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SYNOPSIS

Study Title: Phase 3, Open Label, Single Arm Study to Evaluate Efficacy and Safety of FIX Gene Transfer With PF-06838435 (rAAV-Spark100-hFIX-Padua) in Adult Male Participants With Moderately Severe to Severe Hemophilia B (FIX:C≤2%) (BeneGene-2)

Study Number: C0371002

Regulatory Agency or Public Disclosure Identifier Number: 2018-003086-33, NCT03861273

Study Phase: 3

Name of Study Intervention:
PF-06838435 /fidanacogene elaparvovec

Trade Name : PF-06838435 (trade name not yet assigned)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Final CSR (primary completion date) Version 1.0	22 February 2023

Number of Study Center(s) and Investigator(s):

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not Applicable

Study Period:

Study Initiation Date: FSFV 29 July 2019
Primary Completion Date: 16 November 2022

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List of Abbreviations

Abbreviation	Definition
AAV	adeno-associated virus vector
ABR	annualized bleeding rate
ADA	antidrug antibody
AESI	adverse events of special interest
AIR	annualized (FIX) infusion rate
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BU	Bethesda Unit
CD4	cluster of differentiation 4
CSR	clinical study report
dL	deciliter
DNA	deoxyribonucleic acid
EQ-5D-5L	EuroQol, 5 dimensions, 5 levels
FIX	Factor IX
FIX:C	Factor IX circulating
FSFV	first subject first visit
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List

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Abbreviation	Definition
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hFIX-Padua	Padua mutation (R338L) of the human factor IX gene
HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HLIQ	Hemophilia Life Impacts Questionnaire
INR	international normalized ratio
IV	intravenous
MRI	magnetic resonance imaging
nAb	neutralizing antibody
PBMC	peripheral blood mononuclear cell
PRO	patient reported outcome
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	Standardized MedDRA Queries
TAT	thrombin antithrombin level
TEAE	treatment-emergent adverse event

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Abbreviation	Definition
TGA	thrombin generation assay
ULN	upper limit of normal
vg/kg	vector genomes per kilogram

Rationale:

The published data from the Phase 1/2a study for fidanacogene elaparvovec (SPK-9001-101) indicate that treatment of hemophilia B with fidanacogene elaparvovec offers considerable clinical advantage over routine prophylactic treatment with FIX product. A single infusion of fidanacogene elaparvovec results in sustained FIX activity levels in the mild to normal range with associated low bleeding rates and a marked reduction in the number of infusions of FIX product. This Phase 3 confirmatory study will compare the efficacy of fidanacogene elaparvovec treatment with routine prophylaxis administered as a part of usual care with the objective to establish non inferiority and possibly superiority.

Objectives, Endpoints, and Statistical Methods:

The objectives and endpoints are provided in Table 1.

Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Efficacy	• To demonstrate the efficacy of a single infusion of fidanacogene elaparvovec in male participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%).	Primary endpoint: • Non-inferiority on ABR for total bleeds (treated and untreated) from Week 12 to Month 15 versus standard of care FIX prophylaxis replacement regimen, comparing pre- and post-IP infusion.

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Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
Secondary		

Efficacy	• Key secondary objectives: To demonstrate the efficacy of fidanacogene elaparvovec in terms of the use of exogenous FIX, the treated bleeds, and FIX:C.	• Key secondary endpoints:
		  • Non-inferiority on ABR for treated bleeds from Week 12 to Month 15 versus standard of care FIX prophylaxis replacement regimen, comparing pre- and post-IP infusion.
		  • AIR of exogenous FIX from Week 12 to Month 15 versus AIR of FIX with standard of care FIX replacement regimen pre-IP infusion.
		  • Vector-derived FIX:C level at steady state (from Week 12 to 15 months) demonstrated to be greater than 5%. FIX:C will also be summarized descriptively by study visit.

Efficacy	• To compare additional efficacy parameters post- fidanacogene elaparvovec infusion to baseline in order to further characterize fidanacogene elaparvovec treatment, including use of exogenous FIX, information on bleeding events, and patient reported outcomes addressing health related quality of life, activities of daily living and general health status.	The following parameters were compared with standard of care FIX replacement regimen, comparing pre- and post-IP infusion from Week 12 to Month 15:
		• Annualized FIX consumption.
		• Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated.
		• Frequency of target joint bleeds.
		• Percentage of the participants without bleeds.
		The following parameters were compared with standard of care FIX replacement regimen, comparing pre- and post-IP infusion at 12 months:
		• Change in joint health as measured by the HJHS instrument.
		• PRO instruments:
		  • Haem-A-QoL Physical Health domain.
		  • HAL Complex Lower Extremity Activities Component Score.

