BLA Clinical Review Memorandum

Application Type	Biologic Licensing Application (BLA)
STN	125786
CBER Received Date	April 28, 2023
PDUFA Goal Date	April 26, 2024
Division / Office	DCEH/OTP
Priority Review (Yes/No)	No
Reviewer Name(s)	Kavita Natrajan, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Megha Kaushal, MD, MSc, Acting Branch Chief Benign Hematology Lola Fashoyin-Aje, MD, MPH, Acting DCEH Director, OCE Director
Applicant	Pfizer Inc.
Established Name	Fidanacogene elaparvovec
(Proposed) Trade Name	BEQVEZ
Pharmacologic Class	Gene therapy [adeno-associated virus (AAV) vector based]
Formulation(s), including Adjuvants, etc.	Frozen, light-sensitive solution with nominal concentration of 1 x 10^{13} vg/ml; 1 mL/vial. To be re-constituted with 0.9% sodium chloride and 0.25% human serum albumin for infusion
Dosage Form(s) and Route(s) of Administration	Single-use intravenous infusion
Dosing Regimen	5 x 10^{11} vg/kg body weight. Dose based on adjusted body weight for those with a BMI > 30kg/m^2
Indication(s) and Intended Population(s)	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.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AAV	adeno-associated virus
AAV5	adeno-associated virus serotype 5
AAVRh74var	adeno-associated virus serotype Rh74var
ABR	annualized bleeding rate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BEQVEZ	fidanacogene elaparvovec
BLA	biologics license application
BMI	body mass index
CAG	chicken beta-actin
CDRH	Center for Devices and Radiological Health
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CSA	chromogenic assay
EEP	efficacy evaluation period
FIX	clotting factor IX
FIX:C	circulating levels of FIX
LTFU	long-term follow-up
nAb	neutralizing antibody
NI	non-inferiority
OSA	one-stage assay
PI	package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient-reported outcome
REMS	risk evaluation and mitigation strategy
RP	routine prophylaxis
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
vg	vector genomes

1. EXECUTIVE SUMMARY

On April 28, 2023, Pfizer Inc. (the Applicant) submitted an original Biologics License Application (BLA) for BEQVEZ), seeking approval for the following proposed indication and dosage:

- For the treatment of hemophilia B in patients ≥18 years of age. Selection of patients for treatment will be selected based on an FDA-approved companion diagnostic test for neutralizing antibodies (nAbs) to the viral capsid.
- Dosage: 5×10^{11} vector genomes per kilogram of body weight

Hemophilia B is an X-linked, congenital deficiency of clotting factor IX (FIX) due to a mutation in the *FIX* gene that results in impaired hemostasis. The prevalence is about 1 in 25,000 to 30,000 males. Disease severity is classified by residual FIX activity with severe, moderate, and mild disorder based on FIX activity levels below the lower limit of normal. Recurrent bleeding into the joints is the hallmark of hemophilia, resulting in joint inflammation, chronic arthropathy, and disability. Routine prophylaxis (RP) with FIX products (recombinant or plasma-derived) is the standard of care for subjects with severe hemophilia B and those with moderate hemophilia B with a more severe bleeding phenotype wherein the goal is to prevent or reduce the frequency of spontaneous bleeds, and thus preserve joint function. Recombinant or plasma-derived FIX products are also given to treat a bleeding episode. Drawbacks for the use of FIX products include the need for lifelong, repeated intravenous administration, the occurrence of breakthrough bleeds despite prophylactic administration of product, hypersensitivity reactions, development of antibodies (termed inhibitors) that render administered FIX product ineffective, and risk of infection with plasma-derived products. Hemgenix is the sole currently approved gene therapy for hemophilia B, which can serve as an option for patients as an alternative to exogenous FIX replacement therapy in lieu of RP; however, patients receiving gene therapy may still need use of exogenous FIX in certain situations (e.g., surgery).

Fidanacogene elaparvovec (PF-06838435, hereafter referred to as BEQVEZ) comprises a recombinant adeno-associated virus (AAV) vector (capsid designated as adeno-associated virus serotype Rh74var [AAVRh74var]) and human FIX Padua, a codon-optimized expression cassette that encodes for the naturally occurring FIX variant, FIX Padua, under the control of a liver-specific modified promoter that raises the circulating levels of FIX (FIX:C). FIX Padua is an inherited thrombophilia wherein a gain-of-function variant (R338L) in the *FIX* gene results in increased clotting activity of FIX (~eight times normal) due to a faster rate of factor X activation, but FIX antigen levels are normal.

The Applicant's request approval is based on demonstration of substantial evidence effectiveness and safety in Study C0371002. Study C0371002 was a Phase 3, prospective, open-label, single-dose, multinational study investigating BEQVEZ in adult subjects with severe or moderately severe hemophilia B (FIX activity ≤2%). The primary outcome measure was to demonstrate non-inferiority (NI) in annualized bleeding rate (ABR) for treated and untreated bleeds from Week 12 onward [efficacy evaluation period (EEP)] compared to baseline. Eligible patients were required to have baseline ABR data collected prospectively during a lead-in period of at least 6 months on RP with a FIX product, and not have had preexisting nAbs to AAVRh74var capsid prior to entry into the study. The study enrolled a total of 51 patients. A total of 45 subjects received a single dose of 5×10^{11} vector genomes (vg) per kilogram of body weight of BEQVEZ. The median (min, max) duration of follow-up for all 45 subjects was 2.06 (0.41, 3.23) years. The efficacy evaluable population consisted of all 45 subjects who received BEQVEZ. The model derived mean ABR at baseline was 4.5 bleeds/year (95% confidence interval [CI]: 1.9, 7.2) and 2.5 bleeds/year (95% CI 1.0, 3.9) during the efficacy evaluation period

(EEP). The difference in the mean ABR between the baseline period and the EEP was -2.1 bleeds/year (95% CI: -4.8, 0.7), which meets the NI margin as upper bound of the 95% CI is <3.0 bleeds/year. FIX activity was measured by three different assays. The mean (standard deviation [SD]) FIX activity at Month 15 (n=35) by the SynthASil, chromogenic, and Actin-FSL assays was 27 (25.7)%, 16 (17.0)%, and 13 (12.8.0)%, respectively. The FIX activity was maintained at Month 24 (n=22) with mean (SD) FIX activity at Month 15 by the SynthASil, chromogenic, and Actin-FSL assays being 25 (22.6)%, 15 (18.8)%, and 13 (11.9)%, respectively. Six subjects (13%) were deemed to have lost response to BEQVEZ during follow-up and resumed RP between 0.4 and 1.7 years. An additional subject had intermittent, exogenous factor IX preventative use, a higher ABR of 5.0 bleeds/year in the EEP compared to baseline ABR of 1.2 bleeds/year, with an FIX activity of <5% (SynthASil assay) starting at 0.4 years despite not resuming RP.

The safety evaluable population consisted of 60 subjects who received BEQVEZ at a dose of 5×10^{11} vg/kg in Study C0371002 (n=45) and a Phase 1/2 study, Study C0371005 (n=15). However, safety was analyzed and presented in the label separately for the two studies given differences in hepatic transaminase elevation and use of corticosteroids. In Study C0371002, a total of 205 treatment-emergent adverse events (TEAEs) were reported in 38 (84%) of subjects, with increase in alanine aminotransferase (ALT), arthralgia, and nasopharyngitis being the most common adverse events (AEs). The majority of AEs were mild to moderate in severity; severe AEs occurred in 7 subjects. ALT and/or aspartate aminotransferase (AST) elevation, as defined in the protocol for consideration of corticosteroid therapy, occurred in 29 subjects. Twenty-eight subjects received corticosteroids for transaminase elevation as defined in the protocol and/or decrease in FIX activity. The mean (SD) time to start of the first corticosteroid dose was 45 (30) with a range of 11 to 123 days. The mean (SD) duration of corticosteroid treatment was 113 (58.6) days with a range of 41 to 276 days. All transaminase elevations resolved with corticosteroid therapy. No transaminase elevation was greater than Grade 2. There were 11 serious adverse events (SAEs) in 7 subjects, none of which were related to BEQVEZ and all of which resolved. Two SAEs of upper gastrointestinal hemorrhage with anemia were attributed to corticosteroid therapy in absence of gastric-acid blocking therapy and resolved. Seven of 15 subjects in Study C0371005 had transaminase elevation of ≥1.5×baseline; three subjects received corticosteroids for transaminase elevation and/or decline in FIX activity with time to initiation and duration of corticosteroid use within the range as for Study C0371002. There were no infusion reactions, malignancies, thromboembolism, inhibitors to FIX, or deaths in either study.

Study C0371002 utilized a clinical study cell-based antibody-mediated neutralization assay to assess preexisting nAbs to AAVRh74var. Subjects with a positive titer were excluded from receiving gene therapy. The data for the assay to detect antibodies to AAVRh74var was (b) (4)

No postmarketing requirements (PMRs) post approval are being issued. A chemistry, manufacturing, and controls (CMC) postmarketing commitment (PMC) for introduction of system suitability control materials is being issued. The Applicant will have an extended long-term, follow-up study, Study C0371017, for 15-year follow-up for clinical study subjects. In addition to routine pharmacovigilance, there is also a post-approval, long-term follow-up study, Study C0371007, which is a multicountry, observational, cohort study to evaluate long-term safety and effectiveness of BEQVEZ using real-world data and existing hemophilia registries, wherein subjects are to be followed for 20 years. A risk evaluation and mitigation strategy (REMS) was determined by the clinical review team not to be required for this product.

In summary, 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 that is supported by an early clinical investigation and preclinical studies. The overall benefit-risk assessment is favorable, and the clinical review team recommends traditional approval of BEQVEZ for the treatment of adults with moderate to severe hemophilia B (congenital FIX 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.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1. Demographic Characteristics (Study C0371002)

Parameter	Efficacy Population N=45
Sex, n (%)	-
Male	45 (100)
Age	-
Mean (SD)	33.18 (10.94)
Median (range)	29 (18, 62)
Race, n (%)	-
White	33 (73)
Asian	7 (15.5)
Black	1 (2.2)
Not reported	4 (9)
Ethnicity, n (%)	-
Non-Hispanic or Latino	35 (78)
Hispanic or Latino	2 (4.4)
Not reported	8 (18)

Source: FDA Analysis of ADSL Dataset. Percentages may be rounded to nearest integer
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation

Reviewer Comment:

- *The demographic table reflects all 45 subjects who received a dose of study product in Study C0371002. Four of 45 subjects had a follow-up of less than 15 months but were included in the efficacy analysis.*
- *The inclusion of just one Black subject in the study is an underrepresentation of this population compared to the ~10% of hemophilia B subjects in registry and hemophilia treatment center data (Centers for Disease Control and Prevention 2023).*
- *Older adults are also underrepresented in the study compared to disease prevalence in the group.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.2

☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B is a congenital, X-linked, recessive deficiency of FIX that occurs in approximately 1 in 15,000 to 30,000 live male births (Hoots and Malec 2023). It is the second most common coagulation factor deficiency that results from mutations in the *FIX* gene. The severity of hemophilia B is characterized as either severe, moderate, or mild and is based on the residual FIX activity of <1 IU/dL (international units per deciliter), 1 to <5 IU/dL, or 5 to <40 IU/dL, respectively. The clinical phenotype correlates with the severity of the disorder based on residual FIX activity, with patients with severe hemophilia having repetitive, spontaneous bleeds in the absence of prophylactic FIX replacement therapy while patients with moderate and mild hemophilia have occasional to rare spontaneous bleeding, respectively, and require a greater degree of trauma to manifest bleeding compared to those with severe disease. Although bleeding secondary to hemophilia can occur in any organ, spontaneous bleeding into large joints is most common, followed by soft tissue bleeds. Intracranial hemorrhage, although rare, remains the most feared complication and can occur in individuals of all ages either spontaneously or after trauma (Nelson et al. 1999; Ljung 2008).

