The framework of research and development

- *Title of the study:*

  C0371002 - A Phase 3, open-label, single-arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV Spark100-hFIX-R338L) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene 2).

- *Brief description of the project:*

  The GMO will be used in a Phase 3, global, single-arm, multi-center, open-label study in adult male participants, who completed at least 6 months of prospectively collected data while receiving blood coagulation Factor IX (FIX) prophylaxis replacement therapy as per their usual care during the lead-in study (C0371004). Eligible participants will receive a single intravenous (IV) infusion of PF-06838435 (Fidanacogene elaparvovec). All participants will be followed for six years after the administration of PF-06838435.

  The primary objective is to demonstrate the efficacy of a single infusion of PF-06838435 in male participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%).

  At the time of the clinical trial application to Belgian Regulatory Authority through EU CTR process there are ongoing participants in the C0371004 lead-in study in Belgium. As These participants entered C0371004 with the understanding that upon the successful completion of C0371004 they would be offered the opportunity to consent into C0371002 and be dosed with gene therapy (provided they still meet eligibility criteria) the sponsor remains committed in dosing these participants. Data from all the participants will provide additional clinical experience on durability of efficacy and add to the overall safety database. At the time of the application in Belgium Pfizer is already conducting this C0371002 clinical study in Australia, Canada, France, Germany, Greece, Japan, Korea, Saudi Arabia, Sweden, Taiwan, Turkey, United Kingdom and United States.

Description of the GMO

PF-06838435 is a non-replicating recombinant vector derived from adeno-associated virus containing an expression cassette encoding a naturally occurring blood coagulation Factor IX.

The intended outcome of the genetic modification was to generate a recombinant AAV vector lacking viral genes so that the vector would be replication incompetent and serve only to introduce the transgene and to include the sequence coding for FIX to treat patients with moderately severe to severe hemophilia B.

The nature and goal of the foreseen deliberate release

The deliberate release of PF-06838435 is associated with vector shedding from patients who were administered with it.

AAV vector shedding is commonly observed in studies involving AAV based vectors. Shedding occurs at very low levels, and taking into consideration that PF-06838435 is

unable to replicate is not considered as posing a risk to people and the environment. Shedding of PF-06838435 will be carefully assessed during the Phase 3 clinical study.

The potential advantages of the deliberate release

The PF-06838435 is intended to be potential gene therapy for hemophilia B. It is expected that the administration of PF-06838435 to the hemophilia B patients will result in the improvement of the patients' condition.

The assessment of the potential risks for human health and the environment linked to the deliberate release

The release of PF 06838435 is not expected to result in adverse environmental impact, including the human patient population, for the following reasons:

1. Lack of pathogenicity of the parental virus and the GMO: Despite an estimated seroprevalence of up to 80% for some common human serotypes, no pathogenic effects of AAV have been identified. The modifications which have led to the generation of the GMO have not raised the pathogenicity (see point 6. below).
2. Replication-incompetent GMO: PF 06838435 is a non-pathogenic recombinant AAV vector that lacks all AAV viral genes and cannot replicate without AAV-specific helper functions and helper virus activities. PF 06838435 replication could only occur in the extremely unlikely event of a host cell being infected by wild-type AAV and a helper virus such as human adenovirus or herpes simplex virus. If replication occurred, the only expected products would be PF 06838435 and WT AAV, both intrinsically non-pathogenic viruses.
3. Minimal risk of transmission by viral shedding: PF 06838435 is replication-incompetent and is not expected to survive, multiply or disperse if it were to be eliminated intact from the treated patient. AAV-based gene therapies are known to shed via bodily fluids. It has been shown consistently that vectors are shed for a short period of time, but then become undetectable in bodily fluids. The viral load shed in bodily fluids is expected to be low, compared to the necessary dose required to achieve detectable gene expression in humans. Vector shedding will be monitored and will be measured in plasma, peripheral blood, saliva, semen and urine of participants following administration of PF-06838435 until 3 consecutive samples with negative reading. Minimal exposure, such as environmental exposure, of persons other than study participants would not be of sufficient dose to result in significant gene expression in humans. Other than potential human hosts, exposure to PF 06838435 is not expected to affect any non-target organisms, either directly or indirectly. The risk to humans and the environment associated with viral shedding of PF 06838435 is thus negligible.
4. Minimal risk of insertional mutagenesis: Data from mice, dogs, NHPs and humans suggest that the integration of AAV vectors into the host genome is a rare event, with most of the vector assimilating into concatemeric episomes. Unlike retroviral vectors, which encode viral proteins to create double-stranded breaks, when AAV integration does occur, it does so at pre-existing chromosomal breaks. The results of integration are deletions in the AAV ITRs and duplications of host sequences. Given the tissue tropism of AAV9 and the results of non-clinical studies, the greatest potential for integration is within hepatocytes, skeletal and cardiac

