



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology**

**Pharmacovigilance Plan Review Memorandum
fidanacogene elaparvovec (BLA 125786/0)**

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STN: Original BLA 125786/0

Product: Proposed brand name: BEQVEZ (fidanacogene elaparvovec)

Proposed indication: Treatment of hemophilia B in patients ≥ 18 years of age
based on an FDA-approved companion diagnostic.

Sponsor: Pfizer, Inc.

Action Due Date: April 26, 2024

1. INTRODUCTION

Objectives and Scope

The sponsor, Pfizer, Inc., submitted an original BLA 125786/0 on April 28, 2023, seeking licensure for the product with proposed proprietary name BEQVEZ for the treatment of hemophilia B in patients ≥ 18 years of age, based on companion diagnostic seeking simultaneous approval. The companion diagnostic is a (b) (4) which, upon marketing authorization and commercialization, will be used to screen candidates for BEQVEZ treatment eligibility.

BEQVEZ is also referred to as fidanacogene elaparvovec in the submission.

The purpose of this memorandum is to review the pharmacovigilance plan proposed by the sponsor for postmarketing safety monitoring and to identify potential safety concerns that may require further additional postmarketing safety surveillance, studies, or other pharmacovigilance activities if the product, BEQVEZ, is licensed.

Product Description

BEQVEZ is a recombinant adeno-associated viral (AAV) vector that uses AAVRh74var capsid derived from naturally occurring AAV serotype (Rh74), containing (b) (4) encoding the human coagulation factor IX (FIX) transgene modified to a high-specific factor IX activity variant known as FIX-R338L human factor IX variant FIXR338L to deliver a functional human factor IX transgene.

This vector-based gene therapy is a fluid concentrate for infusion, with each mL of the product containing 1×10^{13} vector genomes (vg) of fidanacogene elaparvovec. The proposed recommended single dose is 5×10^{11} vector genomes per kilogram (vg/kg) of body weight.

This gene therapy is designed and expected to introduce a functional copy of a high-activity variant of the factor IX gene (FIX-R338L) in the transduced cells to address the underlying deficiency in patients with hemophilia B.

Per the sponsor, fidanacogene elaparvovec is a “non-replicating” recombinant AAV vector that delivers “a stable, fully functional human factor IX transgene” and the AAVRh74var capsid derived from the Rh74 AAV is “not known to cause disease in humans.”

Mechanism of action

Patients with hemophilia B are at risk for bleeding into muscles and joints, leading to arthropathy over time, and for mucosal bleeds and associated anemia. BEQVEZ introduces a functional copy of a high-activity variant of the factor IX gene (FIX-R338L) in the transduced cells to address the monogenic root cause of hemophilia B, providing an alternative active source of factor IX protein that is secreted into the plasma with the expectation of restoring hemostasis.

Of note, several types of adverse events (AEs) have been seen with products with similar indications and mechanisms of action as BEQVEZ. Liver function abnormalities have been seen in other clinical trials for AAV vectors targeting liver cells for transduction. Vector capsid sequences trigger a cytotoxic T cells immune reaction which can lead to selective transduced hepatocyte death, and transaminase increase. Corticosteroids are used as treatment and patients may experience adverse events associated with use of corticosteroids. Finally, inhibitory antibodies may form to the AAV capsid and to the Factor IX, leading to decreased efficacy.

Proposed indication

The indication sought is for treatment of hemophilia B in patients ≥ 18 years of age, based on FDA-approved companion diagnostic.

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the applicant for the final agreed-upon indication after FDA review.

Regulatory and Development History

The initial IND (IND 016437) was received by the FDA on April 10, 2015. Fidanacogene elaparovect was granted orphan designation on September 21, 2015, Breakthrough Therapy designation on July 15, 2016, and Regenerative Medicine Advanced Therapy designation on February 02, 2018.

SPARK Therapeutics LLC was the original sponsor (submitted IND 016437) until July 10, 2018 – Pfizer Inc. has been the sponsor since July 10, 2018.

On April 28, 2023, the sponsor, Pfizer Inc., submitted BLA 125786 for licensure of BEQVEZ in the US.

This product is not approved anywhere in the world.

2. MATERIALS REVIEWED

Materials reviewed in support of this pharmacovigilance plan assessment are listed below.

Original BLA submission

STN 125786/0

- Module 1.16.1: Pharmacovigilance Plan/Risk Management Plans
- Module 1.14.1.2: Draft Labeling (annotated draft labeling)
- Module 2.5: Clinical Overview
- Module 2.7.4: Summary of Clinical Safety
- Module 5.3.5.1: Clinical trial C0371002 study report body

STN 125786/0/14

- Module 5.3.5.1 and 5.3.5.3: Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication - 4-Month Safety Update Report (dated August, 25 2023)

STN 125876/0/32

- Module 1.11.3: Clinical Information Amendments - IR Response dated December 21, 2023 to IR dated December 15, 2023, requesting milestone dates for post authorization study C0371007.