Hemophilia B is typically treated with FIX replacement therapy either in response to bleeding, termed as on-demand treatment, or prophylactically to keep FIX levels in the moderate to mild hemophilia range to prevent spontaneous bleeding, termed as RP. All subjects with severe hemophilia and those with moderate hemophilia with a phenotypically severe phenotype are recommended to receive RP to prevent the long-term consequences of repetitive joint bleeding

and for preservation of joint function (Manco-Johnson et al. 2007). RP is burdensome in that it translates into the need for repetitive intravenous infusions and carries risk of infection (Journeycake et al. 2001; Ljung 2007). The most serious complication of exogenously administered FIX replacement therapy is inhibitor development i.e., antibody to FIX replacement product that renders therapy with FIX product ineffective and necessitates the need for immune tolerance induction for eradication of the inhibitor and use of bypassing agents for control of bleeding (Puetz et al. 2014). Inhibitor titers are measured in Bethesda units; inhibitors between 0.6 and <5 Bethesda units are classified as low titer inhibitors, while inhibitor titer of ≥5 Bethesda units is considered a high titer inhibitor. Other complications of FIX replacement therapy include risk of allergic reactions, nephrotic syndrome, and thrombosis. A gene therapy for hemophilia B is now an option for patients (see below) as an alternative to exogenous FIX replacement therapy in lieu of RP but may still necessitate exogenous FIX use in certain situations (e.g., surgery).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Commercially available recombinant or plasma-derived FIX products with viral inactivation serve as exogenous FIX replacement therapy in hemophilia B, with recombinant products serving as the mainstay of treatment. Recombinant products with extended half-life to reduce the burden of more frequent infusions have been developed and include Alprolix (FIX with fusion to Fc domain of monomeric human immunoglobulin), Idelvion (FIX-albumin fusion), and Rebinyn (glycoPEGylated FIX). A list of available products is given below (Table 2).

Table 2. Approved FIX Products

Product	Category	Half-life (Hours)	Year Approved
Alphanine SD	Plasma derived	21-25	1990
Mononine	Plasma derived	23-31	1992
Benefix	Recombinant	23.8	1997
Rixubis	Recombinant	26.7	2013
Alprolix	Recombinant fusion protein	86-97	2014
Ixinity	Recombinant	17-31	2015
Idelvion	Recombinant Albumin Fusion Protein	104	2016
Rebinyn	Recombinant Glyco-PEGylated	115	2017

Source: Data from USPI of products. Half-lives are approximate, may be shorter in pediatric age groups and, for some products, may vary with the dose used.
Abbreviations: FIX, clotting factor IX; PEG, polyethylene glycol

Alphanine SD, Mononine, and Idelvion are approved only in adults. Ixinity is approved in subjects 12 years of age and older. Approved indications include treatment and control of bleeding episodes, perioperative management, and RP.

Etranacogene dezaparvovec-drlb (Hemgenix) is a one-time, intravenous, AAV-based gene therapy that was approved in 2022 for the treatment of hemophilia B in adults (see below for details).

2.3 Safety and Efficacy of Pharmacologically Related Products

Hemgenix is an AAV-based gene therapy that is available for the treatment of adults with hemophilia B. It is a nonreplicating, recombinant, adeno-associated virus serotype 5 (AAV5) containing a codon-optimized DNA sequence of the gain-of-function Padua variant (R338L) of human FIX under the control of a liver-specific promoter. Efficacy was evaluated in 54 adult subjects (19 to 75 years of age) in a prospective, single-arm, multinational study at a dose of

2×10^{13} genome copies/kg of body weight and who had completed a lead-in period of at least 6 months on RP with exogenous FIX product. Subjects were allowed to continue on RP for up to 6 months post infusion. Fifty-three of 54 subjects completed at least 18 months of follow-up post infusion. The main efficacy outcome was an NI test of ABR (all bleeds irrespective of treatment or not) during months 7 to 18 after infusion compared to ABR during the lead-in period. The ABR ratio (months 7 to 18 post treatment/lead in) was 0.46 (95% CI: 0.26, 0.81), demonstrating NI of ABR post gene therapy compared to ABR on RP prior to gene therapy. Two subjects were unable to stop RP following Hemgenix and thus considered never to have responded to the treatment. The median (min, max) FIX activity in 50 subjects at months 18 and 24 as measured by the one-stage assay (OSA) was 33.6% (4.5, 122.9) and 33.9% (4.7, 99.2), respectively.

AEs included infusion-related reactions, elevated hepatic transaminases, and hepatocellular carcinoma in 1 subject, which was deemed not related to the product but due to preexisting risk factors for hepatocellular carcinoma. Nine of 24 subjects with ALT elevation received corticosteroids for a mean duration of 81.4 days for cellular response to AAV5 capsid. No subject in the study developed inhibitor to FIX. Although patients were screened for antibodies to AAV5 prior to receiving therapy using an unvalidated clinical study assay, enrollment was not restricted to those with a negative test. No companion diagnostic for preexisting AAV5 antibodies was approved contemporaneously with Hemgenix, and a PMR study is ongoing to address this issue.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

BEQVEZ is approved in Canada as of January 2024 for the treatment of adults (18 years of age or older) with moderately severe to severe hemophilia B (congenital FIX deficiency) who are negative for nAbs to AAVRh74var. The approval was based on the results of the same study that is currently under FDA review for this BLA submission.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

Table 3. Regulatory Milestones Related to the Submission

Date	Type of Meeting/Correspondence	Description
July 2014	Pre-IND	CMC, clinical and preclinical
July 2016	Letter	BTD granted
March 2017	Type B	CMC (potency, comparability), toxicity studies and clinical pharmacology, Phase 3 study design
December 2017	Type B	Multidisciplinary; Phase 3 study design, vector shedding, statistical and regulatory
February 2018	Letter	RMAT granted
July 2018	IND transfer	Change in Sponsor from Spark Therapeutics to Pfizer Inc.
October 2018	Type B EOP2	Phase 3 study design, CMC, BLA plans
January 2019	Type B	CMC
April 2019	Type B WRO	Pertaining to electronic bleed and infusion data
November 2019	Type B	Pediatric development plans
October 2020	Type B	Pre-submission topics
January 2021	Type B	Pre-submission topics to support registration

Date	Type of Meeting/Correspondence	Description
November 2022	Type B WRO	CMC
February 2023	Type B	Pre-BLA
April 2023	Pfizer Request for clarification on pre-BLA minutes	Required clinical data from subjects dosed using nominal titer concentration prior to and during BLA review

Source: Adapted from Module 1.6.3 of BLA 125786/0
Abbreviations: BLA, biologics license application; BTD, Breakthrough Therapy designation; CMC, chemistry, manufacturing, and controls; IND, investigational new drug application; RMAT, Regenerative Medicine Advanced Therapy; WRO, written response only

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. It was adequately organized and integrated to conduct a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant noted that the study complied with good clinical practices. There were no clinical study conduct or data integrity issues that impacted the clinical review of this submission.

Bioresearch Monitoring inspections were issued for three foreign and one domestic clinical investigator sites participating in the conduct of study protocols for C0371004 (lead-in study) and C0371002 (licensing study). The inspections did not reveal significant problems impacting the data submitted in support of this original BLA. See Table 4 below.

Table 4. BIMO Inspection Summary

Site ID	Number of Subjects Enrolled	Location	483 Issued	Final Inspection Classification
1004	C371004: 3 C0371002: 1	Acibadem Adana Hospital Pediatric Hematology Seyhan, Adana, Turkey	No	No Action Indicated (NAI)
1046	C371004: 5 C0371002: 4	Hopital Necker Service d'Hematologie Adulte Paris, France	No	NAI
1047	C371004: 2 C0371002: 2	McMaster University Medical Centre – Hamilton Health Sciences Hamilton, Ontario, Canada	No	NAI
1059	C371004: 4 C0371002: 4	Penn Blood Disorder Center Philadelphia, PA	No	NAI

Source: BIMO Reviewer Memo
Abbreviation: BIMO, Bioresearch Monitoring

3.3 Financial Disclosures

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 313
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 17
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 97 Is an attachment provided with the reason? X Yes ☐ No (Request explanation from applicant)

Reviewer Comment: *Review of financial disclosures for investigators who received payments revealed that the majority of the payments were made to the institution of the investigators. Review does not raise any substantial concerns that the outcome of the study was influenced by payments made to few investigators.*

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see the CMC review memo for details. Forty-two of 45 subjects received drug product using Process (b) (4) and the remaining 3 of 45 subjects received Process (b) (4) drug product. Product was deemed comparable between (b) (4) processes and to that used in the Phase 1 study with 15 subjects. Subjects in the licensing study were not dosed using (b) (4) dosing. Therefore, additional data for 20 subjects using (b) (4) dosing was requested. This data was submitted In January 2024 and preliminary efficacy and safety do not raise any concerns, although follow-up is very limited.

Reviewer Comment: *The follow-up on (b) (4) subjects dosed with (b) (4) dosing is very limited to make any conclusions on long-term safety or efficacy. However, the assay variability in determining dose based on actual concentration in the licensing study appears to cover some of the variability expected with (b) (4) dosing. Thus, it is expected that subjects dosed with (b) (4) dosing should have results similar to those dosed with actual concentration. Long-term data on subjects dosed with (b) (4) dosing is expected in the future.*

4.2 Assay Validation

Please refer to the CMC reviewer report on coagulation factor assay validation details.

There were three assays for FIX activity utilized throughout the clinical studies: two one-stage clotting assays and one chromogenic substrate assay. They were deemed to be appropriately validated per CMC review. All the three assays result in variable FIX activity values for a given timepoint.

The SynthASil assay (silica-based) results in consistently higher FIX activity values compared to Actin FSL (ellagic acid-based assay). Activity of transgene FIX measured by ellagic acid-based Actin FSL assay closely corresponds to the activity by chromogenic assay.

This observed discrepancy is likely an indication of differences between the transgene FIX Padua protein (circulating in plasma of BEQVEZ-treated patients) and endogenous human FIX-WT, which is used as a reference standard in clinical FIX activity assays. Additionally, the disagreement between the clotting assays is likely rooted in differences in interaction of transgene FIX with assay reagents, specifically phospholipids. Assay discrepancy has been noted for all Hemophilia gene therapy trials and not isolated to BEQVEZ.

Data on the (b) (4) antibody-mediated neutralization assay using an AAV vector expressing a (b) (4) utilized for screening subjects with preexisting antibodies to the AAVRh74var and precluding them from receiving drug product, (b) (4) as a companion diagnostic for commercial drug product. The anti-AAVRh74var nAb activity is assessed by (b) (4)

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology reviewer memo for details.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology reviewer memo for details.

4.4.1 Mechanism of Action

BEQVEZ is a recombinant AAV vector comprising AAV-(b) (4) AAV capsid) and hFIX39-Padua (a codon-optimized expression cassette encoding a naturally occurring FIX variant, FIX Padua) under the regulatory control of the liver-specific, (b) (4) The capsid is engineered from a naturally occurring AAV serotype that shows (b) (4) A single infusion of BEQVEZ results in increase in FIX:C from hepatocytes transduced with the AAV vector containing the transgene.

4.4.2 Human Pharmacodynamics

FIX expression increased following a one-time administration of BEQVEZ. Please refer to Section 6.1.11.2 for analysis of FIX activity following drug product administration.

