Summary Basis for Regulatory Action

Date:	April 25, 2024
From:	Ronit Jolles-Mazor, PhD Review Committee Chair Office of Gene Therapy (OGT) Office of Therapeutic Products (OTP)
BLA STN:	125786/0
Applicant:	Pfizer, Inc.
Submission Receipt Date:	April 28, 2023
Action Due Date:	April 26, 2024
Proper Name:	fidanacogene elaparvovec-dzkt
Proprietary Name:	**BEQVEZ**
Indication:	Treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who: • Currently use factor IX prophylaxis therapy, or • Have current or historical life-threatening hemorrhage, or • Have repeated, serious spontaneous bleeding episodes, and, • Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Clinical Evaluation

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OTP, OCBQ/DMPQ, and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Pre-License Inspection and Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Ronit Mazor, OGT/DGT2 Anurag Sharma, OGT/DGT1 Bo Liang, OGT/DGT1 Jianyang Wang, OGT/DGT1 Iryna Zubkova, OCBQ/DMPQ Wei Wang, OCBQ/DMPQ Jie He, OCBQ/DMPQ Kevin J Matthews, OCBQ/DMPQ Simleen Kaur, OCBQ/DBSQC Wei Tu, OCBQ/DBSQC Kouassi Ayikoe, OCBQ/DBSQC Marie Anderson, OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Kavita Natrajan, OCE/DCEH Megha Kaushal, OCE/DCEH Firoozeh Alvandi, OBPV/DPV Jennifer Chan, OCBQ/DIS Haecin Chun, OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Yuqun (Abigail) Luo, OBPV/DB Harry Houghton, OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Angelo Mao, OPT/DPT2
Clinical Pharmacology	Million Tegenge, OCE/DCEGM
Labeling • Promotional (OCBQ/APLB)	Kristine Khuc, OCBQ/DCM Lisa Stockbridge, OCBQ/DCM
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Consults: Leonid Parunov, OPPT/DH Andrey Sarafanov, OPPT/DH
Advisory Committee Summary	N/A

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1. Introduction

Pfizer, Inc. submitted a Biologics License Application (BLA), STN 125786, for licensure of fidanacogene elaparvovec-dzkt, with the proprietary name of BEQVEZ. BEQVEZ is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who:

- Currently use factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes, and,
- Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.

Hemophilia B is an X-chromosome-linked recessive disease in which coagulation factor IX (FIX) deficiency results in impaired hemostasis and increased bleeding. BEQVEZ is designed to introduce a functional copy of a gene encoding a high activity variant of human Factor IX protein [FIX-Padua (R338L)] to restore FIX activity in hemophilia B patients.

This document summarizes the basis for traditional approval of BEQVEZ. An ongoing pivotal Phase 3 clinical trial (n=45) provides the primary evidence of safety and effectiveness for the treatment of adult patients with Hemophilia B. A completed Phase 1/2a clinical trial provides additional safety data for BEQVEZ and proof-of-concept of efficacy in patients with hemophilia B. The recommendation for approval is based on a demonstration of non-inferior annualized bleeding rate (ABR) compared to routine prophylaxis (RP) with exogenous FIX product administration; a demonstration of an increase in Factor IX activity in the ongoing Phase 3 trial is supportive to the primary efficacy outcome. The risk of BEQVEZ include hepatotoxicity as evidenced by increase in transaminases that may result in decreased FIX activity; this risk may be mitigated by corticosteroid treatment. Other potential risks of BEQVEZ include infusion reactions, malignancy, and the development of inhibitors to Factor IX.

The Applicant has provided substantial evidence of effectiveness and safety based on a single, adequate and well controlled clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical Phase 1/2 study and preclinical studies. The review team recommends traditional approval of this BLA with one Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitment (PMC) listed in Section 11.c of this document.

2. Background

Disease Background

Hemophilia B, is a rare X-chromosome-linked congenital bleeding disorder, caused by mutations in coagulation factor IX (FIX) gene that result in deficiency of FIX. Given the mode of inheritance, the majority of patients are males but more than 50% of patients do not have a known family history of the disease. Hemophilia B occurs at a rate of approximately 3.33 to 5.0 per 100,000 male live births per year globally and a

prevalence of 0.5 to 8.1 per 100,000 men among the male population of Western European countries, the United States (US), and Canada.