STN 125785/0/47

- Module 1.11.3: Clinical Information Amendments - IR Response dated February 12, 2024 to IR dated February 08, 2024, requesting clarification regarding additional adverse events during the 4-Month Safety Update.

3. CLINICAL STUDIES

OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our focused review of the applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA be approved.

In support of the BLA submission, the sponsor submitted safety data from an ongoing pivotal Phase 3 safety/efficacy clinical trial: "C0371002."

Study Description

This study, titled "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 \leq 2%) (BeneGene-2)," involved 45 patients ages 18-62 years of age treated with a single intravenous infusion dose of 5×10^{11} vg/kg body weight fidanacogene elaparvovec (safety population).

Study duration: The study was initiated on July 29, 2019, and was ongoing at the time of submission of the BLA. The interim data has a database lock point of November 16, 2022. Study duration for each patient is 6 years post single dose administration of fidanacogene elaparvovec, followed by enrollment in a planned long-term follow up study (C0371007) for at least an additional 15 years. At the time of submission (data lock point November 16, 2022), median duration of followup was 2.06 years (range 0.4 and 3.2 years) with 41 patients having completed 15 months of followup.

Key inclusion criteria:

- Male
- Completion of at least 6 months of routine FIX prophylaxis therapy during the lead-in study (C0371004)) at time of screening
- Documented moderately severe to severe hemophilia B, defined as FIX:C \leq 2%.
- Suspension of prophylaxis therapy for hemophilia B after administration of the study intervention (FIX replacement therapy allowed as needed)
- Hemoglobin \geq 11 g/dL
- Platelets \geq 100,000 cells/ μ L
- Creatinine \leq 2.0 mg/dL

- Abstinence (on long term and persistent basis) from heterosexual or homosexual intercourse, agreement to either remain abstinent or use contraceptive barrier, and to not donate sperm

Key exclusion criteria:

- Anti-AAVRh74var nAb titer $\geq 1:1$ (i.e., positive for neutralizing antibodies (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.
- Sensitivity to heparin
- Heparin induced thrombocytopenia
- Chronic infection or other chronic disease that investigator deems as an unacceptable risk
- Liver disease, as defined by pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy
- ALT, AST, ALP $> 2 \times \text{ULN}$, based on central laboratory results
- Bilirubin $> 1.5 \times \text{ULN}$ (isolated bilirubin $> 1.5 \times \text{ULN}$ was acceptable if bilirubin was fractionated and direct bilirubin $< 35\%$), based on central laboratory results
- Previous administration of a gene therapy
- Active hepatitis B or C; HBsAg, HBV-DNA positivity, or HCV-RNA positivity

Safety endpoints:

The safety population consists of all 45 participants. Safety endpoints consisted of incidence and severity of adverse events for study duration of 6 years after fidanacogene elaparovvec infusion, including 1) laboratory data demonstrative of immunogenicity and immune response to AAV capsid protein and/or to FIX transgene, including neutralizing antibodies against vector capsid or the transgene (i.e. viral derived factor IX), and 2) adverse events of special interest including hypersensitivity reactions, clinical thrombotic events, FIX inhibitors, hepatic malignancies, drug related elevated hepatic transaminases that fail to improve or resolve, and malignancy.

Safety Review Study C0371002

Treatment Emergent Adverse Events (TEAEs)

AEs that occurred during or after drug product infusion (Day 1 to Month 24) were considered TEAEs. There were 205 total TEAEs reported in 38 participants (84.4%) during the study, including 14 SAEs in 7 participants. No TEAEs lead to study discontinuation.

The most common TEAEs experienced (by ≥ 5 patients) were alanine aminotransferase increase in 12 (26.7%) participants, arthralgia in 8 participants (17.8%), nasopharyngitis in 8 participants (17.8%), COVID-19 in 6 participants (13.3%) and headache in 6 participants (13.3%).

Reviewer Comment: Transaminase elevations are an expected AE as a manifestation of toxicity associated with hepatic transduction. The other AEs are non-specific.