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Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint

Safety	• Safety and tolerability of fidanacogene elaparvovec, including immunogenicity, for the study duration of 6 years after fidanacogene elaparvovec infusion	• Incidence and severity of adverse events collected during the study.
		• Adverse Events of special interest:
		  • Hypersensitivity reactions;
		  • Clinical thrombotic events;
		  • FIX inhibitors,
		  • Hepatic malignancies.
		  • Drug related elevated hepatic transaminases that fail to improve or resolve
		  • Malignancy assessed as having reasonable possibility of being related to study drug
		• Other immunogenicity-based laboratory data including: nAb to AAV capsid, immune response (presumed T-cell activation) to AAV capsid protein and/or FIX transgene.

Efficacy	• Assess durability of efficacy up to 6 years.	The following parameters were assessed throughout the 6-year study period. Summaries were provided for the overall follow-up period, as well as by yearly intervals: • ABR for total bleeds (treated and untreated). • ABR for treated bleeds. • AIR of exogenous FIX. • Vector-derived FIX:C level by study visit and the geometric mean at each yearly interval. • Annualized FIX consumption. • Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated. • HJHS total score. • Frequency of target joint bleeds. • PROs instruments: • Haem-A-QoL Physical Health domain. • HAL Complex Lower Extremity Activities Component Score.

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Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
Tertiary/Exploratory		
Pharmacodynamics	• Pharmacodynamics of fidanacogene elaparvovec.	• Vector shedding of fidanacogene elaparvovec as measured by qPCR in plasma, saliva, PBMC, urine, and semen until 3 consecutive specimens test negative for the given specimen type. • FIX antigen levels.
Efficacy	• To compare joint health post-fidanacogene elaparvovec infusion to baseline.	• Number of target joints. • Joint status as assessed by X-ray in some participants who consent to participate in an optional sub-study. • Joint status as assessed by MRI in some participants who consent to participate in an optional sub-study.
Efficacy	• Impact on coagulation.	• [redacted] • [redacted]
Efficacy	• To compare additional efficacy parameters post-fidanacogene elaparvovec infusion in order to further characterize fidanacogene elaparvovec treatment in terms of patient-reported outcomes assessing hemophilia life impacts and global health status.	• PRO instruments: Haem-A-QoL (domains not previously specified), HAL (scores not previously specified), HLIQ, and EQ-5D-5L, in the first 12 months and annually in the follow-up period, years 2-6.

The planned analyses, analysis populations, statistical tests, and determination of sample size are described in the final version of the SAP and in the protocol. Any major modifications of the primary endpoint definition and/or its analysis subsequent to the protocol finalization were reflected in a protocol amendment.

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Methodology:

This Phase 3, open-label, single arm, multi-site study compared the efficacy of a single IV infusion of fidanacogene elaparvovec with routine FIX prophylaxis in adult male participants from the lead-in study (C0371004) with moderately severe to severe hemophilia B (FIX:C ≤2%). Study C0371004 prospectively collected efficacy data and selected safety data on participants for at least 6 months and these data are utilized as the FIX prophylaxis control for comparison with data post-fidanacogene elaparvovec infusion in Study C0371002. Eligible study participants completed a minimum 6 months of routine FIX prophylaxis therapy during the lead in study (C0371004). The planned study duration for each participant in this study was 312 weeks.

Number of Participants (planned and analyzed):

This study was conducted at 28 sites. A total of 45 participants were randomized in 27 centers in 13 countries.

A total of 51 participants who completed the lead-in study (C0371004) were screened in this study and 45 participants received a single dose of fidanacogene elaparvovec. Since no more than a single dose of study treatment on Day 1 was administered during the study, there were no treatment discontinuations.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Key inclusion criteria were as follows:

- Participants completed at least 6 months of routine FIX prophylaxis therapy during the lead-in study (C0371004) prior to providing consent at the screening visit for this study.
- Participants had documented moderately severe to severe hemophilia B, defined as FIX:C ≤2%.
- Participants agreed to suspend prophylaxis therapy for hemophilia B after administration of the study intervention. FIX replacement therapy was allowed as needed.
- Acceptable screening laboratory values as follows:
  - Hemoglobin ≥11 g/dL;
  - Platelets ≥100,000 cells/µL;
  - Creatinine ≤2.0 mg/dL.
- Male.