Recurrent bleeding into joints (hemarthrosis) and soft tissues, either spontaneous or trauma induced, is the hallmark of hemophilia B. However, bleeding into any organ can occur with life-threatening consequences e.g., intracranial hemorrhage with neurologic sequelae. The clinical phenotype correlates with the severity of the disorder based on residual FIX activity with patients with severe (<1% FIX activity) hemophilia having repetitive, spontaneous bleeds in absence of prophylactic FIX replacement therapy, while patients with moderate (1% to < 5% FIX activity) and mild (5 to < 40% FIX activity) hemophilia have occasional to rare spontaneous bleeding, respectively, and require a greater degree of trauma to manifest bleeding compared to those with severe disease. Chronic complications from bleeding include arthropathy, muscle atrophy, and chronic pain.

A goal of hemophilia B management is prevention of spontaneous bleeds by intravenous (IV) administration of FIX replacement product which transiently raises the circulating FIX activity level to achieve FIX activity in the moderate hemophilia range- an approach termed routine prophylaxis. Treatment of bleeds with exogenous FIX product is termed “on-demand” treatment. Drawbacks for the use of FIX administration include the need for life-long repeated IV administration of FIX product, inhibitor development to FIX necessitating use of alternate agents for control of bleeding, infection, and breakthrough bleeding. Gene therapy for hemophilia B is now an option for patients as an alternative to exogenous FIX replacement therapy in lieu of routine prophlyaxis. There is currently one approved AAV-5 based gene therapy for hemophilia B.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND submission	April 10, 2015
2. Orphan Drug designation granted	September 21, 2015
3. Breakthrough Therapy designation granted	July 15, 2016
4. Regenerative Medicine Therapy designation granted	February 2, 2018
5. Pre-BLA meeting	February 10, 2023
6. BLA 125786/0 submission	April 28, 2023
7. BLA filed	June 26, 2023
8. Mid-Cycle communication	October 19, 2023
9. Late-Cycle meeting	January 10, 2024
10. Action Due Date	April 26 2024

3. Chemistry Manufacturing and Controls (CMC)

The CMC review team concludes that the BEQVEZ manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval. BEQVEZ is a recombinant adeno-associated viral (AAV) vector carrying a genome that encodes the human coagulation factor IX (FIX) R338L variant. BEQVEZ drug product is supplied as a sterile, frozen suspension for infusion containing fidanacogene elaparvovec-dzkt in a phosphate buffer containing (b) (4) excipients in a 2 mL cryogenic vial. Each vial has a nominal fill of 1 mL. The drug product should be stored at -60°C to -90°C.

a. Product Quality

Manufacturing Summary

Fidanacogene elaparvovec-dzkt is produced using (b) (4)

Fidanacogene elaparvovec-dskt is (b) (4)

followed by final filtration and fill of the DP.

Each vial of the DP is designed to deliver 1 mL of BEQVEZ at (b) (4) with a nominal concentration of 1E13 vector genomes (vg) per mL. Each vial also includes 0.3mg Sodium Phosphate (monobasic), 2.2mg Sodium Phosphate (dibasic), 10.5mg Sodium Chloride, 0.01 Poloxamer 188 and water for injection. The drug product is supplied in a clear 2 mL cyclic olefin copolymer vial with pre-assembled elastomeric stopper and plastic, snap-fit cap. The drug product contains no preservative and is for single use only. The secondary packaging is a carton that contains 4-7 vials (depending on the weight and/or the BMI of the patient).

Manufacturing Control strategy

Manufacturing process consistency is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) lot release tests. The manufacturer accepts raw materials based on specified quality attributes, including identity, concentration, and purity and routinely performs tests upon receipt. Each raw material has a corresponding raw material specification and unique tracking identification number. Raw materials derived from animals and humans are used in the establishment of the (b) (4) fidanacogene elaparvovec-dzkt drug substance manufacturing. All raw materials derived from animals are appropriately controlled to ensure the absence of microbial contaminants. The control strategy includes testing of the (b) (4) drug product (DP), (b) (4) materials for microbial contaminants, identity, purity, strength, and potency. (b) (4) DP quality are controlled and characterized by several release tests (see Table 2). These tests include a (b) (4)

(b) (4) . These tests also include (b) (4) potency assays that (b) (4) using an (b) (4) and a (b) (4) In addition, the (b) (4) DP are controlled by several assays measuring the purity of the product. The applicant committed to improve the control of the (b) (4) potency assays by adding negative and positive controls. The post-change revalidation will be provided as a post-marketing commitment and submitted as a supplement.

