Because of the potential risk for thromboembolism with the use of Factor IX concentrates, patients receiving etranacogene dezaparvovec should be monitored to determine their stable Factor IX expression. Factor IX expression following the administration of etranacogene dezaparvovec can be monitored with either one stage activated partial thromboplastin time (aPTT-based) or chromogenic Factor IX assays.

Current text in the SmPC addresses the risk in the patient population. Information on this safety concern is provided in the patient card, health care professional guide and patient guide (See Section V.2 and Annex 6).

Impact on the risk-benefit balance of the product:

Given the multi-morbidity (incl. life-threatening complications) of the target population, this safety concern has a low impact on the benefit-risk balance in this indication.

Public health impact:

The impact on public health is expected to be low. Thrombogenicity can be managed by appropriate monitoring of Factor IX expression and its corresponding activity.

Important Potential Risk 4: Germline transmission

Potential mechanisms:

Several (non)clinical studies, including studies from scientific literature indicated that infectious particles are not present in semen following IV administration for longer than 4 days post infusion. Vector DNA is only temporarily present in semen, mainly in the seminal fluid instead of the cellular fraction of semen (Schuettrumpf et al, 2006; Favaro et al, 2009; Rangarajan et al, 2017; Fonck et al, 2022).

Transduction-competent AAV particles are short-lived, even in cases of a prolonged positive shedding signal. AAV vector particles are removed and / or inactivated from bodily fluids either via fast receptor-mediated uptake of transduction competent AAV particles into organs (within hours, assessed via biodistribution studies), via excretion via urine, feces etc., or through the effective development of an anti AAV5 humoral immune response.

Evidence source(s) and strength of evidence:

The question whether recombinant AAV vector sequences may transduce male spermatogonial stem cells and generate vector DNA-positive mature sperm cells (i.e., vertical germline transmission) has been extensively investigated and reported in the scientific literature. Schuettrumpf et al, 2006, as well as Jakob et al, 2005; Favaro et al, 2009; Arruda et al, 2001 and Fonck et al, 2022 did not detect vector sequences in sperm derived from dozens of cumulative spermatogenesis cycles in mice or rabbits after infusion of recombinant AAV. This indicates that biodistribution to male gonadal tissues does not lead to production of sperm carrying vector DNA. Together with the aforementioned absence of a vector signal in reproductive tissue of females, this indicates an extremely low likelihood of inadvertent germ line transfer (horizontal or vertical) of etranacogene dezaparvovec in patients treated with CSL222.

There is no risk of shedding of transduction competent vector particles via bodily fluids after more than a few days post infusion (Schuettrumpf et al, 2006; Favaro et al, 2009; Rangarajan et al, 2017; Fonck et al, 2022). Following cellular uptake of transduction competent virus particles in the immediate post-infusion period, remaining capsid bearing vector particles will be rendered transduction incompetent and removed via the development of an effective NAb response against the AAV5 capsid protein in bodily fluids. All subjects in the CSL222 clinical trials have developed such an immune response within 2-3 weeks post vector infusion. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. Therefore, there is no relevant exposure risk of transduction competent AAV Particles and thus there is no prolonged relevant exposure risk of transduction to contacts. Exposure risk to close contacts in the immediate post-infusion period is further mitigated by the recommendation for a 1-year use of barrier contraception following Hemgenix administration (as outlined in the Hemgenix SmPC).

Based on the low level of vector DNA in semen, its presence in the seminal fluid instead of the cellular fraction of semen, the low integration potential of non-replicating rAAV vectors, and the recommendation of barrier contraception during the time when transduction competent particles are present in semen, the likelihood of horizontal germline transmission is considered negligible.

Characterization of the risk:

A GLP-compliant paternal germline transmission / reproduction performance study was conducted in mice with AAV5-hFIX (NR-060-14-001). The dose levels ranged from a low pharmacological effect level to a dose corresponding to 10 times the envisioned clinical dose, or the highest technically feasible dose, whichever was higher. This non-clinical study in male mice revealed no paternal germline transmission at a dose level of 10 × the proposed clinical vector dose. Fertility of male mice treated with AAV5-hFIX was not diminished. These studies did not raise concerns regarding impairment of male fertility as findings for AAV5-hFIX are considered equally relevant for etranacogene dezaparvovec.

Vector DNA was present in the testis of mice and Cynomolgus macaques at terminal sacrifice, 3 or 6 months after IV administration of etranacogene dezaparvovec or AMT-060. Trace amounts of vector DNA were detected in semen of cynomolgus monkeys at 6 months after treatment with CSL220 (AMT-060). Clinical studies CSL220_1001 and CSL222_2001 revealed vector DNA in the semen of the subjects up to a maximal 365 days after administration. In CSL222_3001 study, shedding negative was defined as the first of

3 consecutive measures with a result of either 0 or below the limit of detection. Clearance of vector DNA from semen was established in 33/54 subjects at Week 53 post-treatment. This proportion was still the same at Week 72 (Month 18). The fact that the proportion of subjects with that definition did not change between weeks 53 and 72 is due to the non-submission of further samples after the subjects returned the first, or second, below LOD sample. As indicated above, presence of a qPCR detectable shedding signal does not equate to transduction-competent vector particles in blood or semen.

To further assess the likelihood of germline transmission, a study has been performed in mice to investigate whether, following IV administration, vector DNA could actually be transmitted to the offspring. CSL220 (AMT-060), the predecessor of etranacogene dezaparvovec was administered to adult male mice at a dose of 2.3×10^{14} gc/kg, i.e., approximately 10 times the recommended human dose. Subsequently, these males were paired with untreated females on Day 6 after treatment (corresponding to the expected highest levels of vector DNA in male gonadal tissue). Vector DNA was detected in all tissue types examined (epididymis, seminal vesicle, sperm, and testes) from the CSL220 (AMT-060) treated males, but no vector DNA was detected in any of the tissue types examined (uterus, fetus, and placenta) from the untreated females that mated with the treated males. No indication of paternal germline transmission to the offspring was observed. Similarly, studies using other AAV serotype-based vectors have not shown germline transmission via the male line and maternal-fetal transmission (Salmon et al, 2014; Arruda et al, 2001; Jakob et al, 2005; Fonck et al, 2022). This is in line with the findings in an *in-vivo* study in rabbits, which indicated that the vector sequences are mainly present in the seminal fluid and not in the cellular fraction of the semen samples (Schuettrumpf et al, 2006; Favaro et al, 2009). Likewise, AAV sequences were not detected in the sperm cells of AAV positive semen samples of human subjects following administration of rAAV (Rangarajan et al, 2017). No evidence of vector DNA transmission from males treated with CSL220 (AMT-060) to reproductive tissues and fetuses of mated females was found in the preclinical germline transmission study.

In Study CSL222_2001 (CT-AMT-061-01), 2/3 (66.7%) subjects attained the status of no longer shedding vector DNA. The earliest that subjects were considered to be no longer shedding vector DNA from semen was 26.1 weeks (range: 26.1 to 26.3 weeks) after etranacogene dezaparvovec treatment. A subject was considered to no longer be shedding vector DNA if they had a negative laboratory result for 3 or more consecutive timepoints.

In Study CSL222_3001 (CT-AMT-061-02), clearance of vector DNA from semen, indicating the absence of shedding, was confirmed in 33/54 (61.1%) subjects in the post-CSL222 (AMT-061) treatment period. The earliest that subjects were considered to no longer be shedding vector DNA from semen was 6 weeks post-CSL222 (AMT-061) treatment (1.9% of subjects [95% CI: 0.3, 12.4]). Median time to absence of shedding (submission of a 3rd negative sample) was 48 weeks (95% CI: 38.6, NE). The proportion of subjects testing negative increased at a continuous rate until Week 53, at which time 61.1% of subjects (95% CI: 48.5, 74.0) reached absence of shedding from semen; the proportion was the same at Week 72 (Month 18). Of note, the Week 6 semen sample for one subject was analyzed outside of the testing stability period. This sample was positive for vector DNA and the subject continued to test positive through the 18-month post-treatment period. Upon sample accountability/traceability by Sponsor, it was identified that the sample was collected but inadvertently not analyzed. Sponsor approved the analysis of the sample and inclusion in the study analysis, with the result flagged as being outside of test stability period.

As discussed above, presence of a qPCR detectable shedding signal is highly unlikely to equate to transduction-competent (infectious) vector particles in semen.

Risk factors and risk groups:

In theory, an immediate effect of germline transmission is the addition of a hFIX-Padua expression cassette to the genome of progeny. Whether this addition will actually lead to the expression of hFIX-Padua protein depends on whether the vector genome will integrate in the host genome of progeny. If the vector genome remains episomal, it most likely will be lost during the many cell divisions in the development of the fetus. However, in the hypothetical situation that the complete expression cassette will be integrated, the expression of hFIXco-Padua can potentially materialize. Based on experience in the nonclinical and clinical studies the severity of overexpression of hFIX-Padua protein is considered low.

Women of childbearing potential and male patients, including vasectomized males, are defined as risk groups.

Preventability:

For 1 year after administration of etranacogene dezaparvovec, treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception method. Males treated with etranacogene dezaparvovec must not donate semen to minimize the risk of paternal germline transmission.

Additionally, etranacogene dezaparvovec is not recommended in women of childbearing potential (Hemgenix SmPC).

Information on this safety concern is provided in the patient card, health care professional guide and patient guide (See Section V.2 and Annex 6).

Impact on the risk-benefit balance of the product:

Several (non)clinical studies, including studies from scientific literature indicated that infectious particles are not present in semen following IV administration for more than 2-4 days (Schuettrumpf et al, 2006; Fonck et al, 2022). Vector DNA is only temporarily present in semen and mainly available in the seminal fluid instead of the cellular fraction of semen (Rangarajan et al, 2017). Moreover, non-replicating rAAV vectors show a very low integration potential, minimizing the likelihood of stable transduction of germline cells. Additionally, and in line with the above constraints, no paternal germline transmission was observed in the performed nonclinical study. Similarly, studies using other AAV serotype-based vectors have not shown germline transmission via the male line and maternal-fetal transmission (Salmon et al, 2014).