Serious Treatment Emergent Adverse Events

There were 14 SAEs experienced by 7 participants. Two events of anemia associated with 2 events of duodenal ulcer were reported in 2 patients (4.4%), as described below:

- Dizziness and fatigue on day 96 and found to have low hemoglobin and duodenal ulcer bleed documented by endoscopy on day 97; resolved by day 106. These AEs were considered unrelated to study drug and considered related to corticosteroids administered for treatment of underlying condition. Outcome was reported as resolved.
- Anemia in context of duodenal ulcer/upper GI hemorrhage reported on day 127 when patient presented with abdominal pain, melena (non-serious), and dizziness (non-serious). Endoscopy showed gastritis, duodenitis, and peptic ulcer disease likely associated with corticosteroid use without use of gastric acid secretion inhibitor; these events were reported as resolved by day 129. Outcome reported as resolved.

The additional 10 SAEs occurred once, including upper gastrointestinal hemorrhage (associated with anemia as described above), drug induced liver injury (see Table 1 below), COVID-19, COVID-19 pneumonia, pilonidal disease, alcohol poisoning, femoral neck fracture, coagulation factor IX decreased, hypokalemia, and seizure.

There were no deaths reported in study C0371002 as of data cut off point of November 16, 2022.

Reviewer comment: While DPV agrees that the serious events of duodenal ulcer and anemia were likely unrelated directly to the product, the events are likely related to product administration. Use of corticosteroids to mitigate product-related hepatotoxicity without protecting the gastrointestinal (GI) mucosa with a gastric acid secretion inhibitor proton pump inhibitor is a risk factor for duodenal ulcer, which can cause GI bleeding and resultant anemia. Of note, the proposed product label advises practitioners to refer to corticosteroid product information for precautions regarding use of corticosteroids.

Adverse Events of Special Interest

There were 6 (13.3%) participants with AEs of 'hepatic function abnormal' and 1 (2.2%) participant who experienced 'liver function test abnormal.' AEs related to hepatic injury are summarized in the table below:

Table 1. AEs Associated with Hepatic Injury in Study C0371002

Patient ID	TEAEs	Outcome	Days post BEQVEZ / Comments
(b) (6)	Alcohol poisoning	Resolved	Alcohol poisoning (with ALT and AST elevation) due to alcohol

			abuse on day 634 (b) (6); resolved by day 635. Unrelated to study drug.
(b) (6)	<p>Drug induced liver injury</p> <p>Anemia</p> <p>Duodenal ulcer/upper gastrointestinal hemorrhage</p>	Resolved	<p>Serious drug induced liver injury started on day 105, in patient with underlying hepatic steatosis, concurrent azithromycin, and acetaminophen treatment, for non-serious upper respiratory infection; liver function was reported as not impacted; reported as resolved by day 113.</p> <p>Anemia in context of duodenal ulcer/upper GI hemorrhage reported on day 127 when patient presented with abdominal pain, melena (non-serious), and dizziness (non-serious), and endoscopy showed gastritis, duodenitis, and peptic ulcer disease associated with corticosteroid use without use of gastric acid secretion inhibitor; these events were reported as resolved by day 129.</p>
(b) (6)	<p>COVID-19</p> <p>COVID-19 pneumonia</p> <p>Coagulation factor IX level decreased</p> <p>Liver function test</p> <p>Abnormal (non-serious TEAE of special interest)</p>	Resolved	<p>Nonvaccinated for COVID 19, acquired COVID-19 diagnosed on day 75, and COVID-19 pneumonia onset on day 81, treated with COVID-10 monoclonal antibody, casirivimab, and imdevimab, and moxifloxacin, and reported as resolved by day 100, with COVID-19 negative PCR on day 127; biologically plausibly and mechanistically unrelated to study treatment.</p> <p>Coagulation FIX level decreased on day 304 (2% on day 304 compared to 21% on day 212), believed per sponsor to have been due to "second delayed immune response to the vector causing loss of the transgene," treated with methylprednisolone/ corticosteroid taper and, reported by investigator as unrelated to study treatment; outcome was reported as resolved by day 410.</p>

			Non-serious event of liver function test abnormal on day 20 in patient with preexisting fatty liver and abnormal liver echotexture and hepatic steatosis, treated with corticosteroids, and reported as resolved by day 31.
(b) (6)	Hepatic function abnormal (non-serious TEAE of special interest)	Resolved	Non-serious mild increase in both ALT and AST initially after treatment and subsequent upward trend of ALT levels, reported on day 94 in patient with past history of hepatitis B, and chronic hepatitis C; treated with corticosteroid taper, and hepatic function returned to baseline and reported as resolved by day 115; deemed by investigator as unrelated, although based on review, contributory role of underlying hepatic disease or possible association with study treatment cannot be conclusively ruled out.
(b) (6)	Hepatic function abnormal (non-serious TEAE of special interest)	Resolved	Non-serious elevation of hepatic function tests (ALT and AST) on day 44, treated with corticosteroid taper and reported as not having impacted liver function clinically, no further levels over upper limit of normal reported. Investigator deemed non-serious increased hepatic function test likely related to study treatment; reported as resolved by day 115.
(b) (6)	Hepatic function abnormal (non-serious TEAE of special interest)	Resolved	Non-serious elevation of hepatic function tests (ALT and AST) on day 11, treated with corticosteroid, and reported as resolved by day 37. Levels increased again by day 44, and corticosteroid treatment continued and event was reported as resolved by day 176. Levels increased again by day 207 (8 days post completion of corticosteroid taper) and subsequently decreased without further corticosteroid administration and event was