Process Validation
The validation of the fidanacogene elaparvovec-dzkt (b) (4) manufacturing process has been successfully completed and includes (b) (4) successful process performance qualification (PPQ) batches. All (b) (4) batches met all pre-defined PPQ acceptance criteria. Sanitary processing capability was successfully demonstrated at manufacturing scale by consistently meeting in-process (b) (4) acceptance criteria.

Process validation for the DP manufacturing process was conducted by manufacturing (b) (4) PPQ DP lots that are derived from (b) (4) . In-process (b) (4) were validated at full scale to demonstrate biochemical or physicochemical stability and microbiological integrity of fidanacogene elaparvovec-dzkt over a set period of time, under controlled conditions and in containers representative of those used in manufacturing. Additional validation studies were also performed, including aseptic filling, sterilizing (b) (4) and shipping.

Impurity profile
Impurities can be classified into product-related and process-related impurities. Product-related impurities include (b) (4) products, varying proportion of (b) (4) Process-related impurities may include (b) (4) leachables from process components contacting with (b) (4) used for product manufacturing that are not intended to be present in the final product (b) (4) . Most process-related impurities are removed; however, (b) (4) impurities that may be derived from the (b) (4) cannot be completely removed because they are (b) (4) . The levels of these (b) (4) impurities are controlled by lot release specifications. The typical level of (b) (4) that is derived from the (b) (4) is approximately (b) (4) and (b) (4) derived from (b) (4) is approximately (b) (4). The leachables profile in final product was found below safety concern threshold.

Manufacturing Risks
A science and risk-based approach was used to develop the understanding of fidanacogene elaparvovec-szkt critical risk. The control strategy includes routine elements of ongoing monitoring and controls to ensure a continuous state of control as well as process validation and process verification through lifecycle management. The risk of product contamination with other adventitious agents is minimized by ensuring

adequate control of raw materials, especially those of biological origin that are used in the (b) (4) , and DP manufacturing; testing of the (b) (4) for adventitious agents; and demonstration of robust viral clearance by the (b) (4) process. The risk for Extractables and Leachables that could originate from (b) (4) DP process components other than sterilizing filters and the container closure system was analyzed and appropriate studies were performed to mitigate these risks.

Stability
The DP is stable for 36 months when stored at the recommended temperature of -60° to -90°C. The DS is stable for (b) (4) when stored at (b) (4) temperature of (b) (4) Prior to administration, the DP is diluted in 0.9% sodium chloride and 0.25% w/v human serum albumin (HSA). Once diluted, the DP in the infusion bag protected from light is stable for up to 24 hours at ambient temperatures up to 30°C.

Comparability
Throughout clinical trials the manufacturing process was optimized and scaled up. The current manufacturing process produces the DP with critical quality attributes that are comparable to those of DP lots used in clinical studies.

b. Testing Specifications

Table 2. Drug Product Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance (Clarity)	(b) (4)	(b) (4)
Appearance (Color)		
Appearance (Visible Particulates)		Essentially free from visible particulates
(b) (4)		(b) (4)
Extractable Volume		Not less than labeled volume
(b) (4)		(b) (4)
Poloxamer 188		
(b) (4)		
(b) (4)		
Vector Genome (b) (4)		
(b) (4)		
(b) (4)		
Vector Capsid (b) (4)		
(b) (4)		

(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	(b) (4)	(b) (4)
Factor IX Activity (b) (4)		
Factor IX Expression ((b) (4)		
(b) (4)		
Endotoxin		
Sterility		No Growth Detected

[a] Action limit of (b) (4)

The analytical methods, validations and verifications for BEQVEZ (b) (4) drug product, as well as their acceptance criteria were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. Inspection histories and activities for facilities involved in the manufacture of BEQVEZ are summarized in the table below.