The use of barrier contraception is recommended for 1 year after administration in patients of reproductive potential and their female partners of childbearing potential (Hemgenix SmPC).

Therefore, the impact on the benefit-risk balance is considered negligible.

Public health impact:

Based on the low level of vector DNA in semen, its presence in the seminal fluid instead of the cellular fraction of semen, the low integration potential of non-replicating rAAV vectors and the protection afforded by the recommendation for temporary barrier contraception, the likelihood of germline transmission is considered negligible, and thereby the risk of germline transmission to human health is considered negligible as well.

Important Potential Risk 5: Transmission to third parties (horizontal transmission)

Potential mechanisms:

In the hypothetical situation that unintended exposure of third parties to infectious etranacogene dezaparvovec would take place within the immediate post-infusion period, an immune response to the particles, expression of hFIX-Padua, or occurrence of adverse events relating to this exposure could occur. The probability that such an unintended exposure will

lead to the mentioned outcomes is extremely low, as will be discussed in the following paragraphs.

Evidence source(s) and strength of evidence:

Shedding and clearance of AAV5-hFIX-Padua were evaluated in pre-clinical and clinical studies. In Studies CSL222_2001 and CSL222_3001, clearance of vector DNA from blood was confirmed in 2/3 and 25/54 subjects, respectively, at the earliest 17 and 31.1 weeks after administration. It is anticipated that qPCR-detectable etranacogene dezaparvovec DNA fragments will be present in body fluids and excreta for several weeks after administration. However, the detected vector DNA does not equate infectious vector particles. Apart from an infectious particle, it can also represent DNA from a degraded vector particle, a particle that has been taken up by a cell, or a cell that has been transduced by the vector (e.g., leukocytes or epithelial cells of the bladder). Furthermore, the development of anti-AAV5 neutralizing antibodies in the immediate post-infusion period, will render any remaining capsid-bearing vector particles in the patients' blood and seminal compartments non-transmissible. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. Therefore, the presence of vector DNA in body fluids and secretions is not expected to have any impact on individuals potentially exposed.

Characterization of the risk:

In Study CSL222_3001/ CT-AMT-061-02, clearance of vector DNA from blood was confirmed in 25/54 (46.3%) subjects after etranacogene dezaparvovec treatment. The earliest that subjects were considered to be no longer shedding vector DNA from blood was 17 weeks postdose (1.9% of subjects [95% CI: 0.3, 12.4]). The proportion of subjects testing negative increased at a continuous rate until Week 50, at which time 46.3% of subjects (95% CI: 34.1, 60.4) reached absence of shedding from blood; the proportion was the same at Month 18.

In Study CSL222_2001 CT-AMT-061-01, clearance of vector DNA from blood, indicating the absence of shedding, was determined for 2 subjects during the Post-treatment Period. The earliest that subjects were considered to be no longer shedding vector DNA from blood was 31.1 weeks (range: 31.3 to 78.3 weeks) after etranacogene dezaparvovec treatment. Mean time to absence of shedding was 54.71 weeks.

Clearance of CSL220 (AMT-060) vector DNA was studied in samples of serum, saliva, urine, and feces from Cynomolgus macaques, that were collected at several time points after dosing. Clearance curves in saliva and urine mainly followed the clearance from the serum albeit

with vector DNA concentrations being multiple logs lower. Levels of vector DNA in serum declined over the 26-week observation period. Saliva was cleared between weeks 8 and 12 Vector DNA levels in urine were low and reached the LOD around week 8. Similarly, the clearance of etranacogene dezaparvovec vector DNA was analyzed in plasma and urine from Cynomolgus macaques. The clearance observed in both plasma and urine confirmed the earlier clearance profiles with the CSL220 (AMT-060) vector. For urine, etranacogene dezaparvovec vector DNA was not detectable 3 months after administration of the highest dose of 9 x 10^{13} gc/kg. It is noted that shedding was assessed using a highly sensitive qPCR-based method that detects vector DNA sequences including fragments which are not representative of the amount of infectious particles.

Risk factors and risk groups:

The following risk groups are identified for this hypothetical risk:

- Recipients of blood, organs, tissues, or cells originated from Hemgenix-treated individuals
- Close contacts of patients
- Laboratory staff handling patient's samples that may contain (parts of) the vector

Preventability:

Laboratory staff will wear protective clothing and equipment according to the relevant guidelines.

Patients treated with Hemgenix must not donate blood, organs, tissues and cells for transplantation (Hemgenix SmPC). Information on this safety concern is provided in the patient card, health care professional guide and patient guide (See Section V.2 and Annex 6).

Impact on the risk-benefit balance of the product:

In the hypothetical situation that infectious particles will be shed, the concentration will be extremely low. Shedding of these particles may lead to exposure of third parties which theoretically may result in transmission of the vector DNA. However, as shedding of infectious vector particles is already considered unlikely, the likelihood of exposure to and infection of third parties is even further reduced. Of note, Patients treated with Hemgenix must not donate blood, organs, tissues and cells for transplantation (Hemgenix SmPC).

Public health impact:

The impact to public health is considered negligible, due to the unlikelihood of infectious vector particles' shedding.

Important Potential Risk 6: Development of FIX inhibitors

Potential mechanisms:

The formation of inhibitory antibodies against coagulation factors is a major complication of factor replacement therapy. Inhibitors form in approximately 3-5% of patients with Hemophilia B on FIX replacement therapy (Perrin et al, 2019). Although the incidence of inhibitors in Hemophilia B patients on FIX replacement therapy is low, most are "high titer" and frequently associated with the development of severe allergic or anaphylactic reactions (Bon et al, 2015). To date, there has been no association between gene therapy in Hemophilia B patients and formation of FIX inhibitors.

Evidence source(s) and strength of evidence:

No subjects developed FIX inhibitors in the clinical development program of etranacogene dezaparvovec.

Characterization of the risk:

All 57 (100%) subjects in Studies CSL222_2001/CT-AMT-061-01 and CSL222_3001/CT-AMT-061-02 were negative at baseline (before administration) for FIX inhibitors and have remained negative up the DLP of this RMP.

No factor IX alloantibody inhibitor formation was seen in clinical trials reported in literature, where patients were exposed to human factor IX or human factor IX-Padua gene transfer and where the expressed levels of factor IX were measurable (Manno et al, 2003; Manno et al, 2006; Nathwani et al, 2011; Nathwani et al, 2014; Nathwani et al, 2018 and George, 2017).

Interestingly, data from canine and murine hemophilia models have suggested that AAV-derived gene therapy may provide immunological tolerance to FVIII/FIX (Batty and Lillicrap, 2019). Crudele et al, 2015 reported that AAV liver expression of FIX-Padua prevented and eradicated FIX inhibitors in Hemophilia B dogs and mice. They concluded that the safe immunological profile of FIX-Padua in the inhibitor-prone dogs would allow the inclusion of Hemophilia B patients with factor 9 gene null mutations in gene

therapy clinical trials. Null mutations of the factor 9 gene are a known risk factor for development of inhibitors (Collins et al, 2013).

Risk factors and risk groups:

History of FIX inhibitors and positive FIX inhibitor test at screening were exclusion criteria in the etranacogene dezaparvovec clinical development program. Subjects with at least 150 EDs of treatment with FIX protein were included in the CSL222 clinical studies. Although the likelihood of FIX inhibitors development following administration of gene therapy is very low, patients with less than 150 EDs to FIX concentrates could be considered at higher risk, due to the limited clinical experience.

Preventability:

The use of Hemgenix is not indicated in patients with a history of Factor IX inhibitors. In case increased plasma Factor IX activity levels are not achieved, decrease, or bleeding is not controlled or returns, post-dose testing for Factor IX inhibitors is recommended along with Factor IX activity testing. (Hemgenix SmPC).

Information on this safety concern is provided in the patient card, health care professional guide and patient guide (See Section V.2 and Annex 6).

Impact on the risk-benefit balance of the product:

In the hypothetical scenario of FIX inhibitors formation, a patient would be at risk of gene therapy lack of effect and consequently spontaneous bleedings, as well as a risk of hypersensitivity reactions. However, as discussed above, there is no known relationship between Hemophilia B gene therapy and development of FIX inhibitors.

Public health impact:

The impact to public health is considered negligible, due to the very low risk of developing FIX inhibitors.

SVII.3.2 Presentation of the missing information

Missing information 1: Use in patients with severe hepatic impairment

Evidence source:

Population in need of further characterization:

Patients with severe hepatic impairment.

Patients with known medical condition that may impact the intended transduction of the vector and/or expression and activity of the protein (ie., advanced liver disease including cirrhosis or liver fibrosis (suggestive of or equal to METAVIR Stage 3 disease, eg., a FibroScan™ score of $\geq$ 9 kPa is considered equivalent) and patients with ALT > 2 times upper normal limit, AST > 2 times upper normal limit, total bilirubin > 2 times upper normal limit and ALP > 2 times upper normal limit), were excluded from participation in clinical trials. However, two patients with moderate hepatic impairment and seven patients with mild hepatic impairment were included in the HOPE B trial without indication of particular safety or efficacy issues. Etranacogene dezaparvovec is a liver-directed gene therapy and therefore patients with pre-existing severe hepatic impairment may experience more severe hepatic function AEs and potential negative effect on efficacy.

Missing information 2: Long-term effect

Evidence source:

The need for long-term follow-up is communicated by regulatory guidelines, which recognize the potential risk of declining treatment efficacy over time (CHMP, 2009).

