Information for the public

Pfizer Inc.

Study C3391003

The framework of research and development

- *Title of the study:*

  Phase 3, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of PF-07055480 (Recombinant AAV2/6 Human Factor VIII Gene Therapy) in Adult Male Participants with Moderately Severe to Severe Hemophilia A (FVIII:C≤1%)

- *Brief description of the project:*

  The Genetically Modified Organism (GMO) will be investigated in a pivotal Phase 3 study to evaluate the clinical efficacy and safety of a single IV infusion of PF-07055480 (INN: giroctocogene fitelparvovec) in adult male participants with moderately severe to severe hemophilia A (FVIII:C≤1%) for a study duration of approximately 5 years for each participant. the study treatment, a single infusion of PF-07055480, a gene transfer agent, will be administered on Day 1 at a dose of $3x10^{13}$ vg/kg of body weight. A minimum of 50 patients will be dosed will be dosed with PF-07055480 worldwide.

  The primary objective of the study is to evaluate the efficacy of a single infusion of PF-07055480 in participants ≥18 and <65 years of age with moderately severe to severe hemophilia A (FVIII C ≤ 1%). Main endpoints include the annual bleeding rate, FVIII activity levels and the use of exogenous FVIII.

  Before commencing Phase 3 clinical study, PF-07055480 was tested in animals. Five separate *in vivo* studies were conducted with PF-07055480, including two mouse models and one in immunosuppressed cynomolgus monkeys. In addition, one cynomolgus monkey study, conducted early on the development pathway, evaluated a highly related variant of PF-07055480 and provided supportive data. Overall, the results of the nonclinical pharmacology studies were remarkably consistent in demonstrating that treatment with PF-07055480 (or a highly related variant) results in circulating levels of biologically active hFVIII that appear sufficient to have an efficacious impact in human subjects.

  PF-07055480 is being evaluated in an open-label, adaptive, dose-ranging Phase 1/2 study (SB-525-1603) to assess the safety and efficacy in male participants ≥18 years of age with severe hemophilia A. Specifically, these data indicate that treatment of hemophilia A with PF-07055480 is generally well tolerated and demonstrated a dose-dependent increase in FVIII levels, achieving clinically relevant increases in FVIII activity in the higher dose cohorts and FVIII levels in the mild to normal range in the 3.0E1013 vg/kg dose cohort. A dose-dependent reduction in the use of FVIII replacement therapy was also observed, with participants in the highest dose cohort not requiring factor replacement therapy after initial use of prophylactic factor and experiencing no bleeding events to date.

Description of the GMO

PF-07055480 is a non-replicating recombinant vector derived from adeno-associated virus containing a codon-optimised version of the human Factor VIII gene, that may be effective for the treatment of patients with hemophilia A.

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 which includes the sequence coding for the B-domain deleted hFVIII to treat Hemophilia A.

The vector genome comprises a liver-specific promoter module, a transgene encoding the B-domain deleted human Factor VIII and a polyadenylation signal, flanked by AAV inverted terminal repeats (ITRs). Only the vector genome is present in the final GMO. In addition, the recombinant Baculovirus (rBV) contains the Baculovirus backbone, including the Gentamycin resistance gene. These elements are not transferred to the final GMO.

It is expected that administration of PF-07055480 will result in sustained hepatic production of FVIII in hemophilia A participants to reduce or eliminate the need for FVIII replacement therapy.

The nature and goal of the foreseen deliberate release

The deliberate release of PF-07055480 is associated with vector shedding from patients who were administered with it.

AAV vector shedding in biological fluids is commonly observed in studies involving intravenous infusions of AAV based vectors. Shedding occurs at very low levels and, taking into consideration that PF-07055480 is unable to replicate, is not considered as posing a risk to people and the environment. Shedding of PF-07055480 will be carefully assessed during the Phase 3 clinical study.

The potential advantages of the deliberate release

The PF-07055480 is being tested as a potential gene therapy for hemophilia A. It is hoped that the administration of PF-07055480 to patients with moderately severe to severe hemophilia A 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-07055480 as described in this application is not expected to result in adverse environmental impact, including on the human patient population, for the following reasons:

1. Lack of pathogenicity of the parental virus and the GMO: Despite an estimated seroprevalence of ~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-07055480 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-07055480 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-07055480 and WT AAV, both intrinsically non-pathogenic viruses.

3. Risk of transmission by viral shedding: PF-07055480 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 assessed in Plasma, PBMC, saliva, semen, and urine. Specimens will be collected at baseline and every week after study intervention until 3 consecutive specimens test negative for the given specimen type. Participants are eligible to participate if they agree to the following during the intervention period and for at least the time required for 3 consecutive ejaculate samples to test negative for vector shedding: -Refrain from donating sperm. Be abstinent from heterosexual or homosexual intercourse or must agree to use contraception/barrier.

   Minimal exposure to the PF-07055480, 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-07055480 is not expected to affect any non-target organisms, either directly or indirectly.

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

5. Tissue-specific transgene expression: PF-07055480 shows a strong tropism for the liver following IV administration. PF-07055480 transgene expression is driven by a liver-specific promoter. Therefore, transduction of non-hepatocyte cells should not result in transgene expression.

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. Comprehensive toxicity studies failed to demonstrate any toxic effect of PF-07055480 at the intended dose. The protein encoded by the transgene is a naturally occurring protein 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-07055480 to humans, the only foreign proteins that the immune system will be exposed to are the viral capsid proteins.

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

PF-07055480 will be shipped to study sites in line with standard recommendations for the transport of biohazardous materials. PF-07055480 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 C3731003. 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 IMP. It also includes directions for documenting the control of the IMP 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-07055480 by a one-time IV infusion in a clinical setting, will remain at the infusion center or study site for at least 24 hours after being dosed. Additionally, viral vector shedding will be assessed in this study. This will indicate when vector shedding in plasma, saliva, peripheral blood mononuclear cells (PBMCs), urine and semen has ceased (negativity has to be confirmed at 3 consecutive occasions). As PF-07055480 is non-replicative, shed viral particles are unable to multiply and thus, the spread of the GMO is inherently limited.

Procedures for use of all batches of PF-07055480 are described in the component-specific Material Safety Datasheet (MSDS). In addition, unless stated in the IP manual that will also be provided to staff at the site, local procedures and guidelines for the management and disposal of a RG1 product should be followed by all personnel responsible for transporting, preparing, administering, disposing of PF-07055480 IMP or equipment/consumables that have come into contact with the product designated for use in clinical study. **Table 1** summarises the procedures that will be used by staff to manage incidents related to PF-07055480.

Table 1: Management of incidents related to PF-07055480 product

Incident	Procedure
Accidental spillage	In the event that the contents of the PF-07055480 vial/s or diluted product for infusion are accidentally released and come in contact with shipping materials, pharmacy/ hospital surfaces, the spillage should be decontaminated and removed according to institutional practice.
Sharps injury	The use of needles is to be kept to a minimum. In the event of injury, follow local institutional procedures and report to Principle Investigator (PI). PI to notify CRA.
Contact with skin and clothing	Remove contaminated clothing. Flush area with large amounts of water. Use soap. Seek medical attention
Contact with eyes.	Flush with water while holding eyelids open for at least 15 minutes. Seek medical attention immediately.

PF-07055480 is stored in clear 10 mL closed vials, each containing 6 mL. Staff will be advised that care must be taken when manipulating vials and that the use of needles should be kept to a minimum. In the event of injury, staff will follow local institutional procedures.