4.4.3 Human Pharmacokinetics

FIX expression increased following administration of BEQVEZ. Vector biodistribution and viral shedding were evaluated with this product. The package insert (PI) appropriately discusses vector shedding.

4.5 Statistical

Please refer to the Statistical reviewer memo for details and to Section 6.1.9 below.

The statistical reviewer noted the study design was adequate and accepted the proposed NI margin. The statistical reviewer agreed that the total ABR, the primary efficacy endpoint, will be analyzed using a repeated measures generalized linear model with a negative binomial distribution. Key points from the statistical reviewer memo are summarized below:

1) The primary efficacy analysis results confirm that BEQVEZ is non-inferior to RP in reducing annualized bleeding rate in hemophilia B patients.

2) The primary efficacy analysis includes imputation of 20 for 7 subjects during period of exogenous FIX use following BEQVEZ- for 6 subjects who resumed RP due to ineffectiveness of BEQVEZ after a period of time and for an additional subject who had not resumed RP but had a period of 78 days of RP-like FIX use.

3) Subjects who had one-time, intermittent use of FIX product post BEQVEZ did not have ABR imputation of 20 since occasional use for limited periods of time would not impact the analysis.

4) The imputed ABR would need to be at least 40 bleeds/year in order for NI not to hold. This analysis demonstrates the robustness of the NI conclusion.

5) Analysis of primary efficacy endpoint excluding subject with a very high baseline ABR of 53.9 bleeds/year did not result in change to the to the efficacy conclusion.

6) Secondary efficacy endpoints were considered and analyzed as stand-alone endpoints. The ABR (treated bleeds) and annualized infusion rate were not included in the label, consistent with practice for other products. FIX activity was used to assess durability of treatment effect in a descriptive way and has been included in the label.

4.6 Pharmacovigilance

Please refer to the Office of Biostatistics and Pharmacovigilance review memo for further details. No PMRs post approval are being issued. A single CMC PMC is being issued. There are no important identified risks at the current time. Potential risks include FIX inhibitor development, severe hepatotoxicity, thromboembolism, malignancy, horizontal spread, and germline transmission. The Applicant will have an extended long-term follow-up study C0371017 for 15-year follow-up for clinical study subjects. A liver biopsy sub-study is part of this long-term follow-up study for liver samples obtained at biopsy or surgical resection. In addition

to routine pharmacovigilance, there is also a post-approval, long-term follow-up study C0371007, which is a multicountry, observational, cohort study to evaluate long-term safety and effectiveness of BEQVEZ using real-world data and existing hemophilia registries, including but not limited to the World Federation of Hemophilia Gene Therapy Registry, American Thrombosis and Hemostasis Network in the United States, the United Kingdom Haemophilia Centre Doctors' Organisation in the United Kingdom, and FranceCoag in France. About 220 subjects are expected to be studied in the post-approval setting and compared to a cohort of 1,320 subjects not treated with gene therapy. Subjects are expected to be followed for ~20 years. A REMS was determined by the clinical review team not to be required for this product.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical efficacy review focused on the Phase 3 study that was submitted in Module 5 with review of the Phase 1/2 study as supportive.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following materials from the submission were reviewed:

Module	Information
1.2	Cover Letter
1.6	Meetings
1.9	Pediatric Administrative Information
1.14	Labeling
1.16	Risk Management (Non-REMS)
5.2	Tabular Listing of Clinical Studies
5.3.5	Reports of Efficacy and Safety Studies
5.4	Literature References

Additional data from 20 subjects dosed with (b) (4) dosing and submitted in January 2024 were also reviewed.

5.3 Table of Studies/Clinical Trials

Table 5. Studies/Clinical Trials Reviewed for This BLA

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Participants	Demographics (Age/Sex/Race) (No. of Participants)	Treatment Duration/ Duration of Follow-up	Study Initiation Date/ Study Completion or Cutoff Date/Study Status
Clinical Studies						
C0371002 (Australia, Brazil, Canada, France, Germany, Greece, Japan, Saudi Arabia, Sweden, Taiwan, Turkey, United Kingdom, United States)	Phase 3, open-label, single-arm study to evaluate the efficacy and safety of FIX gene transfer with fidanacogene elaparvovec in adult male participants with moderately severe to severe hemophilia B (FIX:C≤2%).	Single IV infusion of $5x10^{11}$ vg/kg fidanacogene elaparvovec	As of data cutoff: 51 enrolled 45 received treatment	Adult males Mean Age (min, max): 33.18 (18.0, 62.0) years Race White: 33 Black or African American: 1 Asian: 7 Not reported: 4	Planned: 6 years Year 1: short-term follow-up Years 2-6: long-term follow-up As of the data cutoff: • The median duration of follow-up is 2.06 years. • 43 participants have 12 to <15 months of follow-up • 24 participants have 2 to <2.5 years of follow-up • 2 participants have 3 to <3.5 years of follow-up	FSFV: 29 Jul 2019 Cutoff date: 16 Nov 2022 Ongoing

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Participants	Demographics (Age/Sex/Race) (No. of Participants)	Treatment Duration/ Duration of Follow-up	Study Initiation Date/ Study Completion or Cutoff Date/Study Status
C0371004[a] (Australia, Belgium, Brazil, Canada, France, Germany, Greece, Israel, Italy, Japan, Korea, Saudi Arabia, Spain, Sweden, Taiwan, Turkey, United Kingdom, United States) Lead in to C0371002 and C0371003	Open-label, non-investigational product, multi-center, lead-in study in adult males to evaluate prospective efficacy and selected safety data of current FIX prophylaxis replacement therapy in the usual care setting of moderately severe to severe adult hemophilia B participants (FIX:C≤2%) who are negative for nAbs to AAVRh74var prior to Studies C0371002 and C0371003[a]	Study participants remain on their current FIX prophylaxis replacement therapy	As of data cutoff: 102 enrolled 59 completed 40 ongoing	Adult males Mean Age (min, max): 31.8 (18, 61) years Race: White: 83 Black or African American: 1 Asian: 17 Multiracial: 1 Not reported: 16	Planned: Minimum of 6 months As of the data cutoff, the median duration of follow-up is 1.22 years.	FSFV: 26 Jul 2018 Cutoff date: 02 Nov 2022 Ongoing
C0371005 (Australia and US)	Phase 1/2a, open-label, non-randomized, dose-escalation, multi-center study in adult male participants with hemophilia B to evaluate safety, tolerability and kinetics with fidanacogene	Single IV infusion of $1×10^{12}$, $2×10^{12}$, or $5×10^{11}$ vg/kg fidanacogene elaparvovec	Study completed: 22 enrolled 15 completed	Adult males Mean Age (min, max): 38.6 (18, 61) years Race: White or Caucasian: 12	Single IV infusion of $1×10^{12}$, $2×10^{12}$, or $5×10^{11}$ vg/kg Duration of follow-up: 1 year	FSFV: 18 Nov 2015 LSLV: 08 Apr 2019 Completed study:

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Participants	Demographics (Age/Sex/Race) (No. of Participants)	Treatment Duration/ Duration of Follow-up	Study Initiation Date/ Study Completion or Cutoff Date/Study Status
	elaparvovec (FIX:C≤2%)			Black or African American: 1 Native Hawaiian or other Pacific Islander: 1 Multiple: 1		08 Apr 2019 Completed
C0371003 (Australia, Canada, Turkey and US)	Phase 2a, open-label, non-randomized, multi-center, LTFU safety and efficacy study in adult males with hemophilia B who previously received a single infusion of fidanacogene elaparvovec in Study C0371005	Single IV infusion of 5×10^{11} vg/kg dosed in C0371005 No IP administration in LTFU	As of data cutoff: Cohort 1: 14 enrolled after completing Study C0371005; 5 completed 7 ongoing	Adult males Cohort 1: Mean Age (min, max): 40.1 (18.0, 61.0) years Race: Black or African American: 1 Native Hawaiian or other Pacific Islander: 1 White: 12	Planned: 5 years As of the data cutoff, the follow-up duration for Cohort 1 ranged from 36 months to 75 months post vector infusion.	FSFV: 22 June 2017 Data cutoff: 02 Nov 2022 Ongoing

Source: BLA 125786/0; 5.2-Tabular Listing of All Clinical Studies
Abbreviations: AAVRh74var, adeno-associated virus serotype Rh74var; BLA, biologics license application; FIX, clotting factor IX; FIX:C, circulating levels of FIX; FSFV, first subject first visit; IP, investigational product; IV, intravenous; nAbs, neutralizing antibodies; LSLV, last subject last visit; LTFU, long-term follow-up; US, United States; vg, vector genomes

Efficacy Considerations for This BLA Application Review:

The efficacy review focused on the study results from the 45 subjects with severe to moderate hemophilia B in Study C0371002. Of these 45 subjects, 4 subjects had <15 months of follow-up following BEQVEZ but were included in the analyses.

Safety Data Considerations for This BLA Application Review:

The safety database comprised 45 subjects in Study C0371002 and 15 subjects in Study C0371005.

Reviewer Comment:

- *Efficacy results from Study C0371005 were not considered in the analyses since, despite product comparability, the enrolled population included subjects on on-demand FIX therapy and baseline ABR was collected retrospectively based on medical records for a period of only 12 weeks. Therefore, this did not align with the key elements of the Phase 3 study design in which only subjects on RP for a minimum of 6 months with prospective data collection are included.*
- *Safety data from Study C0371002 and Study C0371005 were reviewed separately for labeling purposes given lower percentages of transaminase elevations and corticosteroid use in Study C0371005 for unclear reasons.*

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee was not convened for this product. The application did not raise significant safety or efficacy concerns that could not be addressed though information in label,

consultative expertise was not required, and no public health concerns arose upon the review of this file.

5.4.2 External Consults/Collaborations

No external consultations were obtained during review of this BLA.

5.5 Literature Reviewed (if applicable)

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study C0371002 (BeneGene-2) is an ongoing, single-arm, open-label, multinational study.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective

To demonstrate the efficacy of a single infusion of BEQVEZ in male subjects ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%).

Key Secondary Objectives

To demonstrate the efficacy of BEQVEZ in terms of the use of exogenous FIX, the treated bleeds, and FIX:C.

Other Secondary Objectives

Use of exogenous FIX on bleeding events; patient-reported outcomes (PROs) addressing Health-Related Quality of Life, activities of daily living, and general health status; durability of efficacy up to 6 years; and safety, including immunogenicity.

Exploratory Objectives

Pharmacodynamics, joint health pre- and post-BEQVEZ, impact on coagulation, and PROs.

6.1.2 Design Overview

Study C0371002 (BeneGene-2) is an ongoing, open-label, single-arm, single-dose, prospective, multinational study of moderate to severe hemophilia B adult subjects who have completed at least a 6-month lead-in period on routine FIX prophylaxis prior to receiving gene therapy. Each subject serves as their own comparator pre- and post-gene therapy for the primary efficacy endpoint of ABR (total) and other secondary endpoints.

All subjects who received gene therapy first participated in the lead-in study C0371004, where they were required to be on RP with exogenous FIX replacement for a minimum of 6 months along with on-demand treatment as needed for bleeding events prior to providing consent for screening for Study C0371002. All subjects for the lead-in study had to be negative for nAb to viral capsid (AAV-Spark 100, also known as AAV74Rhvar) during screening, and had to have had a minimum of 50 documented exposure days to a FIX product and no history of or current inhibitor to FIX. Subjects entered bleed and FIX use data in an electronic diary.

After the lead-in period, subjects in Study C0371002 received a single dose of 5×10^{11} vg/kg of BEQVEZ. FIX prophylaxis was discontinued following BEQVEZ infusion. Subjects will then be followed for a total of 6 years (12 months of short-term follow-up and then long-term follow-up [LTFU] of 6 years). Subsequently, subjects are to be rolled over into another study for follow-up for up to 15 years.