Published results of a study in severe Hemophilia B patients using a single IV administration of a self-complementary adeno-associated virus (scAAV) vector containing a codon-optimized FIX gene, under control of a synthetic liver specific promoter and pseudo typed with serotype 8 capsid, (scAAV2/8-LP1-hFIXco), reported stable therapeutic expression of FIX over a period of 8 years (Nathwani et al, 2018).

Published results of a decline in FVIII levels was reported in a 4-year follow-up of valoctocogene roxaparvovec phase 1/2 clinical study for severe Hemophilia A, although all patients remained off-prophylaxis (Ozelo et al, 2020). Results from Study CT-AMT-060-01 using a single IV administration of AMT-060, wild-type hFIX and a predecessor to etranacogene showed stable FIX activity up to 5 years post dose.

Declined levels of FIX have been observed in clinical trials results published in the literature, likely due to the cytotoxic T cell-mediated immune response against the vector capsid sequences displayed on hepatocytes which in turn results in the loss of transduced cells and consequent constraint on transgene expression (Manno et al, 2006; Mingozzi et al, 2007; Arruda and Doshi, 2020).

The durability of efficacy and the potential reduction in FIX expression overtime need to be monitored. It is currently unknown whether FIX activity will decrease overtime.

Vectors with the capacity for integration require long-term clinical follow-up considerations because they persist for the lifespan of target cells or tissues. Delayed AEs should therefore be closely, including, but not limited to, carcinogenicity due to vector integration and auto-immunity caused by antibodies interfering with the activity of FIX and cross-reacting with the endogenous FIX (CHMP, 2009).

The number of patients in HEMGENIX clinical studies followed up for >18 months is limited and the safety of HEMGENIX beyond this duration is not known.

In order to better understand the safety and efficacy of long-term use of HEMGENIX, patients from phase 2b and phase 3 studies will be enrolled in a 10-year long-term follow-up extension study (CSL222_3003) to collect safety and efficacy data for a total of 10 years.

Additionally, patients treated with HEMGENIX (within the first 5 years of commercialization) will be followed up for a minimum of 15 years in the post authorization efficacy and safety study CSL222_4001.

Missing information 3: Use in female patients

Evidence source:

Population in need of further characterization:

Women including pregnant women and breastfeeding women.

Women were excluded from participation in initial clinical trials. No information is available on safety and efficacy of etranacogene dezaparvovec in women.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Hepatotoxicity • Infusion reactions (including hypersensitivity)
Important potential risks	• Risk of malignancy in relation to vector integration in the DNA of body cells • Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid • Thromboembolic events • Germline transmission • Transmission to third parties (horizontal transmission) • Development of FIX inhibitors
Missing information	• Use in patients with severe hepatic impairment • Long-term effect • Use in female patients

Part III: Pharmacovigilance plan (including post-authorization safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

- Questionnaire on Liver Toxicity
- Questionnaire on Hemgenix Liver malignancy
- Questionnaire on Thromboembolic Events (TEE)

III.2 Additional pharmacovigilance activities

1. CSL222_3003

Study short name and title

An Extension Study Assessing the Long-term Safety and Efficacy of Etranacogene Dezaparvovec Previously Administered to Adult Male Patients with Hemophilia B during the CSL222_2001 (CT AMT-061-01) and CSL222_3001 (CT AMT-061-02) Studies.

Rationale and study objectives:

This interventional long term follow-up extension study will follow adult male patients with severe or moderately severe Hemophilia B (FIX activity ≤ 2%) who previously received an infusion of AAV5 hFIXco-Padua (etranacogene dezaparvovec) in the parent studies, CSL222_2001 and CSL222_3001 with the aim to assess the long-term safety and efficacy of etranacogene dezaparvovec (6 to 15 years from the time of initial dosing).

The primary objective will be to assess the long-term safety in adult male patients with Hemophilia B who were treated with etranacogene dezaparvovec in Study CSL222_2001 or CSL222_3001.

The secondary objective will be to investigate the long-term efficacy profile in adult male patients with Hemophilia B who were treated with etranacogene dezaparvovec in Study CSL222_2001 or CSL222_3001.

Study design:

This is an open-label, long-term follow-up extension study enrolling patients who participated in study CSL222_2001 or CSL222_3001.

Study Population:

The study population will be defined as all patients who were treated with etranacogene dezaparvovec in Study CSL222_2001 or Study CSL222_3001, completed study participation and signed informed consent for participation in Study CSL222_3003.

Milestones:

Milestones	**Due dates (Estimated)**
Annual updates in the DSUR	DLP: 19 August
Interim reports	3-yearly
Final report	Q1 2036

2. CSL222_5001

Study short name and title

Survey to evaluate the effectiveness of additional risk minimization measures (aRMMs) for Hemgenix among prescribers in the EU.

Rationale and study objectives:

CSL Behring will develop and disseminate aRMM in the form of a Guide for HCP, Patient/Caregiver Guide and a Patient Card to address the important identified risk of hepatotoxicity and the important potential risks of thromboembolic events, germline transmission, risk of malignancy in relation to vector integration in the DNA of body cells and long-term effect as per the Risk Management Plan (RMP). This study is being designed to evaluate the effectiveness of such aRMM tools.

Study objectives:

1. Assess HCP's awareness of the aRMM tools by estimating the proportion of targeted HCPs who acknowledge receiving the tools.
2. Assess HCP's utilization of the aRMM tools by estimating the proportion of targeted HCPs who acknowledge reading and utilizing the tools.
3. Assess HCP's knowledge and behaviour pertaining to the key risk messages detailed in the aRMM by estimating the proportion of targeted HCPs with correct responses to knowledge and behaviour questions pertaining to the key risk messages.

Study design:

The effectiveness evaluation study will consist of a cross-sectional survey among prescribers of Hemgenix. The survey will be conducted in a sample of EU countries representing the highest volume of Hemgenix use across the EU. The actual countries will be determined upon approval of the product and will be communicated to the Agency for alignment prior to conducting the study. Currently it is anticipated that the countries will include Germany, Austria, France, Italy, the Netherlands, Sweden. Additional countries may be included to enhance recruitment. Potential Hemgenix prescribers will be invited to participate, and the survey will include screening questions to identify HCPs who have prescribed Hemgenix and who have not. Data will be collected using a structured, self-administered questionnaire. HCPs will be invited to take the survey online.

Study Population:

Potential Hemgenix prescribers in the specified countries in the EU.

Milestones:

Milestones	**Due dates (Estimated)**
Start of data collection	12 months after commercial launch of Hemgenix. (Actual date to be determined)
Annual updates	No interim analyses or progress reports are planned.
Final report	6 months after end of the survey (Actual date to be determined)

III.3 Summary table of additional pharmacovigilance activities

Table Part III.3-1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
CSL222_3003 An Extension Study Assessing the Long-term Safety and Efficacy of Etranacogene Dezaparvovec Previously Administered to Adult Male Patients with Hemophilia B during the CSL222_2001 (CT AMT-061-01) and CSL222_3001 (CT AMT-061-02) Studies. Planned	<u>Primary Objective</u> To assess the long-term safety in adult male patients with Hemophilia B who were treated with etranacogene dezaparvovec in Study CSL222_2001 or CSL222_3001. <u>Secondary Objective</u> To investigate the long-term efficacy profile in adult male patients with Hemophilia B who were treated with etranacogene dezaparvovec in Study CSL222_2001 or CSL222_3001.	• Hepatotoxicity • Risk of malignancy in relation to vector integration in the DNA of body cells • Thromboembolic events • Development of FIX inhibitors • Long-term effect	Annual updates in the DSUR	DLP: 19 August
			Interim reports	3-yearly
			Final report	Q1 2036

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CSL222_5001 Survey to evaluate the effectiveness of additional risk minimisation measures (aRMMs) for Hemgenix among prescribers in the EU. Planned	Objectives: 1. Assess (Healthcare Professionals') HCP's awareness of the aRMM tools by estimating the proportion of targeted HCPs who acknowledge receiving the tools. 2. Assess HCP's utilization of the aRMM tools by estimating the proportion of targeted HCPs who acknowledge reading and utilizing the tools. 3. Assess HCP's knowledge and behaviour pertaining to the key risk messages detailed in the aRMM by estimating the proportion of targeted HCPs with correct responses to knowledge and behaviour questions pertaining to the key risk messages.	• Hepatotoxicity • Risk of malignancy in relation to vector integration in the DNA of body cells • Thromboembolic events • Germline transmission • Transmission to third parties (horizontal transmission) • Development of FIX inhibitors • Long-term effect	Start of data collection	12 months after commercial launch of Hemgenix. (Actual date to be determined)
			Annual updates	No interim analyses or progress reports are planned.
			Final report	6 months after end of the survey (Actual date to be determined)

Part IV: Plans for post-authorization efficacy studies

Table Part IV-1: Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
CSL222_4001 An observational post-authorization Long-term Follow-up Study to Characterize the Safety and Effectiveness of HEMGENIX (Etranacogene Dezaparvovec) in Patients with Hemophilia B Planned	<u>Primary Objective</u> To investigate the long-term effectiveness profile in adults with hemophilia B who are treated with HEMGENIX or are on continuous FIX prophylaxis by following them for a period of 15 years. <u>Secondary Objective</u> To characterize the long-term safety in adults with hemophilia B who are treated with HEMGENIX or are on continuous FIX prophylaxis by following them for a period of 15 years.	Long term effect <u>Safety concerns also addressed:</u> • Hepatotoxicity • Infusion reactions (including hypersensitivity) • Risk of malignancy in relation to vector integration in the DNA of body cells • Bleeding as a result of lack of efficacy due to immune mediated neutralization of the AAV-5 vector capsid • Thromboembolic events • Germline transmission • Transmission to third parties (horizontal transmission) • Development of FIX inhibitors • Use in patients with severe hepatic impairment • Use in female patients	Protocol submission	31 March 2023
			Start of data collection	30 September 2023
			Study progress reports	Annually
			Interim reports	3-yearly at 3, 6, 9, 12, 15 and 18 years
			End of data collection	Last patient 15 years post dose data collected (2043)
			Final study report submission	31 December 2044