			reported as resolved by day 214. Per the report the episodes of hepatic function abnormality did not appear to impact liver function clinically.
(b) (6)	Hepatic function abnormal (non-serious TEAE of special interest)	Resolved	Non-serious elevation of hepatic function tests (ALT and AST) on day 25, treated with corticosteroid and reported as resolved by day 33. Investigator deemed non-serious increased hepatic function as mild and likely related to study treatment.
(b) (6)	Hepatic function abnormal (non-serious TEAE of special interest)	Resolved	Non-serious elevation of hepatic function tests (ALT) on day 30, treated with corticosteroid and reported as resolved by day 84. Investigator reported event as not affecting liver function clinically and deemed non-serious increased hepatic function as mild and likely related to study treatment.
(b) (6)	Hepatic function abnormal (non-serious TEAE of special interest)	Resolved	Non-serious elevation of hepatic function tests (ALT and AST) on day 72 in patient with history of hepatitis C; event treated with corticosteroid and reported as resolved by day 132. Investigator reported event as mild and likely related to study treatment.

No additional AESIs occurred during the study.

Reviewer comment: Hepatic injury with transaminase increase was the most common AESI. Elevations of transaminases were mild, expected based on mechanism of action (transduction of FIX producing liver cells), resolved with corticosteroid treatment, and did not impact liver function clinically.

4. 120-DAY (4-MONTH) SAFETY UPDATE REPORT

A 120-Day Safety Update was submitted for the interval between the initial DLP of November 16, 2022 and a cutoff date of April 3, 2023. Through April 3, 2023, the median follow up post BEQVEZ administration for patients in Study C0371002 was 2.43 years (range 0.8 year to 3.6 years). No deaths or patient discontinuations have been reported.

The Safety Update reported 1 additional non-serious TEAE, consisting of osteonecrosis in 1 participant. The patient had underlying hemophilic arthropathy and limb asymmetry since 2019 and with no additional medical history provided. The patient experienced non-serious osteonecrosis 1099 days post BEQVEZ administration for which no treatment was administered, and which was reported as not resolved at the time of 120-Day Safety Update data cutoff.

Reviewer comment: The single additional event of non-serious osteonecrosis in this patient with hemophilic arthropathy, reported in the safety update report is biologically and mechanistically unlikely related to BEQVEZ. Osteonecrosis is likely associated with underlying hemophilic arthropathy.¹ The 4 month safety update report does not raise new safety concerns.

5. SPONSOR-PROPOSED PHARMACOVIGILANCE PLAN

The pharmacovigilance plan (PVP) (version 1, dated April 19, 2023) proposed by the sponsor is summarized in Table 2, below.

The sponsor's proposed routine pharmacovigilance includes collection and reporting of AEs, and submission of findings and evaluations communicated in periodic adverse experience reports based on regulatory guidelines in accordance with CFR 600.80, review of individual case reports, followup of AEs, literature reviews, signal identification and evaluation and communication of risk to prescribers and patients.

Table 2. Safety Concerns and Sponsor Proposed Risk Mitigation Plan

Type of Concern	Safety Concern	Planned Pharmacovigilance Activity/Risk Minimization
Important Identified	None	None
Important Potential	Hepatotoxicity	Routine pharmacovigilance Ongoing pivotal study (C0371002) and long-term followup studies (including C0371017, C0371007) [†] Monitoring for and management of transaminase elevations are included in label section 2 Dosage and Administration, 2.2 Preparation and Administration (Monitoring Post-Administration)

¹ Dobón M, Lucía JF, Aguilar C, Mayayo E, Roca M, Solano V, Peña A, Giralto M, Ferrández A. Value of magnetic resonance imaging for the diagnosis and follow-up of haemophilic arthropathy. Haemophilia. 2003 Jan;9(1):76-85