6.1.3 Population

Key Inclusion Criteria

- Adult males (≥18 years of age to <65 years of age) with severe or moderate hemophilia B (FIX activity ≤2%)
- Completion of at least 6 months of RP with FIX product in lead-in Study C0371004
- Agree to suspend RP after drug product administration
- At least 50 exposure days to FIX product (plasma-derived or recombinant)

Key Exclusion Criteria

- nAb titer ≥1:1 for anti-AAV-Spark 100 capsid at screening
- History of or current inhibitor to FIX (≥0.6 Bethesda units)
- Known hypersensitivity to FIX replacement product or intravenous immunoglobulin
- Heparin sensitivity and heparin induced thrombocytopenia
- Active hepatitis B or C or current treatment for the same
- ALT, AST, or alkaline phosphatase >2×ULN (upper limit of normal); Bilirubin >1.5×ULN
- Liver disease: ascites, encephalopathy, coagulopathy, hypoalbuminemia (levels <normal limits) gastrointestinal varices, jaundice, cirrhosis, portal hypertension, splenomegaly, liver fibrosis-FibroScan score >8 kPa units, FibroTest/FibroSure >0.48, or AST-to-Platelet ratio >1
- HIV infection with either CD4 cell count ≤200 mm^3 or viral load >20 copies/mL

Reviewer Comments:

- *Severity of hemophilia required historical documentation of FIX activity ≤2% during screening into the pivotal study (C0371002) and prior to the baseline visit of the lead-in study (Study C0371004). In the absence of such documentation prior to the baseline visit in the lead-in study, a screening sample for FIX activity determination with appropriate washout for any FIX product use was obtained. Subjects with documented FIX activity of <1% and between 1% and 2% were classified as having severe and moderate hemophilia, respectively.*

- *Exclusion of subjects with known hypersensitivity to FIX product was added under "Patient Selection" in section 2 of the USPI. Hypersensitivity to heparin and heparin induced thrombocytopenia were not added since these were just precautionary exclusions in the protocol to mitigate potential immune responses and thromboembolic events and such events were not observed in the study.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

A one-time dose of 5×10^{11} vg/kg body weight intravenously is the recommended dose of BEQVEZ. For subjects with body mass index (BMI) >30 kg/m^2, dose will be calculated based on adjusted body weight that assumes a maximum permissible BMI of 30 kg/m^2.

6.1.5 Directions for Use

Study drug was given as an intravenous infusion.

6.1.6 Sites and Centers

The study was conducted across 28 sites including 5 sites in the United States, 4 sites in Turkey, 3 sites in Taiwan, 2 sites each in Australia, Brazil, Canada, France, Germany, and Japan, and 1 site each in Greece, Saudi Arabia, Sweden, and the United Kingdom.

6.1.7 Surveillance/Monitoring

An external data monitoring committee, independent of the study team, with expertise relevant to the study convened approximately every 6 months for the duration of the study to monitor safety and efficacy.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the NI 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-BEQVEZ infusion ABR. The NI margin was set at 3 bleeds/year.

Reviewer Comment: *The primary endpoint of ABR is appropriate, disease specific, and clinically relevant. Each subject served as their own comparator while on RP with FIX product and subsequent to BEQVEZ, which is appropriate. Demonstration of durability of ABR is considered in the assessment of effectiveness of the drug product.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to Statistical Review memo.

The primary objective of the Phase 3 study was to demonstrate the NI of BEQVEZ ABR, inclusive of treated and untreated bleeds (total). as compared to the comparator (RP).The primary efficacy analysis was an NI comparison between the mean ABR during Week 12 to data cutoff following BEQVEZ to that observed during the prospective evaluation of mean ABR in the lead-in period. The NI margin was set at an ABR difference of 3 bleeds per year. The planned primary analysis used an imputation approach that defined the "at-risk" for bleed time with an intention to isolate the BEQVEZ treatment effect from the confounding effect of FIX replacement product use during the EEP. Per the Applicant, data following resumption of FIX prophylaxis was excluded from the ABR analysis, but FDA did not agree to this and imputed an ABR of 20 upon resumption of RP. No missing data was imputed for the primary endpoint analysis. Forty subjects with at least 15 months of follow-up post BEQVEZ provided 90% power (one-sided test with α=0.025) to demonstrate NI of BEQVEZ to RP on difference in ABR (total) using repeated measure negative binomial regression with the proposed NI margin.

The NI margin was based on the effect of RP over on-demand treatment as the reference treatment. ABR (total)was assumed to be proportional to ABR (treated); ABR (treated) was assumed to be higher by at least 24.4, considered as M1 (M1 is the treatment effect of RP over on-demand treatment); M1 for ABR (total) was estimated to be 28.7 given ratio of ABR (total)/ABR (treated) of 1.17. Given large effect size of RP over on-demand treatment, an appropriate value of M2 (attempt to preserve the effect size of RP versus on-demand treatment by a particular fraction) was considered to be that which preserved a sufficiently large proportion of this effect. Simulations were conducted at preservation levels of 80%, 85%, and 90% of M1, which correspond to NI margin values of 5.7, 4.3, and 2.9 bleeds/year. A value of 3.0 for M2 of ~89.5% of the M1 effect preserved was proposed as both clinically meaningful and yielding a reasonable sample size for establishing efficacy.

FIX activity was a key secondary endpoint and was summarized descriptively. FIX activity was measured using three different assays.

Reviewer Comments:

- *The Applicant had initially proposed ABR and FIX activity (>5%) from Week 12 to Month 15 as co-primary endpoints. The primary endpoint was changed to ABR (all bleeds) based on FDA input.*
- *At the pre-BLA meeting, FDA recommended that the EEP be from Week 12 until data cutoff for analysis of the primary endpoint. The longer follow-up would better help with assessment of durability of efficacy of BEQVEZ and also allow longer period of follow-up to better characterize efficacy and FIX activity off corticosteroids in subjects who required such use to mitigate hepatotoxicity and preserve transgene function.*
- *Since the Applicant proposed that the EEP was Week 12 to Month 15, subjects were required to have a minimum of 15 months of follow-up to be considered efficacy evaluable. By this criterion, 4 of 45 subjects had not met the minimum 15 month follow-up requirement. Since the EEP was changed to week 12 to data cutoff, all 45 subjects were considered efficacy evaluable and a sensitivity analysis was done excluding these 4 subjects with <15 months of follow-up which did not change the efficacy conclusions.*
- *An ABR of 20 was imputed during RP in the EEP. This approach was applied to a prior, approved hemophilia gene therapy. This is a conservative approach and is acceptable from a clinical perspective, although imputations of >20 could have been used.*
- *The baseline ABR calculation included the period in the lead-in study, Study C0371002, and the period between screening and BEQVEZ infusion in Study C0371005.*

- *Subjects who resume RP are considered to have "lost response" to or stopped benefitting from gene therapy. In subjects who do not resume RP, bleeding rates, type of bleeds (e.g., spontaneous bleeds), frequent, single-use, of exogenous FIX products over a period of time and/or FIX activity levels are considered in adjudicating subjects who may never have responded to gene therapy or lost response to therapy after a period of time despite not being placed back on routine prophylaxis.*

6.1.10 Study Population and Disposition

Fifty-one subjects were screened, of which 5 subjects were screen failures. Reasons for screen failure included nAb above threshold titer (n=1), not completing 6 months of RP on FIX prior to gene therapy (n=1), liver disease (n=1), inability to comply with study visits (n=1), and screening laboratory values outside of acceptable range (n=1). In addition, one subject withdrew consent due to the COVID-19 pandemic and hepatocellular carcinoma risk. Thus 45 adult males with moderate or severe hemophilia B enrolled and received BEQVEZ.

6.1.10.1 Populations Enrolled/Analyzed

All subjects who received the study drug were analyzed (n=45).

6.1.10.1.1 Demographics

The majority (73%) of subjects were White. Please see Table 1 in Section 1.1 above for demographics.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Forty-five subjects, 7 with moderate and 38 with severe hemophilia B, constituted the efficacy population for analysis. All subjects were adult males, with the majority being White and <35 years of age (see Table 1 for demographics). All 45 subjects had a documented mutation responsible for the underlying disorder, with missense mutations (20/45; 44.4%) being the most common, followed by deletion (9/45, 20%) and nonsense (7/45; 15.6%) mutations. Target joints at baseline were identified in about a third (28.9%) of subjects. Approximately one third of the study population had hepatitis B (13/45; 28.9%) or C (15/45; 33.3%), respectively. One subject had HIV infection; two other subjects had positive antibodies for HIV with an undetectable viral load and no history of HIV. Approximately half of the study population (22/45; 48.9%) had medical history of musculoskeletal and connective tissue disorders and prior surgical/medical procedures (21/45; 36.7%). Fifteen of 45 subjects (33.3%) had a BMI >30 kg/m^2, with 6 subjects with a BMI between 30 and 31 kg/m^2, 4 subjects with a BMI between 31 and 33, and the remaining 5 subjects with a BMI between 33.8 and 48.4.

Reviewer Comment: *There was only one subject with HIV included in Study C0371002. Hence, there is limited data of the safety and effectiveness of BEQVEZ in this population. Given the prevalence of HIV infection in the hemophilia population, a statement to reflect the limited data in HIV subjects was incorporated in the Highlights and full PI under section 8—Use in Specific Populations.*

6.1.10.1.3 Subject Disposition

Please see Section 6.1.10 above for population screened and enrolled. All 45 subjects completed the treatment. Six of 45 subjects had resumed RP at the time of the data cutoff. One subject withdrew from the study at Day 910 (week 130) due to "lack of efficacy"; this subject had

resumed RP at Week 53 (Day 368). The median (min, max) duration of follow-up for 41 subjects with at least 15 months of follow-up was 2.15 (1.21, 3.23) years. The median (min, max) duration of follow-up for all 45 subjects (includes 4 subjects who did not reach 15 months of follow-up) was 2.06 (0.41, 3.23) years. Four subjects not reaching the Month 15 follow-up had a study duration of 150, 241, 374, and 408 days.

6.1.11 Efficacy Analyses

The primary efficacy endpoint was the ABR from Week 12 to data cutoff compared to the lead-in period. ABR difference (between baseline and post treatment) and associated confidence interval (CI) were estimated via repeated measures using a generalized linear model with negative binomial distribution and identity link function. The upper bound of the CI was then compared with the 3.0 NI margin.

6.1.11.1 Analyses of Primary Endpoint(s)

The ABR for all bleeds (treated and untreated) was reduced following BEQVEZ treatment compared to the lead-in period of at least 6 months. The model derived mean ABR was 4.5 (95% CI: 1.9, 7.2) during the baseline period and 2.5 (95% CI 1.0, 3.9) during the post-BEQVEZ EEP. The difference in the mean ABR between the baseline period and post-BEQVEZ EEP is -2.1 (95% CI: -4.8, 0.7), which meets the NI margin as upper bound of the 95% CI is <3.0 bleeds/year.

A summary of the ABR at baseline and post-BEQVEZ treatment as presented in the United States Prescribing Information (USPI) is given below.