Table 3: Manufacturing Facilities for BEQVEZ

Name/Address	FEI Number	Waiver or Inspection	Justification and Results
Pfizer Wyeth Pharmaceutical Division of Wyeth Holdings LLC 4300 Oak Park Rd. Sanford, NC 27330 USA (b) (4) Drug product manufacturing, primary packaging, and testing	1000110954	PLI	CBER/OCBQ November 2023 VAI
(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) VAI
(b) (4)	(b) (4)	Waiver	ORA/ OPQO (b) (4) VAI
(b) (4)	(b) (4)	Waiver	ORA/ OPQO (b) (4) VAI

Name/Address	FEI Number	Waiver or Inspection	Justification and Results
(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) NAI

ORA-Office of Regulatory Affairs (ORA), PLI- Pre-license Inspection, OPQO- Office of Pharmaceutical Quality Operations, NAI- No Action Indicated, VAI- Voluntary Action Indicated

CBER conducted a PLI of the Pfizer Sanford facility in November 2023. All Form FDA 483 observations were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4). All Form FDA 483 observations were resolved, and the inspection was classified as VAI.

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ORA performed a surveillance inspection of (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI.

e. Container/Closure System

The BEQVEZ is aseptically filled into pre-assembled sterile ready-to-use (b) (4) -closed vials, and (b) (4) sealed and capped. Pfizer performed container-closure integrity testing (CCIT) using a (b) (4) method and a (b) (4) analysis method. All acceptance criteria were met.

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25.20(l). The EA provided an assessment of BEQVEZ environmental exposure based on multiple risk factors including environmental persistence and invasiveness, production of a toxic substance and potential for pathogenicity, generation of (b) (4) during manufacturing or in treated patients, integration and insertional mutagenesis, oncological risk related to residual viral sequence DNA, horizontal transfer of viral genes or genetic elements from patients treated with BEQVEZ to other organisms, spread of shed vector from treated patients to other organisms, release of antibiotic resistance genes from treated patients into the

environment, genetic stability and unintended changes leading to novel viral characteristics, germ line transmission of transgene from treated patients to the general population via transduction of germ cells or transmission of vector in sperm and accidental release of vector (inoculation of non-target organisms, incorrect disposal, etc.). The Agency determined that approval of BEQVEZ will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

In vitro and in vivo pharmacology studies were provided to support this BLA. Transduction of a human hepatocyte cell line in vitro with BEQVEZ led to production of the Padua variant (R338) of human FIX (b) (4) -Padua) which correlated with increased FIX activity measured using a one-stage clotting assay (activated partial thromboplastin time; aPTT). In vivo pharmacology was evaluated using a surrogate BEQVEZ product, AAVRh74var-cFIX-R338L, which expresses a transgene encoding canine factor IX, in a juvenile hemophilia B dog model. Following intravenous (IV) administration of 5 x 10^{11} vg/kg to 5 x 10^{12} vg/kg AAVRh74var-cFIX-R338L, shortening of aPTT and whole blood clotting time was observed throughout the study duration, including at time points 370-547 days after administration. No bleeds were observed in recipient animals.

Several toxicology studies were conducted using a closely related predecessor product, AAVRh74var-(b) (4)-Padua, which is similar to BEQVEZ except the (b) (4) Administration of AAVRh74var(b) (4)-Padua in healthy male mice at either 1.04 x 10^9 vg/animal or 1.93 x 10^9 vg/animal led to a dose-dependent increase in plasma expression of hFIX protein. This increased hFIX protein expression correlated with increased plasma FIX clotting activity. Of the 110 animals included in the study, 20 animals were found dead or euthanized in moribund condition during the study. Six of these unscheduled mortalities were considered related to AAVRh74var-(b) (4)-Padua, based upon anatomic pathology findings in the brain and/or skin. An additional eight mice from groups that received a predecessor product encoding the wild type FIX gene at approximately 3x higher dose level also experienced unscheduled mortalities with similar clinical findings. These findings were interpreted as likely test article-related exacerbations following tissue/vascular injury related to multiple blood collection procedures and administration of the product to healthy animals with endogenous FIX activity. The dose levels in this study were between 10 to 2-fold lower than the recommended human dose level for BEQVEZ, extrapolated based on body weight.