Important Potential	FIX Inhibitor Development	<p>Routine pharmacovigilance</p> <p>Ongoing pivotal study (C0371002) and long-term followup studies (including C0371017, C0371007) [†]</p> <p>Instructions for management included in label section 2 Dosage and Administration, 2.2 Preparation and Administration (Monitoring Post-Administration)</p>
Important Potential	Embolic and Thrombotic Events	<p>Routine pharmacovigilance</p> <p>Ongoing pivotal study (C0371002) and long-term followup studies (including C0371017, C0371007) [†]</p>
Important Potential	Enhanced Risk of Malignant Transformation Leading to Cancer	<p>Routine pharmacovigilance</p> <p>Ongoing pivotal study (C0371002) and long-term followup studies (including C0371017, C0371007) [†]</p> <p>Risk of malignancy is discussed in the label sections 5 Warnings and Precautions (5.3 Malignancy)</p>
Important Potential	Transmission of Vector to Third Parties (Horizontal Transmission)	<p>Routine pharmacovigilance</p> <p>Systematic collection and monitoring of vector shedding data and AEs via ongoing pivotal study (C0371002)</p> <p>Instructions for minimization of risk of transmission included in label section 2 Dosage and Administration, 2.2 Preparation and Administration (Precautions to Be Taken After Handling or Administering the Medicinal Product)</p>
Important Potential	Germline Transmission	<p>Routine pharmacovigilance</p> <p>Systematic collection and monitoring of vector shedding data and AEs via ongoing pivotal study (C0371002)</p> <p>Risk mitigation labeling included in Dosage and Administration, 2.2 Preparation and Administration (Precautions to Be Taken</p>

		After Handling or Administering the Medicinal Product) Contraception is discussed in label Section 8 Use in Specific Populations (8.3 Females and Males of Reproductive Potential)
Missing Information	Long-Term Effect	Routine pharmacovigilance Ongoing pivotal study (C0371002) and long-term followup studies (including C0371017, C0371007) [†]
Missing Information	Use in Patients with Severe Hepatic Impairment	Routine pharmacovigilance
Missing Information	Use in Female Patients	Routine pharmacovigilance

Source: PVP plan submission BLA 125786/0 Module 1.16.1 Pharmacovigilance Plan dated April 19, 2023.

[†]Studies:

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

C0371007: A multi-country, non-interventional, observational, cohort study to describe long-term safety and effectiveness of fidanacogene elaparvovec for the treatment of hemophilia B in a real-world setting

C0371017: A Phase 3, non-investigational product, multi country, low-interventional cohort study to describe the long-term safety and effectiveness of a prior single-dose treatment with investigative giroctocogene fitelparvovec or fidanacogene elaparvovec in participants with hemophilia A or hemophilia B, respectively

Postmarket Studies

Following approval, additional safety information for BEQVEZ will be available from the ongoing pivotal study C0371002. Additionally, safety information for BEQVEZ, including regarding the important potential risks of hepatotoxicity, FIX inhibitor development, embolic and thrombotic events, and enhanced risk of malignant transformation leading to cancer, will be accrued from planned long-term followup study C0371017 and planned PASS study C0371007.

Study C0371017 – A Phase 3, non-investigational product, multi country, low-interventional cohort study to describe the long-term safety and effectiveness of a prior single-dose treatment with investigative giroctocogene fitelparvovec or fidanacogene elaparvovec in participants with hemophilia A or hemophilia B, respectively. This will be a long-term safety and efficacy study of giroctocogene fitelparvovec or fidanacogene elaparvovec in patients who have received treatment through participation in Pfizer-sponsored clinical trial(s). In addition to primary safety objective of assessment important potential risks (thromboembolic events, factor inhibitor development, hepatic malignancy, liver abnormalities) and secondary safety objective of incidence of other potential safety (non-hepatic malignancy, autoimmune disorders, SAEs, and all-cause mortality), the study has an exploratory safety objective of incidence of hepatic AAV vector integration. The anticipated total patient enrollment (study size) will depend on total number of patients that receive the corresponding product in ongoing phase 1/2 and 3 clinical trials, and is anticipated to be approximately 250 patients. This study will

follow patients through 15 years post receiving the corresponding study product in clinical trials. Proposed study completion date is March 2038.

Post Authorization Safety Study (PASS) C0371007

The sponsor has submitted a post authorization safety study, PASS C0371007, as a voluntary study.

The sponsor provided the following milestone dates for this PASS on 12/21/2023:

Final Protocol Submission: November 31, 2024

Study Completion Date: December 31, 2044

Final Report Submission: December 31, 2045 (12 months after study end, 6 months after study end if any pediatric patients are enrolled in the study)

Study description: PASS C0371007, “A multi-country, non-interventional, observational, cohort study to describe long-term safety and effectiveness of fidanacogene elaparvovec for the treatment of hemophilia B in a real-world setting,” will follow and evaluate safety for a minimum of 15 years in patients who have been treated with BEQVEZ. The study will be descriptive and no formal hypothesis will be tested.