Figure 1. ABR in Study C0371002

	Baseline (Prospective Lead-in Period)	**Post-BEQVEZ Efficacy Evaluation Period[a]**
Median (range) of follow-up time (years)	1.2 (0.6, 2.4)	1.8 (0.2, 3.0)
Total follow-up time (person-years)	59	83
Median (min, max) ABR (bleeds/year)[b]	1.3 (0.0, 53.9)[c]	0.0 (0.0, 19.0)
Model derived mean ABR [bleeds/year] (95% CI)[b,d]	4.5 (1.9, 7.2)	2.5 (1.0, 3.9)
n (%) of patients without any bleeds	13 (29%)	27 (60%)
Total number of observed bleeds	225	98
Number of observed spontaneous bleeds (proportion of total bleeds)	157 (70%)	60 (61%)
Number of observed joint bleeds (proportion of total bleeds)	184 (82%)	71 (72%)

ABR = Annualized Bleeding Rate for all bleeds (treated and untreated with factor IX, excluding procedural bleeds).
CI = confidence interval; SD = standard deviation
a. Post-BEQVEZ efficacy evaluation period is from Week 12 (Day 82) to data cutoff
b. A total of 7 participants (16%) had used factor IX replacement products during the efficacy evaluation period for extended prophylaxis that confounded the treatment effect of BEQVEZ, with a median start time at 0.8 (range: 0.4 to 1.1) years. An ABR of 20 bleeds/year was imputed for the confounded periods.
c. The results presented in this table included data on a participant with a baseline ABR of 53.9 bleeds/year, which disproportionately influenced the baseline ABR estimate. A post-hoc sensitivity analysis, excluding this participant, still met the non-inferiority study success criterion.
d. Model-based ABR estimates from a repeated measures generalized linear model with negative binomial distribution and identity link function.

Source: BEQVEZ USPI
Abbreviations: ABR, annualized bleed rate; CI, confidence interval; n (%), number of subjects with the specified characteristic

Eighteen of 45 subjects used exogenous FIX product for treatment or prevention of bleeds following BEQVEZ. Thirteen of these 18 subjects used at least 1 preventive dose of exogenous FIX product following BEQVEZ. Of these 13 subjects, 7 resumed RP or used exogenous FIX product in a pattern akin to RP that confounded assessment of efficacy from BEQVEZ and for whom ABR of 20 was imputed. Use of exogenous FIX in the remaining 6 subjects was not of sufficient use or duration to impact analysis.

Reviewer Comment:

- *An imputed ABR of 20 was used for subjects during periods of extended exogenous FIX use that resembled a pattern of RP or resumption of RP. This imputation was proposed by the statistical reviewer based on available literature and chosen from the range of ABR on on-demand FIX therapy. This imputation has been used in a previously approved FIX gene therapy product.*

- *All six subjects who had resumed RP had ABR imputed on day of resumption of RP except for one subject (SUBJID* (b) (6) *wherein ABR imputation was at an earlier timepoint (Day 395; RP was resumed Day 623) given use of multiple doses of FIX product. One additional subject (SUBJID* (b) (6) *with moderate hemophilia who should have ideally resumed RP given higher ABR of 5 bleeds/year in the EEP compared to baseline ABR of 1.2 bleeds/year and FIX activity <5% (SynthASil assay) starting at 0.4 years had ABR imputation starting on Day 162 given use of exogenous FIX in a pattern akin to resumption of RP.*

- *Analysis of the primary efficacy endpoint using 41 subjects (excludes 4 subjects with <15 months of follow-up) does not change the efficacy conclusion. The model-derived mean ABR (95% CI) in the EEP for 41 subjects is 2.6 bleeds/year (1.1, 4.2) compared to baseline of 4.9 bleeds/year (2.0, 7.8) with a difference of -2.3 bleeds/year (-5.3, 0.7) which meets the NI margin of 3 bleeds/year.*

- *Analysis of the primary efficacy endpoint excluding one subject with a baseline ABR of 53.9 despite taking RP consistent with labeling of the exogenous FIX product use does not change the efficacy conclusion. The statistical reviewer considered excluding this subject from the primary analysis, but a final decision was made not to do so for the following reasons: the subject had had high number of bleeding events at baseline despite receiving RP per the label of the product used for RP; presence of six target joints at baseline that could perhaps explain the high number of bleeds; post hoc exclusion would induce selection bias; ABR numbers similar to this have been reported in some subjects in other studies; and the exclusion of an ABR above a certain threshold is arbitrary. The sensitivity analysis excluding this subject reveals a mean baseline ABR of 3.4 bleeds/year (95% CI:1.8, 5.1) and a mean post-BEQVEZ ABR of 2.41 bleeds/year (95% CI: 0.9, 3.9) with a difference of -1.0 bleeds/year (95% CI: -2.9, 0.8) with upper bounds of the 95% CI that still meets the criterion for success of the NI margin of mean difference of <3.0 bleeds/year.*

- *BEQVEZ shows a reduction in ABR post treatment compared to baseline. This treatment effect is more pronounced in those with high baseline ABR.A high baseline ABR could be due to inadequate RP or bleeding despite adherence to prescribed RP (e.g., multiple target joints). There were nine subjects who had a baseline ABR >5, with six of these subjects having ABR >10. Review of their baseline RP data revealed that FIX product use was consistent with the RP labeling for the particular product. Hence, these subjects*

had high baseline ABRs despite taking RP. At baseline, these subjects could have benefited from a more intensive treatment regimen or tailored approach to reduce bleeding at baseline based on pharmacokinetic data but perhaps mimics what one would see in the real world setting. One of these nine subjects resumed RP. Thus, the majority of subjects with a high baseline ABR despite use of RP per label benefited from BEQVEZ.

- *The Applicant proposed to include in the USPI the durability of response data from 15 Phase 1 subjects with much longer follow-up as compared to that of the Phase 3 study subjects. Given the differences in study design, FIX activity, transaminase elevation, and corticosteroid use, which impacts FIX activity levels and possibly durability of FIX expression, data were not pooled and was not included in the PI.*

Six subjects resumed RP during the course of the study, starting from Month 5.1 to Month 20.5. All six subjects had severe hemophilia B and received corticosteroids for presumed T-cell immune response to capsid. Three additional subjects were evaluated for lack of benefit from gene therapy by the clinical reviewer; two of these three subjects had moderate hemophilia. Of these three subjects, one subject should have ideally resumed RP given worse ABR during EEP compared to baseline, use of exogenous FIX use in a pattern akin to RP and FIX activity <5% even with the SynthASil assay starting Day 161. A brief description of these nine subjects —six who resumed RP and three evaluated for loss of response to BEQVEZ—is given below.

1) SUBJID (b) (6) : 18-year-old White male had a baseline ABR (total) of 1.58. Corticosteroids initiated on Day 77 for rise in transaminases to almost 1.5×baseline. FIX activity by the SynthASil, chromogenic, and Actin-FSL assays were 9%, 3%, and 5%, respectively. Steroids discontinued on Day 119. FIX activity declined to 4%, 1%, and 2% by the SynthASil, chromogenic, and Actin-FSL assays, respectively, at the end of steroid treatment. He resumed RP on Day 368; FIX activity had been <2% by the SynthASil assay and <1% by the other assays for 7 months prior to that. He had five bleeds post BEQVEZ, of which one traumatic and one spontaneous joint bleed occurred prior to resumption of RP. He withdrew from the study on Day 910 following BEQVEZ due to perceived lack of efficacy.

2) SUBJID (b) (6) : 22-year-old White male with history of intracranial hemorrhage and baseline ABR (total) of 0.98. Was started on steroids on Day 53 for increased transaminases. FIX activity by the SynthASil, chromogenic, and Actin-FSL assays were 17%, 8%, and 7%, respectively. Steroids discontinued on Day 169. FIX activity levels declined during this time and were 4%, 4%, and 2% by the SynthASil, chromogenic, and Actin-FSL assays, respectively, on Day 168. He resumed RP on Day 198 due to low FIX activity in the context of prior history of intracranial hemorrhage; had no bleeds prior to resumption of RP.

3) SUBJID (b) (6) : 47-year-old Asian male with history of hepatitis B and baseline ABR (total) of 0.62. History of passive seroconversion from fresh frozen plasma (given for a vehicular accident) on Day -260 with subsequent seronegativity on Day -76. Corticosteroids initiated on Day 21 for increased transaminases >1.5×baseline. FIX activity by the SynthASil, chromogenic, and Actin-FSL assays were 11%, 5%, and 5%, respectively. Steroids discontinued on Day 70. FIX activity by the SynthASil, chromogenic, and Actin-FSL assays were 25%, 9%, and 11%, respectively, at end of steroid treatment (increased compared to values at start of steroid therapy). Steroids were restarted on Day 132 for decline in FIX activity (SynthASil, chromogenic, and Actin-

FSL assays were 10%, 3%, and 3%, respectively) and discontinued on Day 216 with FIX activity of 12%, 5%, and 5% by the SynthASil, chromogenic, and Actin-FSL assays, respectively. At the end of Year 1, his FIX activity had declined to 7%, 3%, and 3% (SynthASil, chromogenic, and Actin-FSL assays, respectively) with subsequent decline to <2% by the chromogenic and Actin-FSL assays thereafter. He had nine preventive doses of FIX product between days 395 and 472; resumed RP on Day 623 due to low FIX activity levels. Had one traumatic bleed reported on Day 224 post BEQVEZ.

Reviewer Comment:

- *Loss of response to therapy for this subject was adjudicated to be Day 623 when he resumed RP. Given use of multiple doses of preventive FIX use starting at Day 395, imputation of ABR of 20 started at Day 395 since exogenous FIX would confound assessment of efficacy from gene therapy. He was adjudicated as not having lost response on Day 395 since he had had only one traumatic bleed on Day 224. He had no preventive doses of FIX between days 472 and 623 when he resumed RP.*

4) SUBJID (b) (6) : 24-year-old male with baseline ABR (total) of 22.41 and three target joints. Developed a new target joint (right elbow) post gene therapy. Had ALT elevation on Day 19 with stable FIX activity and for which steroids were not initiated. Had recurrent ALT and AST elevation on Day 64 and was started on steroids on Day 65 with FIX activity of 14%, 5%, and 6% by the SynthASil, chromogenic, and Actin-FSL assays, respectively. Steroids discontinued on Day 145. While the liver function tests resolved, his FIX had declined starting Day 86 and were 5%, 2%, and 1% (SynthASil, chromogenic, and Actin-FSL assays) on Day 104. He resumed RP on Day 155 due to low FIX activity. He had two spontaneous joint bleeds on days 148 and 150 prior to resumption of RP.

5) SUBJID (b) (6) : 21-year-old White male with baseline ABR (total of 3.42). Started on steroids on Day 123 for ALT elevation; FIX activity by SynthASil, chromogenic, and Actin-FSL assays were 18%, 8%, and 6%, respectively. Steroids discontinued on Day 178 following resolution of elevated ALT and with FIX activity of 17%, 9%, and 7% (SynthASil, chromogenic, and Actin-FSL), respectively, at end of steroid treatment (Day 184). He had three traumatic bleeds on days 211, 218, and 248, of which the latter two were treated. He resumed RP on Day 275 due to low FIX activity with FIX levels of 6%, 2%, and 2% by the SynthASil, chromogenic, and Actin-FSL assays, respectively, on Day 218.

6) SUBJID (b) (6) : 35-year-old White male with history of hepatitis C and arthropathy and baseline ABR (total) of 0.95. Steroids started Day 20 for up-trending ALTs. Steroids discontinued on Day 193. FIX activity was 15%, 10%, and 7%, and 31%, 22% and 16% at the beginning and cessation of steroid treatment by the SynthASil, chromogenic, and Actin-FSL assays, respectively. Course complicated by COVID-19 while on steroids (Day 85). Noted to have declining FIX activity of 4% (subsequently 2%) on Day 286 with concomitant increase in liver function tests. Restarted on steroids, which were continued until Day 359 (total 53 days). He resumed RP on Day 410 due to low FIX activity level (chromogenic and SynthASil <2% range) and two spontaneous bleeds on days 366 and 504.