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- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Male participants are eligible to participate if they agree to the following for at least time required for 3 consecutive ejaculate samples to test negative for vector shedding:
    - Refrain from donating sperm.

      PLUS either:

    - Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

      OR

    - Must agree to use contraception/barrier as detailed below:
    - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

Key exclusion criteria were as follows:

- Anti-AAVRh74var nAb titer ≥1:1 (ie, positive for nAb), performed by a central laboratory during screening.
- Prior history of inhibitor to FIX or positive inhibitor testing as measured by the central laboratory ≥0.6 BU during screening. Clinical signs or symptoms of decreased response to FIX.
- Known hypersensitivity to FIX replacement product or IV immunoglobulin administration.
- History of chronic infection or other chronic disease that investigator deems as an unacceptable risk.
- Any concurrent clinically significant major disease or condition that the investigator deems unsuitable for participation or other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior (including alcoholism) or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

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- ALT, AST, ALP >2×ULN, based on central laboratory results.
- Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN was acceptable if bilirubin was fractionated and direct bilirubin <35%), based on central laboratory results.
- Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones) was acceptable if the participant otherwise met entry criteria.
- Previously dosed in a gene therapy research trial at any time or in an interventional clinical study within the last 12 weeks, excluding participation in study C0371004.
- Significant liver disease, as defined by pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy.
- Active hepatitis B or C; HBsAg, HBV-DNA positivity, or HCV-RNA positivity.
- Serological evidence of HIV-1 or HIV-2 infection with either CD4+ cell count ≤200 mm^3 or viral load >20 copies/mL.
- Sensitivity to heparin or heparin induced thrombocytopenia.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Table 2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
PF-06838435 (SPK-9001) Solution for Infusion, 1 mL/vial	265-18001	18-003889	[redacted] vg/ml	SOLUTION
PF-06838435 Solution for Infusion, 1 mL/vial	H000018074-CF0718	19-003791	[redacted] vg/mL	SOLUTION
PF-06838435 Solution for Infusion, 1 mL/vial	H000018074-AH6804	19-002008	[redacted] vg/mL	SOLUTION

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Table 2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
PF-06838435 Solution for Infusion, 1 mL/vial	H000018074-CF0718;19-003791	PA2035938	[redacted] vg/mL	SOLUTION

Duration of Study Intervention:

The study intervention, a single infusion of fidanacogene elaparvovec, a gene transfer agent, was administered on Day 1 at a dose of 5×10^{11} vg/kg of body weight (based on actual lot concentration). For a participant with BMI >30 kg/m^2, dose was calculated based on an adjusted body weight determination that assumes a maximum permissible BMI of 30 kg/m^2.

The manufacturing lot numbers for the study intervention dispensed in this study are provided in Table 2.

Summary of Results:

Demographic and Other Baseline Characteristics:

All participants were male and the majority of the study participants were <35 years of age.

The median age was 29.00 years (min, max 18.0, 62.0 years), White (33 [73.3%]) participants, and not Hispanic or Latino or Spanish origin (35 [77.8%] participants). All (45 [100.0%]) participants had a factor mutation. Target joints at baseline were identified in 13 (28.9%) participants.

Exposure:

The actual dose was adjusted from the planned dose when a participant's BMI was >30kg/m^2.

Efficacy Results:

- With a one-time infusion, fidanacogene elaparvovec at a dose of 5×10^{11} vg/kg resulted in statistically significant reduction in ABR_{total} and ABR_{treat} compared to routine FIX prophylaxis
- A statistically significant reduction in annualized infusion rate (AIR) represents a significant improvement over FIX prophylaxis regimen

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- At Month 15, the mean and median FIX:C was in the mild range across the 3 assays. Mean steady state (geometric mean of measurements from Week 12 to Month 15) FIX:C using One-stage assay with Actin-FSL and SynthASil reagent, and chromogenic assay was significantly higher than the pre-specified fixed threshold of 5%.

- ABR_{total}, ABR_{treat} and AIR are similar during Year 2 and Year 3.

- In parallel with reduced AIR, participants treated with fidanacogene elaparvovec had a significant reduction in mean FIX consumption from Week 12 to Month 15 compared to FIX prophylaxis.