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
CSL222_2001 / CT-AMT-061-01 A phase 2b, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5 hFIX Padua) administered to adult subjects with severe or moderately severe Hemophilia B. Ongoing	Primary objective To confirm that a single dose of 2 x 10^{13} genome copies (gc)/kg AMT-061 will result in factor IX (FIX) activity levels of ≥5% at six weeks after dosing. Secondary objective To assess further efficacy and safety of 2 x 10^{13} gc/kg AMT-061.	Long term effect	Final CSR	30 June 2024
CSL222_3001 / CT-AMT-061-02 A phase 3, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIX-Padua) administered to adult subjects with severe or moderately severe hemophilia B. Ongoing	Primary objective To demonstrate the non-inferiority of AMT-061 (2 × 10^{13} gc/kg) during the 52 weeks following establishment of stable factor IX expression (months 6 to 18) post-treatment (AMT-061) follow-up compared to standard of care continuous routine factor IX prophylaxis during the lead-in phase, as measured by the annualized bleeding rate (ABR). Secondary objective To demonstrate additional efficacy and safety aspects of systemic administration of AMT-061.	Long term effect	Final CSR	31 October 2025

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
CSL222_4001 An observational post-authorization Long-term Follow-up Study to Characterize the Safety and Effectiveness of HEMGENIX (Etranacogene Dezaparvovec) in Patients with Hemophilia B Planned	Primary Objective To investigate the long-term effectiveness profile in adults with hemophilia B who are treated with HEMGENIX or are on continuous FIX prophylaxis by following them for a period of 15 years. Secondary Objective To characterize the long-term safety in adults with hemophilia B who are treated with HEMGENIX or are on continuous FIX prophylaxis by following them for a period of 15 years.	Effect irrespective of baseline anti-AAV5 NAb titer	Protocol submission	31 March 2023
			1-year follow-up interim analysis report after the first 50 subjects are enrolled in Study CSL222_4001	31 December 2026

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

V.1 Routine risk minimization measures

Table Part V.1-1:Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risk: Hepatotoxicity	**Routine risk communication:** • SmPC sections 4.2, 4.4, 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Baseline liver health testing requirement before administration of Hemgenix, in Section 4.2 Posology and method of administration. • Recommendation to closely monitor liver transaminases and consider a corticosteroid taper in the event of ALT increase. Recommendation to assess possible alternative causes of ALT elevation, in section 4.4 Special warnings and precautions for use. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product
Important identified risk: Infusion reactions (including hypersensitivity)	**Routine risk communication:** • SmPC sections 4.2, 4.4, 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders. This medicinal product should be administered in a setting where personnel and equipment are immediately available to treat infusion related reactions, in section 4.2 Posology and method of administration. • Instructions to slow or stop the rate of infusion in the event of infusion reaction, in section 4.2 Posology and method of administration. • Instruction to closely monitor patients for infusion reactions, in section 4.4 Special warnings and precautions for use. • Recommendation to treat patients with infusion reactions based on clinical judgement, in section 4.4 Special warnings and precautions for use. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product

Safety concern	Routine risk minimization activities
Important potential risk: Risk of malignancy in relation to vector integration in the DNA of body cells	**Routine risk communication:** • SmPC section 4.2, 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Baseline liver health testing requirement before administration of Hemgenix, in Section 4.2 Posology and method of administration. • Recommendation for patients with preexisting risk factors for HCC to regularly undergo liver ultrasound screenings and alpha fetoprotein testing. Instructions to the HCP in the event of HCC, in section 4.4 Special warnings and precautions for use. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product.
Important potential risk: Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid	**Routine risk communication:** • SmPC sections 4.2, 4.4, 5.1 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Requirement for baseline testing preexisting neutralizing anti-AAV5 antibodies before Hemgenix administration, in section 4.2 Posology and method of administration and in section 4.4 Special warnings and precautions for use. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product
Important potential risk: Thromboembolic events	**Routine risk communication:** • SmPC sections 4.2, 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product

Safety concern	Routine risk minimization activities
Important potential risk: Germline transmission	**Routine risk communication:** • SmPC section 4.2, 4.4, 4.6 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Need for contraceptive measures in section 4.4 Special warnings and precautions for use. • Recommendation to use barrier contraception and not donate semen, in section 4.6 Fertility, pregnancy and lactation. • Hemgenix is not recommended in women of childbearing potential, in section 4.6 Fertility, pregnancy and lactation. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product
Important potential risk: Transmission to third parties (horizontal transmission)	**Routine risk communication:** • SmPC section 4.4, 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Warning for patients to not donate blood, organ, tissues and cells for transplantation, in section 4.4 Special warnings and precautions for use. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product
Important potential risk: Development of FIX inhibitors	**Routine risk communication:** • SmPC section 4.1, 4.2, 4.4, 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Testing for baseline FIX inhibitors is required before administration of Hemgenix, in Section 4.2 Posology and method of administration. • Recommendation for monitoring of patients for the development of FIX inhibitors through appropriate clinical observations and laboratory tests in section 4.4 Special warnings and precautions for use. • Hemgenix is not indicated in patients with a history of FIX inhibitors, in section 4.1 Therapeutic indications and section 4.4 Special warnings and precautions for use. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only product
Missing information: Use in patients with severe hepatic impairment	**Routine risk communication:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. • Etranacogene dezaparvovec is contraindicated in patients with known advanced hepatic fibrosis, or cirrhosis, in section 4.3 Contraindications. • Recommendation to closely monitor liver transaminases and consider a corticosteroid taper in the event of ALT increase. Recommendation to assess possible alternative causes of ALT elevation, in section 4.4 Special warnings and precautions for use. • Recommendation to avoid concomitant use of hepatotoxic medication or potential hepatotoxic agents, in section 4.5 Interaction with other medicinal products and other forms of interaction. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product.
Missing information: Long-term effect	**Routine risk communication:** • SmPC section 4.2, 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Hemgenix is not indicated in patients with a history of FIX inhibitors, in section 4.1 Therapeutic indications and section 4.4 Special warnings and precautions for use. • Recommendation for patients with preexisting risk factors for HCC to regularly undergo liver ultrasound screenings and alpha fetoprotein testing. Instructions to the HCP in the event of HCC, in section 4.4 Special warnings and precautions for use. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product

Safety concern	Routine risk minimization activities
Missing information: Use in female patients	**Routine risk communication:** • SmPC section 4.2, 4.6 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Hemgenix should not be used during pregnancy. Hemgenix should not be used during breast feeding, in section 4.6 Fertility, pregnancy and lactation. • Hemgenix is not recommended in women of childbearing potential, in section 4.6 Fertility, pregnancy and lactation. • Treatment should be initiated under the supervision of a physician experienced in the treatment of Hemophilia and/or bleeding disorders, in section 4.2 Posology and method of administration. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only product.

V.2 Additional risk minimization measures

Objectives:

A **health care professional guide** and a **patient guide** will be implemented in order to specifically inform HCPs and patients about the following risks:

- Hepatotoxicity
- Thromboembolic events
- Risk of malignancy in relation to vector integration in the DNA of body cells
- Long-term effect
- Germline transmission
- Transmission to third parties (horizontal transmission)
- Development of FIX inhibitors

Further on, a **patient card** will be implemented including information about following risks:

- Hepatotoxicity
- Thromboembolic events
- Risk of malignancy in relation to vector integration in the DNA of body cells
- Germline transmission
- Transmission to third parties (horizontal transmission)
- Development of FIX inhibitors

Rationale for the additional risk minimization activity:

The additional risk minimization activities will educate HCPs and patients about specific risks associated with the therapy and will provide guidance on monitoring these post-treatment.

Target audience and planned distribution path:

Target audience: HCPs and patients (via HCPs and patient organizations)

- Hemophilia Treatment Centers planning to be part of gene therapy administration patient journey (as administration or follow-up center, depending on the care delivery model decided by health authorities in EU member states.
- Potential Hemophilia B patients entering the gene therapy journey – via Hemophilia main patient organizations in EU member states, as well as European Hemophilia Consortium (European umbrella patient organization).

Planned communication plan:

- Training of Hemophilia Treatment Centers by CSL Behring Medical Affairs teams on RMP/RMM/aRMM, during the onboarding process of the center for gene therapy
- Dissemination of HCP and patient training materials and patient cards to Hemophilia Treatment centers planning to be part of gene therapy patient journey
- Dissemination of patient training materials and patient cards to Hemophilia main patient organizations in EU member states, as well as European Hemophilia Consortium (European umbrella patient organization)
- Dissemination of HCP and patient training materials and patient cards via CSL Behring Hemgenix appropriate websites in EU / member states

Plans to evaluate the effectiveness of the interventions and criteria for success:

To evaluate the effectiveness, CSL Behring is planning to perform a Survey to evaluate the effectiveness of aRMMs for Hemgenix among prescribers in the EU, with the objective of assessing HCP’s awareness of aRMM tools, HCP’s utilization of aRMM tools, HCPs knowledge of the risk of key adverse events highlighted in the Hemgenix SmPC and assessing the alignment of HCP’s self-reported behavior/practices of minimizing the risks of key adverse events in accordance with the SmPC.

The effectiveness evaluation study will consist of a cross-sectional survey among potential prescribers of Hemgenix. The survey will be conducted in a sample of EU countries representing the highest volume of Hemgenix use across the EU. Additional countries may be included to enhance recruitment. Data will be collected using a structured, self-administered questionnaire. HCPs will be invited to take the survey online. However, other participation modalities (e.g., telephone, paper-based) may be made available to enhance participation.