7) SUBJID (b) (6) : 29-year-old white male with history of moderate hemophilia, hepatitis B, joint prosthesis, and baseline ABR (total) of 53.87 (39 spontaneous, 2 traumatic), of

which only 15 were treated bleeds. Bilateral knees, ankles, and elbows were target joints at baseline. He received steroids starting Day 47 for transaminase elevation >1.5×baseline. Steroid dose was increased and intravenous steroids added to address increasing transaminase levels and decline in FIX activity. FIX activity of 11%, 4%, and 5% (SynthASil, chromogenic, and Actin-FSL) at start of steroid treatment that declined to 6%, 1%, and 2%, respectively, on steroids on Day 74. Steroids course of 66 days completed on Day 112; no FIX activity levels available at this time point. Following BEQVEZ ABR was 4.72. All 11 joint bleeds starting after start of EEP (Day 82) were spontaneous and in target joints. Last available FIX activity of 10%, 5%, and 6% (SynthASil, chromogenic, and Actin-FSL) on Day 1,002.

Reviewer Comment:

- *The reasons for subject's high ABR pre-BEQVEZ and lack of treatment for majority of his bleeds is not clear. His RP regimen is consistent with the approved dosing regimen for the product. It is not clear if a more intensive regimen based on pharmacokinetic profile was considered.*
- *Despite having an ABR of 8.47 Week 12 to Month 15, which is not optimal, the ABR appears to have improved post BEQVEZ. Additional data provided by the Applicant, showed an ABR of 4.23 as of data cutoff of August 2023. FIX activity by the SynthASil assay was maintained in the 10% to 11 % range. Hence the subject was deemed to have continued benefit from BEQVEZ.*
- *The reason for non-treatment of multiple bleeds is unclear and raises the issue of compliance. Given diminishing frequency of follow-up after Year 1 post-BEQVEZ and sparse sampling of FIX activity levels, the data at later timepoints following treatment are less reliable.*

8) SUBJID (b) (6) : 29-year old with severe hemophilia with baseline ABR of 8.7 (9 spontaneous, 3 traumatic bleeds) with majority (11/12) of bleeds being untreated. Post-gene therapy ABR (total) was 7.63 with 15 bleeds (10 spontaneous, 5 traumatic), which 12 were joint bleeds, with only 3 of 12 being in a target joint. Majority of bleeds (12/15) were treated. Subject was never treated with immunosuppression. FIX activity on Day 224 (day closest to timepoint of deemed loss of response) was 8%, 4%, and 3% by SynthASil, chromogenic, and Actin-FSL assays, respectively.

Reviewer Comment:

- *This subject was adjudicated initially as having lost response to BEQVEZ given multiple spontaneous joint bleeds, especially in nontarget joints, that would warrant resumption of RP. Additional data was provided by the Applicant which showed an ABR of 8.36 as of EEP with data cutoff of August 2023, no decline in FIX activity by SynthASil assay (FIX activity of 16.5% at week 143 that is higher than the previous value of 7.2% at week 104) and non-resumption of RP. Thus, subject was deemed as having continued benefit from BEQVEZ.*

9) SUBJID (b) (6) : 38-year-old with moderate hemophilia with baseline ABR (total) of 1.18 and post-therapy ABR of 3.49. Received steroids days 35 to 126. Had 10 bleeding events from the start of the EEP, of which majority (8/10) were spontaneous joint and soft tissue bleeds; 5 joint bleeds were in non-target joints. He has had low FIX activity (3%, 2%, and 2% by SynthASil, chromogenic, and Actin-FSL assays, respectively) since Day 161, which has essentially remained the same. He also has taken multiple

preventive doses of exogenous FIX, confounding the assessment of efficacy of gene therapy during that time.

Reviewer Comment: *This subject should have ideally resumed RP given multiple spontaneous joint bleeds, especially in non-target joints; worse ABR following gene therapy; and low FIX activity levels. He also had multiple missed visits, making the data less reliable. ABR imputation for confounding due to exogenous FIX use started on Day 162.Additional data provided by the Applicant showed an ABR of 2.97 as of data cutoff of August 2023 and FIX activity <5% by the SynthASil assay. This subject has been descriptively described in section 14 of the label.*

The majority of the 45 subjects (71%) had bleeds in the baseline period; 62% of subjects (28/45) had no bleeds in the EEP post BEQVEZ. ABR was evaluated by subtype of bleeds: spontaneous versus traumatic. The mean ABR (total) for spontaneous bleeding was 3.24 in the baseline period and reduced to 0.69 for the post-BEQVEZ EEP. The observed spontaneous bleed count as a proportion of total bleeds decreased to 58% in the EEP compared to 70% in the baseline period. The observed joint bleed count as a proportion of total bleeds decreased to 68% in the EEP from a baseline of 82%.

Ten subjects had an ABR in the EEP that was higher than in the baseline period. Four of these 10 subjects had resumed RP. Two subjects were included among the nine subjects who were deemed to have lost response but had yet to resume RP. One subject had minimal increase (baseline ABR of 0 to 0.94 in the EEP). One subject had four bleeds in the EEP, of which three were spontaneous bleeds but bleeds occurred infrequently. And FIX activity levels increased over time and were 36%, 27%, and 23% by SynthASil, chromogenic, and Actin-FSL assays, respectively, on Day 918 following BEQVEZ; no bleeds and only 2 doses of preventive FIX use were reported after Day 562. For the remaining two subjects, one had a follow-up of <15 months with ABR increasing to 1.25 from baseline of 0.41 that was due to one traumatic bleed, while the other subject's ABR of 1.88 in the EEP versus 0 at baseline was due to two spontaneous bleed that occurred prior to Month 15; this subject has not had any documented bleeds thereafter and had FIX activity of 25% at the latest timepoint prior to data cutoff.

6.1.11.2 Analyses of Secondary Endpoints

Analysis of FIX Activity

There were three assays used for analysis of FIX activity in Study C0371002: silica-based OSA (SynthASil), chromogenic assay (CSA), and ellagic acid based OSA (Actin-FSL). The SynthASil assay consistently demonstrated higher FIX activity values compared to the other two assays with a value approximately twice that of the other two assays. The CSA and Actin-FSL OSA generally had FIX activity values aligned with each other. The FIX activity over time measured by the three different assays is presented in Table 6 below. Forty-one of 45 subjects completed at least 15 months of follow-up, and 24 subjects completed at least 24 months of follow-up: (6)%, 15 (18.8)%, and 13 (11.9)%, respectively.

Table 6. FIX Activity Over Time, Study C0371002

Timepoint	One-Stage Assay (SynthASil Reagent)* (N=45)	One-Stage Assay (Actin-FSL Reagent)** (N=45)	Chromogenic Assay (N=45)
Week 4	-	-	-
N	42	42	43
Mean (SD)	19 (7.5)	9 (4.4)	9 (4.5)
Median (min, max)	18 (4, 32)	9 (1, 22)	8 (2, 22)

Timepoint	One-Stage Assay (SynthASil Reagent)* (N=45)	One-Stage Assay (Actin-FSL Reagent)** (N=45)	Chromogenic Assay (N=45)
Week 12	-	-	-
N	44	43	44
Mean (SD)	28 (15.2)	14 (8.1)	14 (9.3)
Median (min, max)	26 (3, 69)	13 (2, 35)	12 (1, 36)
Month 6	-	-	-
N	39	41	40
Mean (SD)	28 (21.3)	13 (11.1)	15 (13.0)
Median (min, max)	23 (2, 100)	10 (1, 55)	10 (1, 58)
Month 15	-	-	-
N	35	34	35
Mean (SD)	27 (25.7)	13 (12.8)	16 (17.0)
Median (min, max)	23 (2, 119)	10 (2, 62)	10 (2, 74)
Month 24	-	-	-
N	22	22	22
Mean (SD)	25 (22.6)	13 (11.9)	15 (18.8)
Median (min, max)	23 (2, 95)	9 (1, 47)	10 (1, 80)

Source: Table 8, Clinical Overview, BLA 125786/0
*Silica-based one-stage assay
**Ellagic acid-based OSA
Any samples taken within 7 days (14 days if extended half-life product is used) of exogenous FIX replacement therapy were not included in the analysis.
If a subject withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the assessments at the visits following withdrawal/dropout/resumption were imputed as 1.9%. Of the 6 subjects needing imputation, the following timepoints were imputed: Month 6 (1), Month 15 (5) and Month 24 (3).
Abbreviations: FIX, clotting factor IX; max, maximum; min, minimum; N, number of subjects in the specified group, or the total sample; SD, standard deviation

There is a trend towards higher mean FIX activity with increase in age, BMI, and White race. Subjects >35 years of age (n=17) and those of White race (n=29) and a BMI ≥25 kg/m^2 (n=29) had 1.6-fold (for age >35 and White race) and 1.5-fold higher mean FIX activity, respectively, as compared to subjects 18 to <25 years of age (n=28), of non-White race (n=12), and with a BMI <25kg/m^2 (n=16).

The mean (SD) FIX activity in 28 subjects who received corticosteroids was lower than in the 17 subjects who did not received corticosteroids. Mean (SD) between Week 12 and Month 15 for those who received corticosteroids versus those who did not was 10.7 (8.0) versus 15.8 (9.7) for the Actin-FSL assay, 11.5 (9.2) versus 16.7 (11.6) for the chromogenic assay, and 22.2 (14.8) versus 16.8 (11.6) for the SynthASil assay, respectively.

The ratio between the SynthASil and Actin-FSL assay varied depending on the FIX activity level, with ratios of 1.8 for high FIX activity levels (≥0.4 IU/mL) and 4.3 for low FIX levels (≥0.025 IU/mL).

Refer to the CMC reviewer memo for coagulation assays and the Clinical pharmacology review memo for additional data.

Reviewer Comment:

- *Lower FIX activity in subjects who received corticosteroids likely reflects a decrease in FIX activity due to immune response to capsid and loss of transgene expression.*
- *It is not currently known which assay is best suited to monitor FIX activity post BEQVEZ and which assay reflects the true hemostatic potential in a subject. Therefore, any of the three assays may be used, but it is recommended that subjects be preferably monitored*

with the same assay over time and preferably in the same laboratory to better interpret FIX activity over time.

- *No definitive conclusions can be drawn on the observed differences in FIX activity levels based on age, race and BMI given the small sample size and exploratory nature of these analyses.*

ABR (Treated Bleeds)

The model-based estimate (95% CI) for mean ABR (treated) was 3.34 (1.71, 4.98) for the baseline period compared to 0.60 (0.22, 0.99) for the post-BEQVEZ EEP, with a treatment difference of -2.74 (95% CI: -4.38, -1.10).Sixteen of 45 subjects had no treated bleeds at baseline versus 31 subjects in the post-treatment phase.

Joint Bleeds

The mean model-based estimate (95%CI) joint ABR was 3.73 (1.33, 6.14) at baseline versus 0.87 (0.34, 1.40) post-treatment.

Annual Infusion Rate

The mean (±SD) annual infusion rate from Week 12 to Month 15 was decreased to 4.46 (10) compared to a baseline of 58.8 (29), with 29 of 45 subjects (64%) having no infusions from Week 12 to Month 15. Six of 45 subjects resumed RP, ranging from 5.11 to 20.5 months.