A toxicology study was also conducted evaluating IV administration of AAVRh74var-(b) (4)-Padua in nonhuman primates (NHP) at dose levels ranging from 1 x 10^{12} vg/kg to 5 x 10^{12} vg/kg. Vector administration resulted in detection of hFIX protein expression in plasma and increased mean plasma FIX clotting activity, as determined by aPTT, compared to concurrent controls. Plasma FIX clotting activity peaked 3 weeks post-dosing to 2-4x normal human activity and subsequently declined. Antibodies that targeted the hFIX protein and the AAV capsid were detected in most dosed animals.

The levels of both anti-hFIX and anti-AAV antibodies increased with time, which correlated with a decline in plasma hFIX protein levels. No test article-related adverse findings were observed in this study, including any findings of thrombosis by microscopic histopathology. The dose levels in this study were between 2 to 10-fold higher than the recommended clinical dose level for BEQVEZ.

The biodistribution of AAVRh74var-(b) (4)-Padua was assessed in NHPs. At days 30 and 92 after administration of 5 x 10^{12} vg/kg AAVRh74var-(b) (4)-Padua, vector DNA was detected in all tissues assessed, including the brain and testes. The highest vector DNA concentrations were detected in the liver, spleen, and inguinal lymph nodes. In NHPs administered dose levels from 1 x 10^{12} vg/kg to 5 x 10^{12} vg/kg, dose-dependent vector DNA levels were present in liver through the final time point evaluated, at 542 days after administration.

Shedding of AAVRh74var (b) (4)-Padua in semen was evaluated in healthy (b) (4) rabbits. Vector DNA was detectable in semen until 4 months after dosing. No analysis of potential impact on fertility or transmission to offspring was performed.

Integration site analysis was performed on host genomic DNA isolated from liver tissue collected in juvenile hemophiliac dogs at 1-2 months post-administration of the canine surrogate vector, and in NHPs at 92 days or between 742 – 757 days following administration of BEQVEZ. For both species, most of the identified vector DNA sequences were episomal and were not integrated into the host DNA. In dogs, liver biopsies performed to quantify integration of AAVRh74var -cFIX-R338L DNA found (b) (4) unique integration sites (IS). A low level of integrated vector DNA was distributed throughout the host genome with no clear preference to specific integration sites or genes associated with malignant transformation in humans. In a 2-year vector integration study in NHPs administered 5 × 10^{12} vg/kg, there was no indication that integration of vector DNA into host cell DNA resulted in altered liver function, hepatocellular hyperplasia or carcinoma.

Studies to evaluate the safety pharmacology, developmental and reproductive toxicity, and carcinogenicity/tumorigenicity of BEQVEZ were not conducted. These studies are not warranted based on the product characteristics, results from the biodistribution and toxicology studies, and patient population.

5. Clinical Pharmacology

BEQVEZ is a gene therapy designed to introduce in the transduced cells a functional copy of the factor IX gene encoding a high-activity FIX variant (FIX-R338L, hFIX Padua). The AAVRh74var capsid is able to transduce hepatocytes, the natural site of factor IX synthesis.

The clinical pharmacology of BEQVEZ is supported by two clinical studies (Phase 1/2a # C0371005/ C0371003 and Phase 3 # C0371002). In Phase 1/2a and Phase 3 studies, a single dose of 5×10^{11} vg/kg was administered as intravenous (IV) infusion.

Dose
For subjects with body mass index (BMI) >30 kg/m^2, dose was calculated based on an adjusted body weight that uses a maximum permissible BMI of 30 kg/m^2 (i.e., the actual height is used to achieve a BMI of 30 kg/m^2 for dose calculation). The median dose infused (vg/kg) for subjects with BMI ≤30 kg/m^2 (n=40) was 5×10^{11} vg/kg (range: 4.9×10^{11} to 5.6×10^{11} vg/kg) and the median dose for subjects >30 kg/m^2 (n=20) was 4.9×10^{11} vg/kg (range: 3.1×10^{11} to 6.1×10^{11} vg/kg).

