Protocol Number: CSL222_3004

Protocol Title: Phase 3, Open-label, Single-dose, Multicenter Study Investigating Efficacy, Safety, and Tolerability of CSL222 (Etranacogene Dezaparvovec) Administered to Adolescent Male Subjects (≥ 12 to < 18 Years of Age) with Severe or Moderately Severe Hemophilia B.

IMP: CSL222 (previously termed AMT061)

Sponsor: CSL Behring

Background:

Congenital hemophilia B is an inherited bleeding disorder characterized by an increased bleeding tendency due to either a partial or complete deficiency of the essential blood coagulation protein, factor IX (FIX), resulting from mutations of the respective clotting factor gene. Hemophilia B is an X-linked, recessive condition that occurs primarily in males.

CSL222 (previously termed AMT061; International Nonproprietary Name: etranacogene dezaparvovec; HEMGENIX®) is a somatic gene therapy product that aims to deliver a nucleic acid expression cassette capable of driving expression and synthesis of functional FIX to the liver of patients with hemophilia B. CSL222 is a recombinant adeno-associated viral vector serotype 5 (AAV5) containing the coding sequence for the Padua variant of the human FIX (hFIX Padua), codon-optimized for optimal expression in humans, under the control of a liver specific promoter (CSL222 is also known as AAV5-hFIXco-Padua). One-time treatment with CSL222 allows the patient to continuously produce functional hFIX-Padua protein at levels which modify the severity of their hemophilia B disease and is currently approved for use in adults

Clinical Study

The clinical study is to be conducted globally and is an open-label, single-dose study that intends to generate the clinical data needed to assess an advancement of CSL222 gene therapy in the adolescent population of patients with severe or moderately severe hemophilia B by evaluating annualized bleed rate, FIX activity and to characterize the safety profile.

This clinical trial will enroll adolescent male subjects (≥ 12 to < 18 years of age) with severe or moderately severe hemophilia B, at University Hospital Leuven (UZ Leuven) and is expected to take place between 01-Oct-2025 and 23-Oct-2033.

Enrolled subjects will receive a single intravenous infusion of CSL222. Subjects will be followed for a total of 5 years after administration of CSL222 to assess the durability of efficacy and long-term safety.

Assessment of potential risks to human health and the environment

CSL222 is a recombinant replication-deficient adeno-associated viral vector (rAAV). CSL222 administration is limited to a few hospitals and a small number of subjects. At the hospital level, healthcare professionals involved in the study will be duly trained in the handling of GMOs. In order to minimize any accidental product exposure to personnel, close contacts or the environment, the centers will implement best practices in biosafety. In addition, mitigation procedures will be applied in the event of a spill or unintended direct contact with the GMO.

The subjects administered CSL222 are provided guidance to minimize the risk of transmission to third parties such as not donating blood, or organs, tissues, or cells for transplantation any time after CSL222 treatment and are also advised to use barrier contraception for 1 year starting on the day of CSL222 treatment. Several (non) clinical studies, as well as studies from scientific literature indicated that infectious rAAV particles are not present in semen following IV administration for longer than 4 days after infusion.

Additionally, caregivers are advised on the proper handling of waste material generated from contaminated medicinal ancillaries during CSL222 preparation and infusion.

The risk of an adverse event due to (horizonal) transmission to third parties is unlikely due to the extremely low particle concentration present in biological fluids shed by CSL222 treated patients onto close contacts or into the environment. In the hypothetical situation that unintended exposure of third parties to infectious CSL222 would take place within the immediate period after infusion, an immune response to the particles, expression of hFIX-Padua, or occurrence of AEs relating to this exposure could occur. The probability that such an unintended exposure will lead to these outcomes is extremely low.

Furthermore, in the unlikely event that horizontal gene transfer occurs, there is little risk that the CSL222 sequences will confer a selective advantage to bacteria; CSL222 does not contain any prokaryotic promoters, antibiotic or other type of resistance genes, or any genes that could promote or inhibit their proliferation. Therefore, CSL222 is unlikely to interfere with the control of pathogenic microorganisms or influence the natural dynamics of microbial populations or the biogeochemical cycles of the environment of the centers involved.

The rAAV is missing the rep and cap genes from natural adeno-associated virus (also called wild-type AAV). Due to the absence of rep and cap genes, the vector will persist as a non genome-integrated episome and will not replicate or produce viral particles. The rAAV expression cassette will be processed by the host liver cells, resulting in the expression of functional human factor IX (Padua) protein in blood.

Although human infections with wild-type AAV are common, there is no evidence that they are pathogenic to humans. As such, AAV have be classified as a group 1 biological agent, defined as agents that are unlikely to cause disease in humans according to European Directive 2000/54/EC on the protection of workers from the risks related to exposure to biological agents at work.

The potential disadvantages or risk of a deliberate release are of low and could be considered negligible, as with treatment with CSL222, as, wild-type AAV does not appear to be involved in environmental processes, and none of the genetic modifications made to wild-type AAV during the construction of CSL222 are expected to alter this property. Therefore, the release of CSL222 is not expected to be associated with any environmental impacts.

Patients treated with CSL222 should not donate blood, semen, or organs, tissues and cells for transplantation to avoid unintended exposure to those not treated. Additionally, after a male patient has been treated with CSL222, the patient and any female partner must avoid pregnancy for 12 months and should use effective contraception (e.g. barrier contraception such as condom or diaphragm). This is to prevent the theoretical risk that the Factor IX gene from a father's CSL222 treatment is transmitted to a child with unknown consequences. In the event of unintended release (deliberate or accidental), follow-up would include the "Measures to take in the case of accidental exposure" outlined in the product Summary of Product Characteristics available at https://www.ema.europa.eu/en/medicines/human/EPAR/hemgenix and continued monitoring in the case of pregnancies, as outlined in the subject informed consent form.

Given the low risk posed by CSL222 to humans and the environment, and in view of the bio-risk management measures put in place to minimize exposure to the vector, the overall risk of the latter to humans and the environment can be considered negligible.