Patient-Reported Outcomes

The mean (±SD) Haemophilia Quality of Life Questionnaire for Adults physical and sports and leisure scores decreased to 22.5 (23.5) at Week 52 from a baseline of 31 (25) and 29 (25) at Week 52 from baseline of 46 (25) respectively. The total score decreased to 17.2 (13.5) at Week 52 from baseline of 29 (15),

The mean (±SD) Hemophilia Activities List Complex Lower Extremity Activities component score at Week 52 was 74.4 (24.7) compared to a baseline of 67 (25), with a change of 7.6 (19.6) having a p-value of 0.02. Similarly, the mean (±SD) Hemophilia Activities List Basic Lower Extremity Activities component score at Week 52 was 86.5 (17) compared to a baseline of 75 (23).

Reviewer Comment: *Due to the single-arm study, reliable estimate of the treatment effect of BEQVEZ on PROs is limited by the lack of a comparator arm. This information was not included in the label.*

6.1.11.3 Subpopulation Analyses

Please see the above efficacy sections wherein analysis of subgroups have been described as deemed relevant.

6.1.11.4 Dropouts and/or Discontinuations

One subject of the 45 dosed subjects withdrew from the study at Day 910 due to “lack of efficacy”; he had resumed RP prior to that.

Reviewer Comment: *This subject who withdrew from the study was included in the efficacy analysis for the period prior to withdrawal from the study.*

6.1.11.5 Exploratory and Post Hoc Analyses

Number of Target Joints: Thirteen subjects had at least 1 target joint (defined as ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period) at baseline. Twelve subjects had at least 1 target joint present at baseline that resolved (defined as ≤2 bleeds in a joint over a 12-month period) within Month 15 post BEQVEZ. One subject had a new target joint post BEQVEZ that resolved during follow-up.

Additional PROs: Per the Applicant, Hemophilia Life Impacts Questionnaire showed improvement in most domains while the Patient Global Impression of Change-Hemophilia was at least moderately improved in 32 of 41 subjects (78%), slightly improved in 7 (17%) subjects, and not changed and at least moderately worsened in 1 subject each at Week 52.

Reviewer Comment:

- *The PRO analyses are exploratory and thus no definitive conclusions can be drawn regarding the effect of BEQVEZ on these PRO endpoints.*

6.1.12 Safety Analyses

6.1.12.1 Methods

All evaluations of safety were based on the 45 subjects who received BEQVEZ in the study. The clinical study protocol, clinical study report, draft labeling, Applicant's response to information requests, and analysis of Analysis Dataset Model datasets pertaining to safety were used in assessment of safety. TEAEs include any AEs that occurred on or after infusion of BEQVEZ; after Year 1, only those TEAEs considered related to study product were included in the analysis.

6.1.12.2 Overview of Adverse Events

Overall, there were 205 TEAEs in 38 subjects (84%) during the entire study. Irrespective of relatedness to the study product, the most common AEs were ALT increased 12 (26.7%), arthralgia (17.8%), and nasopharyngitis 8 (17.8%). Most subjects had mild to moderate TEAEs; 7 subjects had severe TEAEs. Increase in transaminases (includes preferred terms ALT increased, AST increased, hepatic enzyme increased, hepatic function abnormal, hepatotoxicity, liver function test abnormal, and transaminases increased) was the most common TEAE related to study product and occurred in 24 subjects.

Reviewer Comment: *Overall, TEAEs were mild, and all events recovered/resolved. Increase in transaminases related to the study product was included in the USPI. There was one subject with mild nausea and pyrexia (Day 5-5/6-6, mild), one subject with mild abdominal pain (days 6 to 10, mild), one subject with severe asthenia (days 8 to 10), and one subject with mild headache (Day 3 to 83) that the clinical reviewer considered to be related to the study product administration.*

6.1.12.3 Deaths

There were no deaths on the study.

6.1.12.4 Nonfatal Serious Adverse Events

There were 11 SAEs (14 preferred terms) in 7 subjects. The 14 preferred terms included anemia (2 different subjects), duodenal ulcer hemorrhage, femoral neck fracture, hypokalemia, alcohol poisoning, drug-induced liver injury, duodenal ulcer with upper gastrointestinal hemorrhage, pilonidal disease, seizure (2 occurrences in the same subject), COVID-19, COVID-19 pneumonia, and coagulation FIX level decreased. All events except femoral neck fracture, hypokalemia, and seizures were severe. Events of anemia, duodenal ulcer hemorrhage, and upper gastrointestinal hemorrhage were related to corticosteroid use. Drug-induced liver injury was due to azithromycin. No SAE was related to BEQVEZ. All events recovered/resolved.

Reviewer Comment:

- *Anemia and duodenal ulcer hemorrhage in one subject were considered by the investigator to be related to BEQVEZ. However, the clinical reviewer agrees with the Applicant analysis that these SAEs are related to corticosteroid use and lack of acid-blocking therapy in the context of steroid use.*
- *The same preferred term in the same subject was considered only once. One subject had a seizure at two different timepoints. Hence, there were 14 preferred terms.*

6.1.12.5 Adverse Events of Special Interest

Hepatotoxicity/Elevated Transaminases (ALT/AST)

Transaminase elevation following BEQVEZ administration could signal T-cell mediated immune response to viral vector capsid and may be accompanied by loss of transgene expression and consequently decline in FIX activity. Elevated ALT or AST meeting protocol-defined criteria of ≥1.5×baseline occurred in 29 subjects. Corticosteroids were initiated for elevated transaminases and/or decline in FIX activity in 28 subjects (62%; 28/45). The mean (SD) and median times to start of the first corticosteroid dose were 45 (30) and 37.5 days, respectively, with a range of 11 to 123 days. Seven subjects repeated a course following discontinuation of steroids. The mean (SD) and median duration of corticosteroid treatment (including second course) was 113 (58.6) and 95 days, respectively, with a range of 41 to 276 days. Fourteen subjects had the corticosteroid dose escalated either prior to weaning (n=5) or during weaning (n=12) for either increase in transaminases, lack of decrease in transaminases, and/or decrease in FIX activity. Three subjects received intravenous corticosteroids in addition to oral steroids. Fourteen subjects received prednisone; 12 subjects received prednisolone while 2 subjects received methylprednisolone. Five subjects received methylprednisolone either alone or in addition to another corticosteroid. One subject received budesonide in addition to prednisolone. All transaminase elevations resolved. Two subjects had upper gastrointestinal hemorrhage resulting in anemia in the setting of corticosteroid use and lack of gastrointestinal protection with H2 blockers or proton pump inhibitors.

Reviewer Comment:

- *Corticosteroid use was recommended for ALT or AST ≥1.5×baseline and/or decline in FIX activity per the protocol. The increase in transaminases could trigger corticosteroid use even if the increased value was still in the normal range of the particular laboratory test. Subsequent increases in transaminases could also trigger corticosteroid use. An example of "significant" decline in FIX activity was stated in the protocol, but what constituted a "significant" decline was left up to the investigator. Per response to an information request dated December 1, 2023, the exact reason for corticosteroid use*

was not mandated to be collected in the case report form. However, the Applicant confirmed that all 28 subjects who received corticosteroids met protocol-defined criteria for initiation.

Infusion Reactions

No subject was deemed to have met criteria for an infusion reaction.

Thromboembolic Events

No subject had a thromboembolic event while on the study. Some subjects appeared to have increased values of FIX activity over time, but limited sampling after Year 1 of follow-up and differences between the three assays and variability in each assay makes interpretation difficult. Most were within the range of mild hemophilia or the lower end of normal. One subject had FIX activity that increased with time into the higher range of normal-peak FIX activity of 97.2 (chromogenic) on Day 569 that declined to 69.9 subsequently on Day 640, peak FIX activity of 92 (Actin-FSL) on Day 640, and peak FIX activity of 120 (SynthASil) on Day 569 that subsequently declined to 107 on Day 640.

Reviewer Comment: *FIX Padua is a naturally occurring hyperactive variant of FIX that carries the risk of thrombosis. Even though FIX activity was at the higher end of normal in one subject, it declined from peak activity levels in at least two of the assays and did not exceed 150% of FIX activity. There was no thrombosis reported in the clinical study. Hence, we did not add thromboembolic risk to section 5 or section 17 of the label.*

Malignancy

Since BEQVEZ is a liver-directed, AAV-based gene therapy, there is concern for integration into hepatic DNA and hepatocellular carcinoma from insertional oncogenesis. Theoretically, the AAV-vector can integrate into the host DNA in any cell. There have been no malignancies reported to date in the study. One subject had a hepatic tumor (possibly localized fat-free area) deemed benign, noted on ultrasound, that was stable at Week 52 and Week 104 visits. There was no increase in alpha-fetoprotein.

FIX Inhibitors

No subject developed inhibitor to FIX.

6.1.12.6 Clinical Test Results

Hepatic transaminase elevation was the most common laboratory abnormality reported in the study with ALT and AST elevation reported in 21 and 20 subjects respectively. ALT levels ≥2×ULN were reported in nine subjects, while values ≥1.5×ULN occurred in nine subjects. There were no transaminase elevations >Grade 2. Protocol-defined elevations in hepatic transaminases are described in Section 6.1.12.5 under “Hepatotoxicity/Elevated Transaminases.”

6.1.12.7 Dropouts and/or Discontinuations

No subject discontinued from the study due to an AE. One subject discontinued due to lack of efficacy and after resumption of RP.

6.1.13 Study Summary and Conclusions

Overall, BEQVEZ demonstrated efficacy with reduction in ABR (total) during the EEP compared to the baseline. 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 the post-BEQVEZ EEP. The difference in the mean ABR between the baseline period and post-BEQVEZ EEP is -2.1 bleeds/year (95% CI: -4.8, 0.7), which meets the prespecified NI margin as upper bound of the 95% CI is <3.0 bleeds/year, indicating the effectiveness of BEQVEZ.

The mean (SD) FIX activity at Month 15 by the SynthASil, chromogenic, and Actin-FSL assays was 27 (25.7)%, 16 (17)%, and 13 (12.8)%, respectively, and was maintained at Month 24 (n=22); mean (SD) FIX activity at Month 15 by the SynthASil, chromogenic, and Actin-FSL assays was 25 (22.6)%, 15 (18.8)%, and 13 (11.9)%, respectively. Six subjects (13%) were deemed to have lost response to BEQVEZ over time and had resumed RP at the time of the data cutoff. An 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 and should have ideally resumed RP. Eighty-four percent of subjects have maintained response to therapy, indicative of durability of effectiveness of BEQVEZ. The main AE and laboratory abnormality related to treatment was increase in hepatic transaminases due to presumed cellular response to capsid. No subject had an event >Grade 2. Twenty-eight subjects were treated with corticosteroids for elevated transaminases and/or decline in FIX activity. Two subjects who received corticosteroids without gastric acid reducing therapy had upper gastrointestinal hemorrhage resulting in anemia that resolved. All subjects initiated corticosteroid treatment within the first 4 months with a mean and median duration of therapy of 113 and 95 days, respectively. The safety profile is acceptable and favors a positive benefit-risk ratio.

6.2. Trial #2 - C0371005

A brief synopsis of this study will be described here. Efficacy data from this study was not incorporated into the analysis and safety data was presented separately in the label for reasons outlined below.

Study C0371005 is a completed Phase 1/2, open-label, non-randomized, dose-escalation, multicenter study in adult subjects with moderate to severe hemophilia B, conducted at clinical sites in Australia and the United States. The goal of the study was to evaluate the safety, tolerability, and kinetics of BEQVEZ. The primary endpoints were related to safety and include: clinically significant changes from baseline in physical exam, vital signs, and laboratory values, incidence of drug-related AEs, FIX incremental recovery, immune response against AAV capsid and FIX transgene. Key study eligibility criteria were adult subjects with moderate or severe hemophilia B (≤2% FIX activity), ≥50 exposure days to exogenous FIX product, absence of FIX inhibitor (history of or on current testing), nAb titer to capsid ≥1:5, active hepatitis B or C infection or on treatment for the same, HIV infection with CD4 count ≤200/mm^3 or viral load ≥50 gc/mL, and hepatic dysfunction (stage 3 fibrosis, portal hypertension, hepatic encephalopathy, splenomegaly, and hypoalbuminemia) Although designed as a dose escalation study (5×10^{11} vg/kg, 1×10^{12}, and 2×10^{12} vg/kg), only a single dose of BEQVEZ at 5×10^{11} vg/kg body weight was studied.