myocytes. No clinical trials to date with AAV have reported incidences of insertional mutagenesis.

5. Tissue-specific transgene expression: PF-06838435 contains a gene encoding a human factor IX protein variant, which has higher specific activity than wtFIX. Expression is driven by both a liver-specific enhancer and promoter encapsidated within a modified capsid derived from a naturally occurring AAV serotype, having strong tropism for the liver, which transduces the liver highly efficiently when administered intravenously.
6. Minimal risk associated with the transgene: The viral vector does not contain any viral sequences, except ITRs, which facilitate transgene expression and do not lead to production of viral proteins, particles or DNA replication. The protein encoded by the transgene is a human coagulation factor and is therefore unlikely to be toxic to humans or other organisms. No genes for toxins, potential oncogenes, growth factors or other genes that could be potentially harmful have been inserted into the GMO. With administration of PF 06838435 to humans, the only foreign proteins that the immune system will be exposed to are the viral capsid proteins.
7. Minimal risk associated to immune responses in patients: Patients will receive corticosteroids in order to minimize the immune response to the viral capsid proteins.

The proposed measures to limit the potential risks, to control and to ensure follow-up of the deliberate release.

PF-06838435 will be shipped to investigational centers in line with standard recommendations for the transport of biohazardous materials. PF-06838435 will be stored, prepared and administered by trained medical professionals, in a hospital setting only, to patients that meet criteria for inclusion into the clinical study C0371002. Staff will follow the waste and disposal policies as per local site requirement to dispose of consumables used in the preparation and administration of the GMO. The use of needles will be kept to a minimum.

A Pharmacy Manual and training material located at sites provides pharmacy personnel and clinical medical staff directions on use, storage and destruction of the tested product and related waste. It also includes directions for documenting the control of the GMO product from the time of receipt at the trial site until final accountability and destruction. In addition, it describes the required processes for managing and documenting any issues, such as shipment or storage, temperature excursions and reporting of technical product complaints. The risks related to the release into the environment of the GMO or risks to personnel in the event there is a breach in container integrity and/or storage or accidental spillage at the site or during shipping/storage, is considered to be negligible. The GMO will only be handled by delegated, trained personnel and in the event that a spillage did occur, the product is non-pathogenic and non-replicative, limiting spread and risks to the environment or personnel.

Patients will receive PF-06838435 by a one-time IV infusion in a clinical setting. Additionally viral vector shedding will be assessed in this study. This will indicate when vector shedding in plasma, peripheral blood, saliva, semen and urine has ceased. As PF-06838435 is non-replicative, shed viral particles are unable to multiply and thus, the spread of the GMO is inherently limited.

A PF-06838435 manual will be provided to staff at the investigational centers, for the management and disposal of PF-06838435, which should be followed by all personnel responsible for transporting, preparing, administering, disposing of PF-06838435 medicinal product or equipment/consumables that have come into contact with the product designated for use in this clinical study.

Location of the clinical trial in Belgium:
Cliniques Universitaires Saint-Luc, Haemostatis and Thrombosis Unit
Avenue Hippocrate 10, Building 54
1200 Woluwe-Saint-Lambert

The estimated number of patients in Belgium is 2.

Study start date in Belgium: approximately May 2024
Study end date in Belgium: approximately July 2030