The survey will be administered 12 months after commercial launch of Hemgenix in the target country to allow sufficient outreach and utilization of the aRMM.

V.3 Summary of risk minimization measures

Table Part V.3-2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8 Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide, patient guide and patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Questionnaire on Liver toxicity Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_5001 • Study CSL222_3003 • Study CSL222_2001 • Study CSL222_3001
Infusion reactions (including hypersensitivity)	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8 Legal status: Prescription only product. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_2001 • Study CSL222_3001

Safety concern	Risk minimization measures	Pharmacovigilance activities
Risk of malignancy in relation to vector integration in the DNA of body cells	Routine risk minimization measures: SmPC section 4.2, 4.4 Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide, patient guide and patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Questionnaire on Hemgenix Liver malignancy Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001
Bleeding as a result of lack of efficacy due to immune -mediated neutralization of the AAV-5 vector capsid	Routine risk minimization measures: SmPC sections 4.2, 4.4, 5.1 Legal status: Prescription only product. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_2001 • Study CSL222_3001
Thromboembolic events	Routine risk minimization measures: SmPC section 4.2., 4.4 Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide, patient guide and patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Questionnaire on Thromboembolic Events (TEE) Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001

Safety concern	Risk minimization measures	Pharmacovigilance activities
Germline transmission	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.6 Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide, patient guide and patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001
Transmission to third parties (horizontal transmission)	Routine risk minimization measures: SmPC sections 4.4, 5.2 Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide, patient guide and patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001
Development of FIX inhibitors	Routine risk minimization measures: SmPC sections 4.1, 4.2, 4.4, 4.8 Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide, patient guide and patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001
Use in patients with severe hepatic impairment	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, 4.5, 5.2 Legal status: Prescription only product. Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Questionnaire on Liver toxicity Additional pharmacovigilance activities: Study CSL222_4001

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	
Long-term effect	Routine risk minimization measures: SmPC section 4.2, 4.4 (risk of carcinogenicity) Legal status: Prescription only product. Additional risk minimization measures: Health care professional guide and patient guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001
Use in female patients	Routine risk minimization measures: SmPC section 4.2, 4.6 (Fertility, pregnancy and lactation) Legal status: Prescription only product. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study CSL222_4001

Part VI: Summary of the risk management plan

Summary of risk management plan for HEMGENIX (etranacogene dezaparvovec)

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

HEMGENIX's SmPC and its package leaflet give essential information to HCPs and patients on how HEMGENIX should be used.

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

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

I. The medicine and what it is used for

HEMGENIX is authorized for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors. It contains etranacogene dezaparvovec as the active substance and it is administered as a single intravenous infusion.

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

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

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs.
- Important advice on the medicine's packaging.

- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

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

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	• Hepatotoxicity • Infusion reactions (including hypersensitivity)
Important potential risks	• Risk of malignancy in relation to vector integration in the DNA of body cells • Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid • Thromboembolic events • Germline transmission • Transmission to third parties (horizontal transmission) • Development of FIX inhibitors
Missing information	• Use in patients with severe hepatic impairment • Long-term effect • Use in female patients

II.B Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	In the majority mild and transient transaminitis events were observed in the preclinical studies and during the clinical development program of etranacogene dezaparvovec. Furthermore, liver function abnormalities have been reported in clinical trials results published in the literature and investigating IV administration of a liver directed AAV vector (Rangarajan et al, 2017; Nathwani et al, 2011; Nathwani et al, 2014; Nathwani et al, 2018; George, 2017; Manno et al, 2006).
Risk factors and risk groups	Common causative/risk factors for hepatotoxicity include: • Elderly patients are at increased risk of hepatic injury due to reduced blood flow to the liver • Drug-drug interactions • Alcohol abuse in patients with cirrhotic liver changes • Concomitant use of hepatotoxic medications
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 4.8 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card

Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk: Infusion reactions (including hypersensitivity)	
Evidence for linking the risk to the medicine	Mild to moderate infusion-related reactions were observed the clinical studies with etranacogene dezaparvovec. In the scientific literature, a small number of infusion-related reactions after intravenous infusion of AAV5-based gene therapy has been reported. These events were successfully mitigated by slowing or pausing the infusion and administering medications such as antihistamines, antipyretics or glycocorticoids (Ozelo et al, 2022).
Risk factors and risk groups	No specific risk factors are known. However, patients with high levels of preexisting neutralizing antibodies against AAV5 might be more likely to experience infusion reactions.
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 4.8 • Legal status: Prescription only product Additional risk minimization measures: None
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Risk of malignancy in relation to vector integration in the DNA of body cells	
Evidence for linking the risk to the medicine	Chromosomal integration of vectors is considered to present a risk for malignant transformation of cells due to insertional mutagenesis and activation, inactivation or alteration of host cell genes. Therefore, viral vectors mediating transfer of their genetic material into the cell nucleus present a risk can have a high risk for delayed adverse reactions (CHMP, 2009). One case of hepatocellular carcinoma was observed in the etranacogene dezaparvovec clinical development program in an elderly subject with multiple risk factors (HCV, HBV, age > 50, alcohol use, family history of cancer). The event was considered as unlikely related to the etranacogene dezaparvovec treatment upon review of detailed genetic and insertion site analysis.

Risk factors and risk groups	The following have been described as risk factors for the development of HCC (Llovet et al, 2021): • Infection with Hepatitis B and/or Hepatitis C • Chronic alcohol consumption • Advanced fibrosis • Cirrhosis • Non-alcoholic steatohepatitis (NASH), associated with diabetes mellitus, or obesity • Non-alcoholic fatty liver disease • Advanced age • Male gender
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.4 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid	
Evidence for linking the risk to the medicine	The etranacogene dezaparvovec clinical studies suggest that although AAV5 neutralizing antibodies were prevalent in humans, the absolute levels at which they were present may not have been adequate to significantly impact the infused dose of etranacogene dezaparvovec in the majority of patients. All patients receiving Hemgenix will develop NAbs against AAV5 in the weeks after administration. However, by that time the vector DNA will have been delivered to the nucleus of the cell where it will direct transgene expression. As such, production of hFIX-Padua is not expected to be impacted by the generation of the anti-capsid humoral immune response.
Risk factors and risk groups	There is a lack of data in patients with neutralizing anti-AAV5 antibodies above 1:678. Therefore, these patients could be considered at higher risk, due to the limited clinical experience.

Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 5.1 • Legal status: Prescription only product Additional risk minimization measures: None
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Thromboembolism (e.g., pulmonary embolism, venous thrombosis, and arterial thrombosis) has occurred when using Factor IX-containing concentrate. One event of pulmonary thrombi was observed in the pre-clinical studies of etranacogene dezaparvovec. Additionally, in the clinical development program of etranacogene dezaparvovec, four events potentially relating to a thromboembolic episode were reported.
Risk factors and risk groups	Additional risks factors for TEEs in the targeted population are the same in the general population and include (Geerts et al, 2008; Previtali et al, 2011): Venous thrombosis risks • Pregnancy • Hormone replacement therapy • Surgery • Immobilization • Trauma • Cancer Arterial thrombosis risks • Smoking • Hypertension • Hypercholesterolemia • Peripheral vascular disease • Diabetes • Obesity

Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.4 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Germline transmission	
Evidence for linking the risk to the medicine	The question whether recombinant AAV vector sequences may transduce male spermatogonial stem cells and generate vector DNA-positive mature sperm cells (i.e., vertical germline transmission) has been extensively investigated and reported in the scientific literature. Schuettrumpf et al, 2006, as well as Jakob et al, 2005; Favaro et al, 2009; Arruda et al, 2001 and Fonck et al, 2022 did not detect vector sequences in sperm derived from dozens of cumulative spermatogenesis cycles in mice or rabbits after infusion of recombinant AAV. This indicates that biodistribution to male gonadal tissues does not lead to production of sperm carrying vector DNA. Together with the aforementioned absence of a vector signal in reproductive tissue of females, this indicates an extremely low likelihood of inadvertent germ line transfer (horizontal or vertical) of etranacogene dezaparvovec in patients treated with CSL222. There is no risk of shedding of transduction competent vector particles via bodily fluids after more than a few days post infusion (Schuettrumpf, 2006; Favaro et al, 2009; Rangarajan et al, 2017; Fonck et al, 2022). Following cellular uptake of transduction competent virus particles in the immediate post-infusion period, remaining capsid bearing vector particles will be rendered transduction incompetent and removed via the development of an effective NAb response against the AAV5 capsid protein in bodily fluids (within days). All subjects in the CSL222 clinical trials have developed such an immune response within 2-3 weeks post vector infusion. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. Therefore, there is no relevant exposure risk of transduction competent AAV Particles and thus there is no prolonged relevant exposure risk of transduction to contacts. Exposure risk to close contacts in the immediate post-infusion period is further mitigated