FIX Activity
The pharmacodynamic activity of BEQVEZ was demonstrated by longitudinal monitoring of FIX activity. Comparative analysis of FIX activity for the two studies showed about 2-fold lower FIX activity in the Phase 3 study. In the Phase 3 study (N=45 subjects), post-treatment geometric mean FIX activity from Week 12 to Month 15 was significantly higher than the fixed threshold of 5% as evaluated by three different assays. There is a trend of higher mean FIX activity (Week 12 to Month 15) with age, higher BMI, as well as in White race. Patients 35-62 years old (n=17) had 1.9-fold higher mean FIX activity as compared to patients 18 to <35 years old (n=28). Patients with BMI ≥25 kg/m^2 (n=29) had 1.5-fold higher mean FIX activity as compared to patients with <25 kg/m^2 (n=16). Patients in White race group (n=29) had 1.6-fold higher mean FIX activity as compared to patients in Non-white race group (n=12). A population pharmacodynamic (popPD) model was developed by pooling the FIX activity data from the Phase 1/2 & Phase 3 studies for covariate screening and to provide additional justification on the use of (b) (4) -based dosing of BEQVEZ. The popPD model adequately described the observed FIX activity vs time data up to 2 years following BEQVEZ administration. The popPD analysis is consistent with the results of the observed FIX activity results for both actual and (b) (4) dosing and provided supporting information for (b) (4) -based dosing.

Immunogenicity
The administration of BEQVEZ has the potential to generate immunity in the form of neutralizing antibodies against the vector capsid, the transgene (virus-derived FIX) and as a cellular response against the transduced cells producing FIX. In clinical studies, all patients receiving treatment were required to screen negative for anti-AAVRh74var neutralizing antibodies and negative for FIX inhibitors (<0.6 BU) following a lifetime minimum of 50 exposure days to FIX replacement therapy. No patients developed FIX inhibitors during the clinical studies using BEQVEZ. A sustained increase in neutralizing anti-AAVRh74var antibodies has been observed after administration of BEQVEZ in all subjects who participated in clinical studies and had neutralizing antibody (nAb) assessment. BEQVEZ-treated patients were tested for cellular immune responses to overall capsid pool and overall FIX pool using an IFN-γ enzyme-linked immunosorbent spot (ELISpot) assay. ELISpot results did not show a trend of presumed T-cell response (based on limited positive ELISpot) as a function of time during the 1-year post-infusion period in clinical studies.

Viral Shedding
Vector DNA fully cleared from plasma, saliva, and semen within a mean of 1 to 4 months after BEQVEZ infusion.

Overall, the descriptive subgroup analysis, dose-response, and popPD analysis of FIX activity data support the proposed dosing regimen of BEQVEZ.

6. Clinical/Statistical

The clinical review team's recommendation for traditional approval of BEQVEZ for the treatment of adults with moderate to severe hemophilia B who currently use factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes, and, do not have neutralizing antibodies to adeno-associated virus serotype Rh74var AAVRh74var capsid as detected by an FDA-approved test is based on 2 clinical studies, Study C0371002 (Efficacy and Safety) and Study C0371005 (Safety).

a. Clinical Program

Study C0371005 was a Phase 1/2a, open-label, single-dose, single-arm, multi-center trial to assess safety of BEQVEZ in 15 subjects with moderate or severe hemophilia B (FIX activity ≤2 %) and was used to provide additional safety data.

Study C0371002 is an ongoing prospective Phase 3, open-label, single-dose, multi-national, multi-center trial investigating BEQVEZ administered to 45 adult subjects with moderate to severe hemophilia B (FIX activity ≤ 2%). Subjects completed a lead-in period of at least 6 months while receiving FIX routine prophylaxis therapy in a non-interventional study-Study C0371004. Baseline ABR data was prospectively collected in Study C037004 and in the phase 3 study prior to BEQVEZ administration. These 45 subjects received a single-dose of 5 x 1011 vg/kg body weight of BEQVEZ and are followed in the study for 6 years prior to entering a long-term follow up study of 15 years. Only subjects without neutralizing antibodies to AAVRh74var received BEQVEZ. The median duration of follow-up following administration of BEQVEZ was 2 years (range 0.4 to 3.2 years).