Study population: The study is anticipated to enroll 2 cohorts, one consisting of 220 patients who have received BEQVEZ, and the other consisting of 1,320 patients with hemophilia B who have not received gene therapy, in a 1:6 ratio (i.e. 1 patient in the BEQVEZ cohort to 6 patients in the gene therapy untreated patients). The sponsor’s rationale for the BEQVEZ study size of 220 is based on epidemiology/incidence of severe hemophilia B and expected number of patients that may be eligible for treatment in the postmarketing setting, per the sponsor. The sponsor also states that, given that actual uptake of BEQVEZ in routine clinical practice may vary, the study size for the BEQVEZ cohort may range from 150 to 300 patients; enrollment in the gene therapy untreated cohort will remain fixed at an anticipated 1,320 patients.

Study enrollment is to begin once BEQVEZ has become commercially available in the US, following the first patient enrollment in the US. Each enrolled patient will be followed for 15 years from time of enrollment, and given a 5-year enrollment period, those who are enrolled at the beginning of the enrollment period may be followed for up to 20 years.

Safety objectives: The primary safety objective is determination of incidences of hepatotoxicity, thromboembolic events, FIX inhibitor, and hepatic malignancy in patients with hemophilia B treated with BEQVEZ and in patients with hemophilia B not exposed to gene therapy. The secondary safety objective is determination of the incidences of autoimmune disorders, liver abnormalities, non-hepatic malignancy, hypersensitivity reactions (including infusion-related reactions), and other serious adverse events (SAEs) and all-cause mortality in patients with hemophilia B treated with approved fidanacogene elaparvovec and in patients with hemophilia B not exposed to gene therapy.

Key inclusion criteria:
BEQVEZ treated cohort

No inclusion criteria other than having received BEQVEZ and having signed informed consent.

Gene therapy untreated cohort[†]

Moderately severe to severe hemophilia B (FIX: $\leq 2\%$).

Previous exposure to FIX replacement products for more than 50 exposure days (consistent with the “previously treated patient (PTP)” criterion employed for the Gene therapy program).

Currently receiving or intended to receive routine prophylaxis regimen.

Not treated with BEQVEZ or any other gene therapy product.

[†]Note: Patients in the gene therapy untreated cohort who receive BEQVEZ during the follow-up period may be switched to the BEQVEZ cohort. Patients who received a gene therapy other than BEQVEZ will be discontinued from the gene therapy untreated cohort and from the study.

Key exclusion criteria:

Current or prior history of inhibitor or hypersensitivity to FIX replacement products

History of hepatocellular carcinoma

History of unstable liver or biliary disease defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, and/or cirrhosis.

Analysis plan: Safety data analysis will be descriptive and no hypothesis will be tested. Time to first occurrence of the event will be calculated for certain safety outcomes such as malignancy and all-cause mortality. The distribution of time to first occurrence of the event will be estimated using the Kaplan-Meier (KM) method. Per the sponsor, interim reports will be prepared annually from the PASS C0371007 start for the BEQVEZ cohort and the for the gene therapy untreated cohort after the date of market authorization in US or EU (whichever is first). Final analysis will be included in the final study report, anticipated to be completed by 2045.

Reviewer comment: The sponsor’s rationale for the proposed anticipated number of study participants (220) is based on epidemiology/incidence of hemophilia B and the expected number of patients that may be eligible for treatment in the postmarketing setting, taking into account a possible 50% market share given the existence of a licensed gene therapy in the market. Search of literature regarding the epidemiology of hemophilia B noted prevalence values consistent with those provided by the sponsor.^{2, 3, 4}

6. REVIEW OF THE SPONSOR’S PHARMACOVIGILANCE PLAN

² Quintana Paris L. Foundations of hemophilia and epidemiology. Blood Coagul Fibrinolysis.2023;34(S1):S35-S36.

³ <https://www.ncbi.nlm.nih.gov/books/NBK560792/> accessed 09/25/2023.

⁴ <https://www.cdc.gov/ncbddd/hemophilia/features/keyfinding-hemophilia-occurrence-us.html> accessed 09/25/2023

The Pharmacovigilance Plan (PVP) (dated August 23, 2021) includes the sponsor's assessment of identified and potential risks and missing information based on the pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information. Review of the safety data did not suggest any additional safety concerns not addressed by the sponsor's proposed PVP.

The applicant has outlined the important identified and potential risks as well as the areas of missing information in the safety specifications in the BEQVEZ pharmacovigilance plan. The applicant has proposed labeling which provides information on the risks and instructions on post-administration monitoring. Additionally, the applicant has proposed the actions outlined and discussed below.