	by the recommendation for a 1-year use of barrier contraception following Hemgenix administration as outlined in the Hemgenix SmPC. Based on the low level of vector DNA in semen, its presence in the seminal fluid instead of the cellular fraction of semen, the low integration potential of non-replicating rAAV vectors, and the recommendation of barrier contraception during the time when transduction competent particles are present in semen, the likelihood of horizontal germline transmission is considered negligible.
Risk factors and risk groups	In theory, an immediate effect of germline transmission is the addition of a hFIX-Padua expression cassette to the genome of progeny. Whether this addition will actually lead to the expression of hFIX-Padua protein depends on whether the vector genome will integrate in the host genome of progeny. If the vector genome remains episomal, it most likely will be lost during the many cell divisions in the development of the fetus. However, in the hypothetical situation that the complete expression cassette will be integrated, the expression of hFIXco-Padua can potentially materialize. Based on experience in the nonclinical and clinical studies the severity of overexpression of hFIX-Padua protein is considered low. However, the integration of part of the vector genome might also lead to insertional mutagenesis including its potential consequences. Women of childbearing potential and male patients, including vasectomized males, are defined as risk groups.
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4, 4.6 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Transmission to third parties (horizontal transmission)	
Evidence for linking the risk to the medicine	Shedding and clearance of AAV5-hFIX-Padua were evaluated in pre-clinical and clinical studies. In Studies CSL222_2001 and CSL222_3001, clearance of vector DNA from blood was confirmed in 2/3 and 25/54 subjects, respectively, at the earliest 17 and 31.1 weeks after administration. It is anticipated that quantitative polymerase chain reaction (qPCR)-detectable etranacogene dezaparvovec DNA fragments will be present in body fluids and excreta for several weeks after administration. However, the detected vector DNA does not equate infectious vector particles. Apart from an infectious particle, it can also represent DNA from a degraded vector particle, a particle that has been taken up by a cell, or a cell that has been transduced by the vector (e.g., leukocytes or epithelial cells of the bladder). Furthermore, the development of anti-AAV5 neutralizing antibodies in the immediate post-infusion period, will render any remaining capsid-bearing vector particles in the patients' blood and seminal compartments. This immune response is long lasting and exceeds the period during which any shedding of vector DNA is observable in trial subjects. Therefore, the presence of vector DNA in body fluids and secretions is not expected to have any impact on individuals potentially exposed.
Risk factors and risk groups	The following risk groups are identified for this hypothetical risk: • Recipients of blood, organs, tissues, or cells originated from Hemgenix-treated individuals • Close contacts of patients • Laboratory staff handling patient's samples that may contain (parts of) the vector
Risk minimization measures	Routine risk minimization measures: • SmPC sections • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Development of FIX inhibitors	
Evidence for linking the risk to the medicine	No subjects developed FIX inhibitors in the clinical development program of etranacogene dezaparvovec.

Risk factors and risk groups	History of FIX inhibitors and positive FIX inhibitor test at screening were exclusion criteria in the etranacogene dezaparvovec clinical development program. Subjects with at least 150 EDs of treatment with FIX protein were included in the CSL222 clinical studies. Although the likelihood of FIX inhibitors development following administration of gene therapy is very low, patients with less than 150 EDs to FIX concentrates could be considered at higher risk, due to the limited clinical experience.
Risk minimization measures	Routine risk minimization measures: • SmPC sections • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide, patient guide and patient card.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Use in patients with severe hepatic impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.3, 4.4, 4.5, 5.2 • Legal status: Prescription only product Additional risk minimization measures: None.
Additional pharmacovigilance activities	• Study CSL222_4001 See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Long-term effect	
Risk minimization measures	Routine risk minimization measures: • SmPC sections 4.2, 4.4 • Legal status: Prescription only product Additional risk minimization measures: Health care professional guide and patient guide.
Additional pharmacovigilance activities	• Study CSL222_4001 • Study CSL222_3003 • Study CSL222_5001 • Study CSL222_2001 • Study CSL222_3001 See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in female patients	
Risk minimization measures	Routine risk minimization measures: • SmPC section 4.2, 4.6 • Legal status: Prescription only product Additional risk minimization measures: None.
Additional pharmacovigilance activities	• Study CSL222_4001 See section II.C of this summary for an overview of the post-authorization development plan.

AAV: adeno-associated virus, DNA: deoxyribonucleic acid, ED: Exposure day, (h)FIX: (human) factor IX, hFIXco-Padua: gain-of-function Padua-variant of the human Factor IX, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, HCV: hepatitis c virus, IV: intravenous, NAb: neutralizing antibody, qPCR: quantitative polymerase chain reaction, SmPC: summary of product characteristics, TEE: thromboembolic event

II.C Post-authorization development plan

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

The following studies are a condition of the marketing authorization:

CSL222_4001: An observational post-authorization Long-term Follow-up Study to Characterize the Safety and Effectiveness of HEMGENIX (Etranacogene Dezaparvovec) in Patients with Hemophilia B

Purpose of the study:

The purpose of this observational Study CSL222_4001 is to evaluate the long-term effectiveness and safety of HEMGENIX in a larger population of adult patients with Hemophilia B treated as per the approved HEMGENIX label in regions where HEMGENIX is approved for use and commercialized. The study will include a cohort of patients with Hemophilia B treated with continuous FIX prophylaxis to enable interpretation of relevant safety findings in patients with Hemophilia B.

CSL222_2001: A phase 2b, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5 hFIX Padua) administered to adult subjects with severe or moderately severe Hemophilia B

Purpose of the study:

The primary aim of this trial is to confirm that a single dose of 2 x 10^{13} gc/kg etranacogene dezaparvovec will result in factor IX activity levels of ≥5%. An objective of the trial is to assess whether observed factor IX activity levels are within an expected range, to determine if 2 x 10^{13} gc/kg AMT-061 is suitable from efficacy point of view for administration in the pivotal Phase 3 trial. In addition, the safety profile of etranacogene dezaparvovec will be demonstrated.

CSL222_3001: A phase 3, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIX-Padua) administered to adult subjects with severe or moderately severe Hemophilia B

Purpose of the study:

The purpose of this Phase III trial is to demonstrate the efficacy of etranacogene dezaparvovec in terms of annualized bleeding rate, to further describe its efficacy in terms of endogenous factor IX activity, and to further describe its safety profile.

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

The following additional pharmacovigilance activities are included in the post-authorization development plan:

CSL222_3003: An Extension Study Assessing the Long-term Safety and Efficacy of Etranacogene Dezaparvovec Previously Administered to Adult Male Patients with Hemophilia B during the CSL222_2001 (CT AMT-061-01) and CSL222_3001 (CT AMT-061-02) Studies.

Purpose of the study:

This interventional long term follow-up extension study will follow adult male patients with severe or moderately severe Hemophilia B (FIX activity ≤ 2%) who previously received an infusion of AAV5 hFIXco-Padua (etranacogene dezaparvovec) in the parent studies, CSL222_2001 and CSL222_3001 with the aim to assess the long-term safety and efficacy of etranacogene dezaparvovec (6 to 15 years from the time of initial dosing).

CSL222_5001: Survey to evaluate the effectiveness of additional risk minimisation measures (aRMMs) for Hemgenix among prescribers in the EU

Purpose of the study:

CSL Behring will develop and disseminate aRMM in the form of a Guide for HCP, Patient/Caregiver Guide and a Patient Card to address the important identified risk of hepatotoxicity and the important potential risks of thromboembolic events, germline transmission, risk of malignancy in relation to vector integration in the DNA of body cells and long-term effect as per the RMP.

CSL Behring will perform this survey in order to evaluate the effectiveness of such aRMM tools.

Part VII: Annexes

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Annex 4 Specific adverse drug reaction follow-up forms

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Questionnaire on Liver Toxicity

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____

☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset) years Or Age Group	**Gender** ☐ Male ☐ Female	**Weight** (at event onset) ☐ kg ☐ lb	**Height** (at event onset) ☐ cm ☐ in	**Race** (where local law allows) ☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Medical History

Check all that apply and include dates of onset as well as status (i.e. active / inactive) and details:

Previously abnormal liver function tests (e.g. ALT, AST, total bilirubin, and alk phosphatase)	Yes ☐	No ☐	Unknown ☐
Viral Hepatitis (e.g. Hepatitis B, Hepatitis C, or both)	Yes ☐	No ☐	Unknown ☐
Other hepatobiliary disease or dysfunction.	Yes ☐	No ☐	Unknown ☐
Non-alcoholic steatohepatitis	Yes ☐	No ☐	Unknown ☐
Liver cirrhosis	Yes ☐	No ☐	Unknown ☐
Ascites	Yes ☐	No ☐	Unknown ☐
Autoimmune disease	Yes ☐	No ☐	Unknown ☐
Acute or chronic pancreatitis	Yes ☐	No ☐	Unknown ☐
Diabetes mellitus (Type I or II)	Yes ☐	No ☐	Unknown ☐
Gilbert's syndrome	Yes ☐	No ☐	Unknown ☐
Spider angioma	Yes ☐	No ☐	Unknown ☐
Thrombocytopenia	Yes ☐	No ☐	Unknown ☐
Portal hypertension	Yes ☐	No ☐	Unknown ☐
Cholecystitis	Yes ☐	No ☐	Unknown ☐
Variceal bleeding/esophageal varices	Yes ☐	No ☐	Unknown ☐
Alcohol intake (Quantify if possible)	Yes ☐	No ☐	Unknown ☐
Transfusion or blood product administration	Yes ☐	No ☐	Unknown ☐
Tattoos	Yes ☐	No ☐	Unknown ☐

CSL Behring Innovation GmbH * Global Clinical Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Clinical Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Clinical Safety & Pharmacovigilance * 45 Poplar Road * Parkville, Victoria Australia 3052 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Drug abuse	Yes ☐	No ☐	Unknown ☐
Foreign travel	Yes ☐	No ☐	Unknown ☐
Other. Specify	Yes ☐	No ☐	Unknown ☐
None	Yes ☐		
If 'yes' for any of the above, specify :			

* **Continue on separate page if you need more space**
****Attach anonymized copies of relevant documentation (medical report, results, laboratory findings, expert's report)**

3. Suspect Drug Details

Product Name: Hemgenix	**Indication**	**Route of administration:**
Dose date **(DD/MMM/YYYY)**:		
Dose:		
Lot Number(s):		

4. Medication History

Sulfonamides (e.g. sulphamethoxazole, sulfalazine etc)	Yes ☐	No ☐	Unknown ☐
Valproic acid / Sodium Valproate	Yes ☐	No ☐	Unknown ☐
Metronidazole	Yes ☐	No ☐	Unknown ☐
COX II inhibitors (e.g. celecoxib)	Yes ☐	No ☐	Unknown ☐
Diuretics (e.g. hydrocholorthiazide, frusemide)	Yes ☐	No ☐	Unknown ☐
Nicotinic acid	Yes ☐	No ☐	Unknown ☐
NSAIDS (e.g. ibuprofen)	Yes ☐	No ☐	Unknown ☐
Acetaminophen/Paracetamol	Yes ☐	No ☐	Unknown ☐
Tetracyclines	Yes ☐	No ☐	Unknown ☐
6-Mercaptopurine	Yes ☐	No ☐	Unknown ☐
Methotrexate	Yes ☐	No ☐	Unknown ☐
ACE Inhibitors	Yes ☐	No ☐	Unknown ☐
Amiodarone	Yes ☐	No ☐	Unknown ☐
Steroids	Yes ☐	No ☐	Unknown ☐
Statins	Yes ☐	No ☐	Unknown ☐
Other	Yes ☐	No ☐	Unknown ☐

None	Yes ☐
If 'yes' for any of the above, please specify :	

* **Continue on separate page if you need more space**

5. Concomitant medications (including those that are hepatoxic)?	Yes ☐ If yes, specify below	No ☐	Unknown ☐

Drug	Dose and Frequency	Route	Indication for Use	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)

* **Continue on separate page if you need more space**

6. Details of Liver Toxicity. Provide the clinical course:

Date of Diagnosis:

Start date: **End date:**

Comment on other contributing factors besides CSLB product administration:

7. Was a liver biopsy carried out?

Yes ☐ If yes, specify below and provide an anonymized copy of the report No ☐ Unknown ☐

Results	Date	

Liver transplant planned?