Efficacy was based on ABR during the efficacy evaluation period (EEP) between Week 12 (day 82) to data cutoff after treatment with BEQVEZ compared with ABR during the baseline period. The ABR included treated and untreated bleeds, excluding procedural bleeds. The pre-specified non-inferiority margin on the difference between the mean ABR during the EEP and the mean baseline ABR was 3.0 bleeds/year. The model derived mean ABR was 4.5 bleeds/year (95% CI: 1.9, 7.2) during the baseline period and 2.5 bleeds/year (95% CI: 1.0, 3.9) during post-BEQVEZ EEP, resulting in a difference between the mean post-BEQVEZ EEP ABR and the baseline ABR of -2.1 bleeds/year (95% CI: -4.8, 0.7). The upper bound of the 95% CI in the difference was less than 3.0 bleeds/year, meeting the NI study success criterion. Six of 45(13%) subjects resumed RP with exogenous FIX product starting 0.4 to 1.7 years following BEQVEZ administration. One additional subject had intermittent exogenous factor IX use and had a higher ABR post BEQVEZ (5.0 bleeds/year) compared to baseline (1.2

bleeds/year) with a factor IX activity < 5% (SynthASil assay) starting at 0.4 years. The mean [standard deviation (SD)] FIX activity by the one-stage SynthAsil, chromogenic and one-stage Actin-FSL assays respectively are: 28 (21.3), 15 (13.0), 13 (11.1) at month 6, 27 (25.7), 16 (17.0), 13 (12.8) at month 15, and 25 (22.6), 15 (18.8), 13 (11.9) at month 24.

A companion diagnostic to exclude subjects with pre-existing, neutralizing antibodies to AAVRh74var is approved contemporaneously.

In summary, the basis of FDA's conclusion of substantial evidence of effectiveness comes from a single, adequate and well controlled trial with clinically meaningful results on the benefit of BEQVEZ characterized by the demonstration of non-inferiority of ABR during the EEP compared to baseline ABR. The evidence submitted supports traditional approval of BEQVEZ.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for three foreign and one domestic clinical investigator study sites that participated in the conduct of Protocols C0371004 and C0371002. The inspections did not reveal significant issues that impacted the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

This application is exempt from the Pediatric Research Equity Act because it is intended for a biologic product for which orphan designation has been granted. This product is not indicated in pediatric subjects.

d. Other Special Populations

The efficacy of BEQVEZ has not been studied in any special populations.

7. Safety and Pharmacovigilance

Forty-five subjects in Study C0371002 and 15 subjects in Study C0371005 constitute the safety population for this application. Since the percentage of subjects with hepatic transaminase elevations and consequently corticosteroid use in the 2 studies are different, the safety data are presented separately here and in the prescribing information.

A total of 81 TEAEs were reported in Study C0371005 (Phase 1/2a) none of which were severe. Seven subjects (46.6%; 7/15) in the Phase 1/2a study had elevation in transaminases (defined as ≥ 1.5 x baseline) of which 3 subjects (20%; 3/15) received corticosteroids for transaminase elevation and/or decline in FIX activity. The time to initiation of corticosteroids and duration of therapy was within the range seen in the Phase 3 study.

A total of 205 treatment emergent adverse events (TEAEs) in 38 of 45 subjects in Study C0371002 (Phase 3) were reported. All except 7 were mild or moderate in severity; severe fatigue in one subject was considered related to study product. Increase in transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] reported either as an adverse event or based on protocol-defined laboratory data (defined as ≥ 1.5 x baseline) was the most common adverse event reported. Transaminase elevation by the protocol-defined criteria occurred in 29 subjects (64.4%). Twenty-eight subjects (62%; 28/45) received corticosteroids for transaminase elevation and/or decline in FIX activity. The mean (SD) time to start of first corticosteroid treatment was 45 (30) days and the mean (SD) duration of use was 113 (58.6) days with a range of 41 to 276 days. There were 11 serious adverse events (SAEs) reported in 7 subjects; none of which were related to BEQVEZ.