Important Identified Risks

None

Important potential Risks

Hepatotoxicity

AAV vectors transduce hepatic cells, which is where FIX production occurs. Vector capsid sequences trigger immune mediated injury of hepatocytes via cytotoxic T cells immune reaction which can lead to selective transduced hepatocyte death and resultant liver function test abnormalities.

While transaminase elevations were detected in study participants, they generally did not affect liver function clinically, and resolved with administration of corticosteroids.

Labeling and patient education will be used to minimize the risk of hepatotoxicity. Per the proposed label, transaminase levels and Factor IX activity are to be monitored and corticosteroid treatment instituted in response to elevations in LT or decrease in FIX. Corticosteroid treatment would occur when elevation of AST/ALT beyond the patient's baseline value is detected. A single transaminase increase ≥ 1.5 fold of the lowest transaminase value since screening into the study and prior to infusion, or consecutive increases (an increase in transaminase on two subsequent blood tests independent of FIX:C values), would constitute an 'elevation.' Treatment with corticosteroids is also recommended if there is a single significant FIX:C decrease not associated with a recent infusion of external FIX product, or consecutive FIX:C decreases (indicated by a decline in FIX activity on two consecutive blood tests independent of transaminase values) if occurring during the first 120 days post-infusion of external FIX product.

Routine pharmacovigilance as well as ongoing pivotal clinical trial C0371002 and long-term followup studies C0371017 and C0371007 are expected to further evaluate and characterize the risk of hepatotoxicity.

The planned pharmacovigilance activities are adequate.

Factor IX inhibitor development

Per the proposed label, Factor IX activity will be monitored based on clinical observation and with laboratory tests (assays) to detect FIX inhibitors if bleeding is not controlled or plasma FIX activity level decreases.

The label discusses Factor IX assays under section 5.4 Monitoring Laboratory Tests.

Routine pharmacovigilance as well as ongoing pivotal clinical trial C0371002 and long-term followup studies including studies C0371017 and C0371007 are expected to further evaluate and characterize the risk of Factor IX inhibitor development.

The planned pharmacovigilance activities are adequate.

Thromboembolic events

There were no reports of thromboembolic events in participants in the clinical trial and administration of BEQVEZ did not result in levels of FIX activity above the threshold (>150% of normal FIX activity) that would raise concern regarding increased risk of thromboembolic events.

Routine pharmacovigilance as well as ongoing pivotal clinical trial C0371002 and long-term followup studies C0371017 and C0371007 are expected to further evaluate and characterize the risk of risk of thromboembolic events.

The planned pharmacovigilance activities are adequate.

Factor IX inhibitor development

There were no cases of inhibitor development. Routine pharmacovigilance as well as ongoing pivotal clinical trial C0371002 and long-term followup studies C0371017 and C0371007 are expected to further evaluate and characterize the risk of Factor IX inhibitor development.

The planned pharmacovigilance activities are adequate.

Enhanced risk of malignant transformation leading to cancer

There were no cases of hepatic carcinoma or other malignancy in the clinical trial. The potential risk is related to vector integration into the host cell DNA; although there is a presumed greater potential for integration into liver cells given the liver is the tissue targeted for transduction, animal studies⁵ suggest that there may be potential for integration into cells of other tissues.⁶

Vectors that have chromosomal integration can be a risk for tumor formation by causing insertional mutagenesis and an alteration of host cell regulation. Per the sponsor, this product leverages a non-replicating recombinant AAV vector. Recombinant AAV vectors remain primarily in episomal form in the nucleus of the transduced cells. While these

⁵ Sabatino DE, Bushman FD, Chandler RJ, et al. Evaluating the state of the science for adeno-associated virus integration: an integrated perspective. *Molecular Therapy* 2022;30(8):2646-2663

⁶ Gaillard C. Gene transfer vector biodistribution: pivotal safety studies in clinical gene therapy development. *Gene Ther.* 2004 Oct;11 Suppl 1:S98-S108.

vectors do not have site-specific integration, there can be a low level of chromosomal integration at random sites.^{7,8,9}

Ongoing pivotal clinical trial C0371002 and long-term follow-up studies C0371017 and C0371007 are expected to further evaluate and characterize the risk of Factor IX inhibitor development. The 2020 FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (available at <https://www.fda.gov/media/113768/download>) recommends up to 5 years of long term follow up for AAV vectors. As per this Guidance document, gene therapy products that are based on vectors such as AAV that do not have a propensity to integrate or reactivate following latency, generally present a lower risk of delayed adverse events. This recommended 5-year follow-up to assess the risk of malignancy and other latent adverse events will be met by the sponsor's long-term (15-year) post authorization safety study, study C0371007.