Yes ☐ No ☐

Liver transplant completed?

Yes ☐ If yes, specify date: No ☐ Unknown ☐

8. Laboratory Results*/**

Liver Function Tests (e.g. Aminotransferases AST, ALT, Total Bilirubin and alk phosphatase; specify below). Provide pre- and post-treatment values.

Test Name	Date / Time (DD/MMM/YYYY)	Results with units	Units Reference range

Test Name: (Provide pre- and post-treatment values)	Date / Time (DD/MMM/YYYY)	Results with units	Reference range
Serology & PCR testings for Hepatitis A, B, C &/or E virus. Specify			
Autoantibody tests: Specify			
Abdominal or hepatobiliary ultrasound (with or without Doppler's): Specify			
Liver elastography			
Abdominal CT scan			
Other (specify)			

* **Continue on separate page if you need more space**

****Attach anonymized copies of relevant documentation (results, laboratory findings, expert's report)**

9. Treatment of Liver Toxicity

Yes ☐ If yes, specify below No ☐ Unknown ☐

10. Seriousness

Fatal ☐ Life Threatening ☐ Hospitalization ☐ Disability Medically Important Condition ☐

CSL	Questionnaire on Liver Toxicity

11. Outcome of Event

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ provide sequelae:

Recovered with treatment ☐ provide details:

If patient recovered, provide date recovered:

If fatal outcome, was an autopsy carried out?	Yes ☐ No ☐ Unknown ☐ If yes, provide the autopsy report	
Autopsy results, especially liver histology:	**Date** (DD/MMM/YYYY)	

12. Causality Assessment to CSL Product:

☐ Related ☐ Not Related ☐ Unknown

Was there any other factors contributing to the event? ☐ Yes ☐ No

Specify:

☐ **No Further Information Available**

13. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see https://www.cslbehring.com/contact/report-an-undesirable-effect for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Questionnaire on Hemgenix Liver Malignancy

CSL EMPLOYEE/AFFILIATE USE ONLY	
Global CSL Reference Number _____ Local tracking number: _____	
Date of awareness of report (dd/mmm/yyyy) _____	☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset) years OR Age group	**Gender** ☐ Male ☐ Female	**Weight** (at event onset) ☐ kg ☐ lb	**Height** (at event onset) ☐ cm ☐ in	**Race** (where local law allows) ☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify):

2. Patient History

Check all that apply and provide details as applicable: (specify medical condition and date of onset)

Medical history

Personal history of malignancy or hepatocellular carcinoma:	Yes ☐	No ☐
Family history of malignancy or hepatocellular carcinoma:	Yes ☐	No ☐
Alcohol use (provide average drinks per week and number of years of alcohol use)	Yes ☐	No ☐
Immunosuppresion condition (e.g. HIV, transplantation).	Yes ☐	No ☐
Autoimmune Disease (e.g. Psoriasis, Sjogren syndrome, rheumatoid arthritis).	Yes ☐	No ☐
Exposure to carcinogens (environmental, occupational).	Yes ☐	No ☐
Immunosuppression therapy	Yes ☐	No ☐
Smoking (quantify if possible)	Yes ☐	No ☐
Diabetes	Yes ☐	No ☐
Pre-diabetes	Yes ☐	No ☐
Metabolic Syndrome	Yes ☐	No ☐
Metabolic associated fatty liver disease (MAFLD)	Yes ☐	No ☐
Nonalcoholic fatty liver disease (NAFLD)	Yes ☐	No ☐
Non-alcoholic steatohepatitis (NASH)	Yes ☐	No ☐

If yes to any of the above, specify

CSL Behring Innovation GmbH * Global Clinical Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Clinical Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Clinical Safety & Pharmacovigilance * 45 Poplar Road * Parkville, Victoria Australia 3052 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Hemgenix Liver Malignancy

History of hepatitis

Past medical History of Hepatitis B ..... Yes ☐ No ☐

Hepatitis B onset year (YYYY)

Hepatitis B core antibody positive – HBV CAb+..... Yes ☐ No ☐

Hepatitis B surface antigen positive – HBV SAg+..... Yes ☐ No ☐

Hepatitis B surface antibody positive – HBV Sab+ ..... Yes ☐ No ☐

Hepatitis B (HBV) viral load – peak

Hepatitis B (HBV) viral load – time (DD-MM-YYYY)

Hepatitis B (HBV) treatment regimens

Hepatitis B (HBV) vaccination

Vaccination – date (DD-MM-YYYY)

Past medical History of Hepatitis C ..... Yes ☐ No ☐

Hepatitis C onset year (YYYY)

Hepatitis C (HCV) genotype Yes ☐ No ☐

☐ 1a ☐ 1b ☐ 2 ☐ 3 ☐ 4 ☐ Other ☐ Unknown

Hepatitis C (HCV) eradication ..... Yes ☐ No ☐

Date eradication initiated (YYYY) Date eradication completed (YYYY)

HCV eradication regimen type: ☐ Interferon ☐ DAA ☐ Both ☐ Unknown

HCV eradication DAA regimen details:

☐ daclatasvir ☐ sofosbuvir/velpatasvir ☐ sofosbuvir/ledipasvir ☐ simeprevir

☐ sofosbuvir ☐ ombitasvir/paritaprevir/ritonavir/dasabuvir ☐ elbasvir-grazoprevir

☐ ribavirin ☐ Other ☐ Unknown

HCV viral load (RNA PCR) prior to clearance

AST to platelet ratio index (APRI) score prior to clearance (if available)

Evidence of cirrhosis/fibrosis prior to clearance ..... Yes ☐ No ☐

Liver cirrhosis score (prior to treatment with Hemgenix):

☐ F0 ☐ F0-F1 ☐ F1 ☐ F1-F2 ☐ F2 ☐ F2-F3 ☐ F3 ☐ F3-F4
☐ F4 ☐ Unknown

Liver biopsy fibrosis score (if biopsy was done):

☐ F0 ☐ F0-F1 ☐ F1 ☐ F1-F2 ☐ F2 ☐ F2-F3 ☐ F3 ☐ F3-F4
☐ F4 ☐ Unknown

Liver inflammation grade:

☐ A0 ☐ A0-A1 ☐ A1 ☐ A1-A2 ☐ A2 ☐ A2-A3 ☐ A3 ☐ Unknown

3. Suspect drug details

Product Name: Hemgenix	**Indication**	**Route of administration:**
Dose date **(DD/MMM/YYYY)**:		
Dose:		
Lot Number:		

4. Clinical description of the event (malignancy / neoplasm)*

Diagnosis:

Date of Diagnosis:

Clinical symptoms:

Was a biopsy done? Yes ☐ No ☐ Unknown ☐

If biopsy was done, does the reporter consent to be contacted by CSL for further information with respect to obtain tissue for molecular analysis? Yes ☐ No ☐

Location of Biopsy site(s) and result:

Histological typing of cancer including immunophenotyping and molecular profile (please provide a copy of report or summary):

Staging of neoplasm:

Status of Patient or Current treatment plan:

* **Continue on separate page if you need more space**
****Attach anonymized copies of relevant documentation (results, laboratory findings, expert's report)**

5. Diagnostic Tests*/**

Test Name	Result	Units/Normal range if applicable	Date and Time
Blood Test (e.g. Complete Blood Count, fasting blood sugar, HbA1C, lipid profile) Please specify			
Imaging tests (e.g. x-ray, Bone scan, CT scan, MRI scan, PET scan, , abdominal ultrasound) Please specify			
Alpha-fetoprotein (AFP) levels			

* **Continue on separate page if you need more space**
*** Attach anonymized copies of relevant documentation (results, laboratory findings, expert's report)**

6. Concomitant medications? (exclude those used as treatment)*

Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose	Route	Indication for Use	Start date	Stop date

***Attach anonymized copies of relevant documentation (results, laboratory findings, expert's report)**

7. Treatment

Describe therapeutic measures (e.g. chemotherapy, radiation therapy, bone marrow transplant, immunotherapy, hormone therapy, targeted drug therapy, clinical trials, palliative treatment, surgery etc.):

8. Seriousness

Fatal ☐ Life Threatening ☐ Hospitalization ☐ Disability ☐ Medically Important Condition ☐

9. Outcome

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

If fatal outcome, was an autopsy carried out?	Yes ☐ No ☐ Unknown ☐ If yes, provide the autopsy report	
Autopsy results:	**Date** (DD/MMM/YYYY)	