There were no infusions reactions, malignancy, inhibitors to FIX, thromboembolic events or deaths reported in either trial.

- The applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80. A voluntary postmarketing sponsor study (Study C0371007) will provide long term safety follow up of 220 patients who receive treatment with BEQVEZ. Study C0371007 is a multicenter, prospective, observational, postmarketing study, in which enrolled patients will be followed for 15 years after product administration.
- The available safety data do not indicate a need for a Risk Evaluation and Mitigation Strategy or postmarketing requirement safety study that is specifically designed to evaluate a particular safety issue as a primary endpoint. There is no agreed-upon postmarketing commitment safety study for this product.

8. Labeling

The proposed proprietary name, BEQVEZ, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on July 19, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 31, 2023. The proper name suffix, -dzkt, was designated on January 26, 2024, making (*fidanacogene elaparvovec-dzkt*) the proper name.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, package and container labels on December 14, 2023, and found them acceptable from a promotional and comprehension perspective. The Applicant's proposed indication was revised during labeling negotiations to reflection the population studied in the pivotal trial (see Section 11a).

9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

BEQVEZ has received Orphan Drug, Breakthrough Therapy, and RMAT designations. The submission was reviewed under the standard review timeline.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well controlled trial with supportive evidence form the initial clinical investigation and preclinical studies. The compelling evidence of treatment effect in the single adequate and well controlled trial is based on clinically meaningful benefit in annualized bleed rates in sufficient number of subjects using the subject's own baseline ABR prior to BEQVEZ administration as the control.

The Applicant has met the statutory requirements for traditional approval and the review team recommends traditional approval of BEQVEZ, an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes, and,
- Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test.

b. Benefit/Risk Assessment

BEQVEZ has demonstrated efficacy with reduction in ABRs. The model derived mean ABR was 2.5 bleeds/year (95% CI: 1.0, 3.9) during week 12 to data cutoff compared to mean ABR of 4.5 bleeds/year (95% CI: 1.9, 7.2) during the baseline period resulting in a difference between the mean post-BEQVEZ ABR and the baseline ABR of -2.1 bleeds/year (95% CI: -4.8, 0.7) with met the prespecified NI margin of 3.0 bleeds/year. A majority of the subjects continued to remain off routine prophylaxis with sustained increase in FIX activity compared to baseline.
The most common adverse event was an increase in hepatic transaminases which can be mitigated with use of corticosteroids if deemed to be secondary to immune response to viral capsid with or without decline in FIX activity. No malignancy has been reported to date. Potential risks of infusion reactions, malignancy including risk of hepatocellular carcinoma, inhibitors to FIX and need and caveats for monitoring FIX for loss of efficacy have been adequately described in the prescribing information.

Subjects in clinical trials and those receiving commercial product will be followed in long-term follow up study and hemophilia registries respectively. Subjects with pre-existing neutralizing antibodies to AAVRh74var capsid as detected from the contemporaneously approved companion diagnostic (b) (4) will be excluded from receiving BEQVEZ. The safety profile is acceptable.

Thus, given the magnitude of benefit in the ABR and the fact that risks are generally mild and/or easily mitigated, the overall benefit-risk profile favors approval of BEQVEZ, an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who:

- Currently use factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes, and,
- Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test

c. Recommendation for Postmarketing Activities

- The applicant's pharmacovigilance plan includes 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 of 220 patients who receive treatment with BEQVEZ.
- The review team has determined that the available safety data do not indicate the need for a Risk Evaluation and Mitigation Strategy (REMS) or a postmarketing requirement (PMR) safety study. There is no agreed-upon postmarketing commitment (PMC) safety study for this product.

PMC#1 For method (b) (4) , Pfizer commits to introduce system suitability control materials, including:
a. A (b) (4) product-specific control material starting from the stage of (b) (4) ,
b. A negative control sample starting from the stage of (b) (4) ,
c. A FIX suitability control material for the chromogenic assay, and
d. A FIX suitability control material for the (b) (4) .

Pfizer commits to perform post-change revalidation and a statistically powered equivalence study for the updated method (b) (4) . The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of a "Postmarketing Study Commitment – Final Study Report".
Final Study Report Submission: September 30, 2025