Risk of malignant transformation will also be monitored and characterized via routine pharmacovigilance.

The planned pharmacovigilance activities are adequate.

Transmission to third parties (horizontal transmission)

There were no events of vector transmission to third parties during the clinical trial.

The proposed label states that BEQVEZ may be transmitted to others through patient excretions and secretions. Temporary vector shedding of intravenously administered AAV-based gene therapies occurs primarily through urine and feces, and to some extent saliva, mucus, and semen. Per the label, to minimize the risk of transmission to other persons, patients should be instructed regarding proper hand hygiene when coming into direct contact with patient secretions or excretions, and precautions should be followed for 6 months after BEQVEZ infusion, especially for close contacts with immunodeficiency or close contacts who are pregnant.

Routine pharmacovigilance as well as ongoing pivotal clinical trial C0371002 is expected to further evaluate and characterize the risk of Factor IX inhibitor development.

The planned pharmacovigilance activities are adequate.

Germline transmission

Germline transmission was not evaluated as a safety endpoint in the pivotal trial. However, vector shedding, the most likely mechanism by which germline transmission would occur, was assessed and labeled in the Pharmacokinetics section of the product insert. The sponsor noted in the submitted PVP that there were two events of maternal exposure via partner during pregnancy reported during the clinical trial. No pregnancy outcome was available for one event; for the other, the outcome was a live birth with no abnormalities, including any suggestive of germline transmission. Per the sponsor PVP and labeling, male

⁷ Smith RH. Adeno-associated virus integration: virus versus vector. *Gene Ther.* 2008 Jun;15(11):817-22.

⁸ Li H, Malani N, Hamilton SR, et al. Assessing the potential for AAV vector genotoxicity in a murine model. *Blood.* 2011 Mar 24;117(12):3311-9.

⁹ Gil-Farina I, Fronza R, Kaepfel C, et al. Recombinant AAV integration is not associated with hepatic genotoxicity in nonhuman primates and patients. *Mol Ther* 2016 Jun;24(6):1100-05.

patients should refrain from sperm donation, be abstinent or use condom for up to 6 months after receiving BEQVEZ. The label discusses use of contraception in label Section 8.3 Females and Males of Reproductive Potential.

Routine pharmacovigilance will allow for assessment of spontaneously reported cases of germline transmission, and vector shedding will continue to be assessed as an exploratory pharmacokinetics endpoint in ongoing pivotal clinical trial C0371002.

The planned pharmacovigilance activities are adequate.

Missing Information

Long-term effect

Durability of effect and safety will continue to be monitored via the ongoing pivotal clinical trial, and long-term followup studies including studies C0371017 and C0371007, discussed above in this review.

Use in patients with severe hepatic impairment

Use of BEQVEZ is not contraindicated in patients with hepatic impairment. New safety signals and reporting trends will be identified through routine pharmacovigilance and evaluated and communicated to prescribers and patients and reported in periodic adverse events experience reports to the FDA.

Use in female patients

New safety signals and reporting trends will be identified through routine pharmacovigilance and evaluated. Use in females will be documented and any adverse events documented and reported in periodic adverse event experience reports to the FDA.

The planned pharmacovigilance activities for missing information are adequate.

7. DPV CONCLUSIONS

The sponsor's proposed pharmacovigilance plan adequately addresses the safety concerns of potential hepatotoxicity, FIX inhibitor development, embolic and thrombotic events, enhanced risk of malignant transformation leading to cancer, horizontal transmission, and germline transmission, and the missing information regarding long-term effect, via ongoing and long-term follow-up studies discussed above.

The sponsor's proposed plan for routine pharmacovigilance is consistent with 21 CFR 600.80.

The review team determined that this product does not require a Risk Evaluation and Mitigation Strategy (REMS).

8. DPV RECOMMENDATIONS

- Should BEQVEZ be approved, OBPV/DPV agrees with the sponsor's proposed pharmacovigilance plan (dated April 19, 2023), which includes routine pharmacovigilance and adverse event reporting in accordance with 21 CFR

600.80, and a voluntary postmarketing, prospective, observational, multicenter study (C0371007) for 15-year long term follow up (LTFU) of 220 patients who receive treatment with BEQVEZ. Study C0371007 will assess the potential serious risks of vector integration, hepatotoxicity, FIX inhibitor development, embolic and thrombotic events, malignant transformation leading to cancer, horizontal vector transmission, and germline transmission.

- The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) or a postmarketing requirement (PMR) safety study that is specifically designed to evaluate a particular safety issue as a primary endpoint. There is no agreed-upon postmarketing commitment (PMC) safety study for this product.

Please see the final version of the package insert submitted by the sponsor for the final agreed upon language for the label.