10. Causality assessment to CSL Product:

☐ Related ☐ Not Related ☐ Unknown

Was there any other factors contributing to the event? ☐ Yes ☐ No

If yes, specify:

☐ **No Further Information Available**

11. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see https://www.cslbehring.com/contact/report-an-undesirable-effect for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Questionnaire on Thromboembolic Events (TEE)

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____ ☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Patient History / Concomitant Diseases / Concomitant Factors

Does the patient have any known previous history of or currently suffer from:

Autoantibody diseases (e.g. antiphospholipid syndrome, lupus erythematosus, collagen-vascular diseases)?	Yes ☐	No ☐
Cerebrovascular accident / Transient Ischemic Attack?	Yes ☐	No ☐
Hypertension?	Yes ☐	No ☐
Nephrotic syndrome	Yes ☐	No ☐
Inflammatory bowel disease?	Yes ☐	No ☐
Malignant diseases / Carcinoma?	Yes ☐	No ☐
Myocardial infarction / Coronary artery disease?	Yes ☐	No ☐
Valvular heart disease?	Yes ☐	No ☐
Polycythemia vera?	Yes ☐	No ☐
Pulmonary embolism?	Yes ☐	No ☐
Recent sepsis?	Yes ☐	No ☐
Recent shock?	Yes ☐	No ☐
Surgical interventions in the past 6 months?	Yes ☐	No ☐
Trauma of lower extremity, hip, abdomen or pelvis	Yes ☐	No ☐
Thrombogenic mutations (FV Leiden, Hyperhomocysteinemia, protein C deficiency, protein S deficiency, antithrombin deficiency, increase of plasminogen activator inhibitor (PAI-1), prothrombin mutation, etc.)?	Yes ☐	No ☐
Thrombophlebitis?	Yes ☐	No ☐
Deep Vein Thrombosis?	Yes ☐	No ☐
Varicosis?	Yes ☐	No ☐
Obesity?	Yes ☐	No ☐
Dehydration?	Yes ☐	No ☐
Hormone Replacement Therapy?	Yes ☐	No ☐
Immobilization?	Yes ☐	No ☐
Oral Contraceptives?	Yes ☐	No ☐

CSL Behring Innovation GmbH * Global Clinical Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Clinical Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Clinical Safety & Pharmacovigilance * 45 Poplar Road * Parkville, Victoria Australia 3052 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Smoking?	Yes ☐	No ☐
Steroid therapy?	Yes ☐	No ☐
Arterial / Venous Catheters?	Yes ☐	No ☐

If 'yes' to any of the above, further specify*:

Does the patient have a known family history of TEEs? Yes ☐ No ☐

If yes, specify:

3. Previous Exposure to Plasma Derived (or Recombinant) Medicinal Products

Had the patient previously been treated with either the same CSL product or other products containing the same active ingredient? Yes ☐ No ☐

If 'yes', provide the therapy dates / total exposure. Specify the name of the product as well as the batch number*:

Have previous applications of the same CSL product or another product containing the same active ingredient been tolerated well? Yes ☐ No ☐

If 'no', describe symptoms and therapeutic measures*:

These questions apply ONLY if Voncento / Biostate / Haemate P / Humate P was used:

- Age of patient when first treated with Voncento / Biostate/Haemate P/Humate P: years
- Age of patient when first treated with other factor VIII / VWF products: years

4. Current Medicinal Product Exposure

Provide all therapy dates with CSL product(s) prior to onset of the TEE, including batch numbers and exact dosage of each single administration:

Product(s):	Batch no(s):	Exact dosage:	Exact therapy dates (dd/mmm/yyyy):

Provide the last known INR value prior to product administration:

INR: Date of measurement: (dd/mmm/yyyy)

Time interval between administration and onset / diagnosis of TEE:

Therapy dates (dd/mmm/yyyy):	Onset of the adverse reaction (dd/mmm/yyyy):

* Continue on separate page if you need more space

Questionnaire on Thromboembolic Events (TEE)

5. Concomitant medications? (with special reference to products known to be associated with TEE)	Yes ☐ If yes, specify below	No ☐	Unknown ☐

Drug	Dose and Frequency	Route	Indication for Use	Start date	Stop date

6. Details of TEE, provide a clinical story of the event:

7. Laboratory results

Provide information on the following laboratory values	Prior to Event (including date & time)	At onset of Event (including date & time)	Units	Reference range
D-dimers				
INR				
Thromboplastin time (or Quick value)				
aPTT				
Thrombin time				
Fibrinogen				
Fibrin monomers				
TAT complexes				

Was thrombosis / embolism confirmed by ultrasound, phlebography, CT scan, V/P scintigraphy, echocardiography etc? Yes ☐ No ☐

If 'yes', specify*:

8. Treatment of adverse event / adverse reaction

Indicate therapeutic measures, e.g. medication [heparins (UFH, LMWH), thrombolytics etc.], surgical intervention:

9. Outcome of event

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

Will the patient continue with CSL products ?

* Continue on separate page if you need more space

CSL Behring Innovation GmbH * Global Clinical Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Clinical Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
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Email: Adverse.Events.Global@cslbehring.com

10. Causality assessment to CSL product:	☐ Related	☐ Not Related	☐ Unknown

☐ **No Further Information Available**

11. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see https://www.cslbehring.com/contact/report-an-undesirable-effect for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Annex 6 Details of proposed additional risk minimization activities

Prior to launch of Hemgenix in each Member State, the marketing authorisation holder (MAH) must agree about the content and format of the educational program with the National Competent Authorities.

The MAH shall ensure that in each Member State where Hemgenix is marketed, all healthcare professionals and patients/carers who are expected to prescribe, use or oversee the administration of Hemgenix have access to/are provided with the following educational packages. These packages will be translated in the local language to ensure understanding of proposed mitigation measures by physicians and patients:

- Physician Educational Material
- Patient Information Pack.

The Physician Educational Material consists of:

- Guide for Healthcare Professionals;
- The Summary of Product Characteristics;
- The Patient/Care-giver guide;
- The Patient Card.

The Patient Information Pack consists of:

- The Patient/Care-giver guide;
- The Patient Card;
- The patient information leaflet.

The Guide for Healthcare Professionals key messages:

- To inform the patient of the important identified risk of hepatotoxicity and the important potential risks of horizontal and germline transmission, development of Factor IX inhibitors, malignancy in relation to vector genome integration, and thromboembolism, and details on how these risks can be minimised.
- Before a treatment decision is made, the healthcare professional should discuss the risks, benefits, and uncertainties of Hemgenix with the patient when presenting Hemgenix as a treatment option, including:
  - That Hemgenix use will require in some cases administration of corticosteroids to manage the liver damage that this medicinal product might induce. This requires adequate monitoring of patients' liver function and avoidance of concomitant use of hepatotoxic medication or agents, to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of Hemgenix.
  - That high preexisting neutralising anti-AAV5 antibodies may reduce the efficacy of Hemgenix therapy; patients should be assessed for the titre of preexisting neutralising anti-AAV5 antibodies before Hemgenix treatment.
  - That there is a possibility of not responding to treatment with Hemgenix. Patients who do not respond are still exposed to long-term risks.
  - That the long-term treatment effect cannot be predicted.
  - That there would be no plans to re-administer the medicinal product for patients who do not respond or have lost the response.
  - That the patients should be tested for Factor IX inhibitors to monitor development of Factor IX inhibitors.
  - Reminding patients about the importance to enroll in a registry for follow up of long-term effects.
  - The healthcare professional should provide the patient guide and patient card to the patient

The Patient/Care-giver guide key messages:

- Importance to fully understand the benefits and risks of Hemgenix treatment, what is known and not yet known about the long-term effects, related to both safety and efficacy.
- Therefore, before a decision is made about starting on the therapy the doctor will discuss with the patient the following:
  - That Hemgenix will, in some cases, require treatment with corticosteroids to overcome the liver damage that this medicine may produce, and that the doctor will ensure that patients are available for regular blood tests to check response to Hemgenix and assess liver health. Patients should inform the healthcare professional about current use of corticosteroids or other immunosuppressants. If the patient cannot take corticosteroids, the doctor may recommend alternative medicines to manage problems with the liver.
  - That high preexisting immunity against the vector may reduce the efficacy of Hemgenix therapy; patients are expected to be assessed for the titre of preexisting neutralising anti-AAV5 antibodies before the Hemgenix treatment.
  - That not all patients may benefit from treatment with Hemgenix. Patients not responding to treatment are still be exposed to long-term risks.
  - Details how the important potential risks of horizontal and germline transmission, development of Factor IX inhibitors, malignancy in relation to vector genome integration, and thromboembolism can be recognised and minimised by regular monitoring as recommended by doctors, including that:
  - The patient should seek immediate medical advice for any symptoms suggestive of a thromboembolic event.
  - Male patients of reproductive potential or their female partners should use barrier contraception for one year after administration of Hemgenix.
  - That Hemgenix has a viral vector component, and it may be associated with an increased risk of malignant tumour. Regular liver monitoring for at least 5 years

after Hemgenix treatment is needed in patients with preexisting risk factors for hepatocellular carcinoma.

- Patients should not donate blood, semen, or organs, tissues, and cells for transplantation
- That the patient will get a patient card that should be shown to any doctor or a nurse whenever the patient has a medical appointment.
- The importance to participate in the patients' registry for long-term surveillance of 15 years.

The Patient Card key messages:

- This card is to inform healthcare professionals that the patient has received Hemgenix for hemophilia B
- The patient should show the patient card to a doctor or a nurse whenever they have an appointment
- The patient should seek medical advice for any symptoms suggestive of a thromboembolic event
- The patient should have regular blood tests and examinations as directed by their doctor
- The card should warn healthcare professionals that the patient may undergo treatment with corticosteroids for minimising the risk of hepatotoxicity with Hemgenix.