- Mean ABR_{total} of specific types (spontaneous, joint, soft tissue/muscle/other and target joint) from Week 12 to Month 15 post-infusion were significantly reduced comparing to mean ABR_{total} collected in the run-in period up to vector infusion

- Hemophilia Joint Health Score (HJHS) improved during the course of the first 12 months post-infusion with fidanacogene elaparvovec.

- Post infusion with fidanacogene elaparvovec, statistically significant improvement from baseline was observed in patient-reported outcomes at Week 52 in Physical Health Domain score of the Haem-A-QoL and in the Complex Lower Extremity Activities component score of the Hemophilia Activities List (HAL), with the same measures assessed annually from baseline throughout the study.

Safety Results:

Over the total follow-up period, the TEAEs reported were generally mild or moderate.

A total of 205 TEAEs were reported in 38 (84.4%) participants during the entire study. SAEs were reported in 7 (15.6%) participants. TEAEs for the first year, regardless of causality were consistent with those reported during the overall follow-up.

- **Safety Conclusions**

  - Fidanacogene elaparvovec was well tolerated in adult hemophilia B participants with long-term follow-up of up to 3 years, based on current data.

  - Overall liver health was stable in the setting of elevation in transaminases in nearly half of the population evaluated (46.7% had ALT elevation and 44.4% had AST elevation) and corticosteroid use in ~60% for presumed cellular immune response.

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- There were no discontinuations from the study due to the occurrence of adverse events.
- Two treatment-related SAEs (duodenal ulcer hemorrhage and associated anemia) occurred in one subject in the setting of corticosteroid use with no concomitant use of gastric acid secretion inhibitor.
- No AESIs of thrombotic events, development of FIX inhibitors, hepatic malignancies, or malignancies related to study drug were observed with fidanacogene elaparvovec. No serious AESIs were observed for hypersensitivity reactions (based on hypersensitivity SMQ) and hepatic transaminases (most elevations in hepatic transaminases were mild to moderate and all events resolved with corticosteroid treatment).

Pharmacokinetic Results:

In 17 participants in the Vector Shedding Substudy Analysis Set, [redacted] time to peak concentrations (mean [±SD]) were:

- Plasma:
  - [redacted]
  - Time to peak concentration (mean [±SD]) was 1.2 (0.39) days
- PBMC:
  - [redacted]
  - Time to peak concentration (mean [±SD]) was 7.4 (22.22) days
- Semen:
  - [redacted]
  - Time to peak concentration (mean [±SD]) was 3.8 (3.65) days
- Saliva:

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- [redacted]
  - Time to peak concentration (mean [±SD]) was 1.2 (0.44) days
- Urine:
  - [redacted]
  - Time to peak concentration (mean [±SD]) was 1.6 (0.50) days

Similar results for peak vector DNA concentrations and time to peak concentrations in the Dosed Analysis Set were observed.

After reaching the peak within a matrix, vector DNA concentration declined steadily until vector DNA concentration was undetectable (below limit of quantification).

In general, PBMCs were the slowest to clear with a mean (±SD) and median (min, max) time to last undetectable vector of 163.3 (109.44) days and 130.0 (39, 513) days in the 45 participants included in the Dosed Analysis Set:

- Plasma was 98.6 (54.69) days and 93.0 (30, 317) days
- Semen was 41.1 (20.09) days and 35.0 (15, 104) days
- Saliva was 42.4 (17.23) days and 37.0 (29, 105) days
- Urine was 20.4 (13.26) days and 21.0 (4, 87) days

Note: This summary is based on central laboratory data without DNase treatment.

[redacted]

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[redacted]

- **Immunogenicity Conclusions**
  - All participants developed nAb against AAVRh74var capsid following fidanacogene elaparvovec infusion that persisted through the 1-year post-treatment period
  - The development of ADA against AAVRh74var in majority of the participants (95.1%) post fidanacogene elaparvovec infusion did not appear to prevent transduction in the 1-year post-treatment period.

Conclusions:

Fidanacogene elaparvovec has demonstrated a favorable benefit risk assessment in the 45 participants that have been treated as part of this study. It demonstrated hemostatic efficacy as demonstrated by a low ABR, FIX activity in the mild range in over 80% of participants and low rate of infusions along with significant improvements in quality-of-life assessments. It was generally well tolerated including overall liver health in the setting of corticosteroid use in over 60% of participants.

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