Twenty-two subjects were screened, of whom 15 subjects received study product at the same dose of BEQVEZ as in the Phase 3 study and were followed for 52 weeks. All 15 subjects completed the study, and 14 of 15 subjects are enrolled in the LTFU study (C0371003). Key demographic characteristics included all male subjects with mean age of 38.6 years of age

(range 18 to 61 years) and 80% White (12/15). Ten of 15 subjects had severe hemophilia with the remainder 5 subjects having moderate severity; 11 of 15 subjects were on RP with the remainder 4 subjects receiving on-demand therapy. No subject had a positive titer for nAb to capsid prior to treatment. Mean (SD) baseline ABR was 8.87 (14). No subject has resumed RP on this study or on follow-up in the LTFU study. Seven subjects had a geometric mean of FIX activity of 24.5% during year 6 assessment. A total of 81 TEAEs irrespective of causality were reported in the study; none were severe. There were 2 TEAEs of transaminase elevation that were considered related to the study drug. Three (20%) subjects met the transaminase elevation criteria for corticosteroid use received therapy for presumed immune mediated response to capsid. There were no malignancies, FIX inhibitors, thromboembolic events, infusion reactions or deaths on the study.

Reviewer Comment:

- *The main differences in the inclusion criteria as compared to the Phase 3 study were that: 1) Subjects on on-demand therapy (defined as ≥4 bleeds in the previous 52 weeks on on-demand therapy and/or chronic hemophilic arthropathy in one or more joints) could be enrolled and, 2) Baseline data on subjects on RP was not prospectively collected; bleeding events and/or FIX product use were based on medical records in the preceding 12 weeks. Subjects with nAb titers (≥1:1 and ≤1:5) were initially slated to be treated at a dose of 1×10^{12} vg/kg as part of the study. The triggers for corticosteroid use in this study were the same as for the Phase 3 study.*
- *Product administered in this study was deemed comparable to that in the Phase 3 study. However, given differences in collection of baseline ABR, inclusion of on-demand subjects, lower percentage of subjects with transaminase elevation and those requiring corticosteroids, lack of resumption of RP despite longer follow-up, and approximately 2-fold higher FIX activity in this study compared to the Phase 3 study, the data were not considered in the assessment of efficacy.*
- *Given differences in percentage of subjects with transaminase elevation and corticosteroid use, safety data was considered separately in the label.*

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

BEQVEZ is not intended for use in women. Clinical studies evaluating BEQVEZ required the use of contraception for the duration of the study and until at least three consecutive semen samples were negative for vector shedding.

Two exposures in partners of study subjects were reported. One subject's wife was calculated to have gestational age of 6 weeks at time of initial exposure. The baby was born at 38 weeks gestation and no birth defects or health problems were reported. The second informed the investigator about the pregnancy on Day 4 following BEQVEZ. Ultrasound at 19 weeks of gestation was reported as normal. The outcome of the pregnancy is not known as of the last available report.

9.1.2 Use During Lactation

BEQVEZ is not intended for use in women. There is no information regarding the presence of BEQVEZ in human milk, the effects on the breastfed infant, or the effects on milk production.

9.1.3 Pediatric Use and PREA Considerations

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.

9.1.4 Immunocompromised Patients

There was only one subject with HIV infection treated in the Phase 3 study. Subjects who have HIV infection were required to have a CD4 count ≤200 mm^3 and viral load <20 copies/mL. Given the prevalence of HIV in hemophilia subjects, the paucity of data in such subjects has been conveyed under "Use in Specific Populations" in the highlights and the full PI.

9.1.5 Geriatric Use

The Phase 3 clinical study did not have any subject ≥65 years of age. The safety and efficacy of BEQVEZ have not been established in geriatric patients.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Study C0371002 did not use (b) (4) dosing in the 45 subjects considered for efficacy and safety evaluations. The Applicant had been advised in a meeting in 2021 that the use of (b) (4) would be necessary for commercial labeling and distribution of the drug product. This issue was addressed at the pre-BLA meeting as well. Recommendations were made to tighten the acceptance criteria for the vector genome titer and improve the precision of the quantitative polymerase chain reaction assay to limit variability in the dose administered. To address the FDA's concerns, the Applicant provided additional CMC data at the pre-BLA meeting, but additional CMC data was requested to address the concern that the commercial product dose range would be broader than that undertaken during the clinical study. The Agency also requested the Applicant to provide the following to address concerns surrounding lack of data with (b) (4) dosing: 1) detailed modeling and simulation data (population pharmacodynamic analysis), and 2) data from (b) (4) subjects dosed with (b) (4) dosing. The Applicant submitted data on (b) (4) subjects dosed with (b) (4) dosing in January of 2024 with a data cutoff of October 26, 2023.

Fourteen of (b) (4) subjects are White and 5 are Asian (1 subject with multiple races) with majority (19/(b) (4) of non-Hispanic ethnicity. The median age is 29 years of age (range: 20 to 53 years). Eighteen and 2 subjects have severe and moderate hemophilia, respectively. The median BMI is 25.6 (range: 18.5 to 33.2). Four subjects with hepatitis C and one subject with HIV have been enrolled. Fifty percent (10/(b) (4) have been enrolled in sites in the Middle East. The mean (SD) duration on the study is 56 (34) days with a range of 1 to 112 days. Only 6 subjects have a follow-up of 12 weeks or longer (i.e., have entered the EEP); majority (11/20) have a follow-up of <9 weeks.

Four bleeds in three subjects have occurred to date: two traumatic bleeds on days 18 and 54 in one subject treated with exogenous FIX on days 20 and 55; one spontaneous bleed in one subject on Day 10 treated with exogenous FIX on Day 13; and one spontaneous bleed on Day 12 in another subject. Two subjects took prophylactic/preventive dose of FIX on days 10 and 77 for a total of five FIX infusions for rescue or preventive therapy in four subjects following product administration.

The FIX activity data available to date is shown in Figure 2 below.

Figure 2. FIX Activity in Subjects Dosed With (b) (4)

Visit		One-stage Assay (Actin-FSL Reagent)	PF-06838435 (N=(b) (4)) One-stage Assay (SynthASil Reagent)	Chromogenic Assay
Week 4	n	15	15	15
	Mean (SD)	11.76 (6.081)	19.23 (9.500)	9.55 (6.124)
	Median (Min, Max)	10.90 (3.9, 26.0)	18.50 (6.6, 42.4)	7.70 (2.5, 24.2)
	(Q1, Q3)	(7.45, 15.57)	(12.05, 25.30)	(5.50, 12.77)
Week 8	n	11	11	10
	Mean (SD)	18.16 (10.413)	27.44 (14.946)	14.82 (8.666)
	Median (Min, Max)	19.43 (3.2, 36.3)	28.67 (7.1, 54.3)	14.45 (1.8, 29.2)
	(Q1, Q3)	(9.93, 23.70)	(16.85, 34.40)	(6.77, 19.90)
Week 12	n	6	6	6
	Mean (SD)	16.02 (12.099)	23.35 (16.564)	12.24 (10.761)
	Median (Min, Max)	12.40 (4.1, 37.3)	17.08 (8.3, 52.4)	7.33 (2.4, 29.9)
	(Q1, Q3)	(7.65, 22.30)	(12.15, 33.13)	(5.50, 21.07)

Note: summary is based on central laboratory data.
Baseline is defined as the last non-missing measurement prior to the IP dosing date (Day 1) in the C0371002 study.
If multiple results were captured for particular visit, average value is considered for analysis.
Any samples taken within 7 days (14 days if EHL product is used) of exogeneous FIX replacement therapy are excluded from the summaries. If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis,

Source: Table 2, Applicant Response to FDA IR #29
Abbreviations: N, number of subjects in the specified group, or the total sample; SD, standard deviation

There were 17 TEAEs in 11 subjects, with no severe TEAEs reported. Four subjects have had TEAEs considered related to the treatment; all of these TEAEs were of mild severity. Aminotransferase elevation in 2 subjects of mild severity was the most common related TEAE. Headache, nausea, and myalgia in 1 subject, and papular rash in another subject occurring in the first week of treatment, were considered related to treatment. Aminotransferase elevation in 1 subject and rash in another subject had not resolved at the time of data cutoff. Four subjects have received corticosteroids for increased transaminases and/or decline in FIX activity.

Reviewer Comment:

- *The efficacy and safety data from subjects dosed with (b) (4) dosing are too preliminary to draw any definitive conclusions. However, the safety profile appears to be consistent with that in the pivotal study, and no unexpected AEs have been seen thus far. Refer to the Clinical Pharmacology memo regarding the population pharmacodynamic analysis.*
- *CMC data submitted on the variability of the assay for dose of study product is stated to have captured the variability in dose expected with (b) (4) dosing to a good extent. Thus, at the current time, there are no major concerns with the lack of long-term data based on (b) (4) dosing.*

10. CONCLUSIONS

BEQVEZ has demonstrated efficacy with reduction in ABR. 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 the post-BEQVEZ EEP with a difference of -2.1 bleeds/year (95%CI -4.8, 0.7), which

meets the prespecified primary efficacy endpoint. Factor IX activity has increased in the majority of subjects who received the study treatment. Six subjects have returned to RP with exogenous FIX product. An additional subject had higher ABR of 5 bleeds/year in the EEP compared to baseline ABR of 1.2, intermittent, exogenous FIX use and FIX activity of <5% by the SynthASil assay and ideally should have been considered for resumption of RP. The majority (84%) of subjects are continuing to benefit from BEQVEZ as of the data cutoff. Transaminase elevation related to the treatment was the most common AE and was mild to moderate in severity. The risk from duration of immunosuppression use required to maintain efficacy and AEs related to corticosteroid use reported in the study do not raise any major safety concerns, are within the scope of practice of medicine, and should be able to be mitigated with careful patient selection and monitoring for such AEs. There have been no FIX inhibitors, malignancies, thromboembolic events, or deaths reported in the Phase 3 study. Overall, the benefit-risk profile is favorable and favors regular approval of BEQVEZ for the treatment of adults with moderate to severe hemophilia B (congenital FIX 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.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table 7.

Table 7. Risk-Benefit Considerations and Recommendations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia B is a hereditary bleeding disorder characterized by recurrent bleeding which, if left untreated, leads to chronic arthropathy, muscular atrophy, and deformities. • Treatment of bleeds may delay these complications but does not prevent them. • Primary prophylaxis with regular FIX injections initiated at an early age is the standard of care. • The short half-life of FIX replacement products requires frequent lifelong infusions. The psychosocial impact of this commitment can also be debilitating.	• Hemophilia B is a hereditary, life-threatening disease. • Hemophilia B can have a debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• Available treatment options requiring lifelong infusions include: • Plasma-derived and recombinant FIX products, approved for treatment and prophylaxis of hemophilia B • AAV5-based gene therapy driving the expression of FIX Padua, available as of November 2022	• Despite approval of an AAV5-based gene therapy in hemophilia B, there is still an unmet medical need in subjects who require lifelong, exogenous FIX therapy. • Subjects with preexisting antibodies to AAV5 may not be candidates for the available gene therapy.
Clinical Benefit	• Two studies were submitted to evaluate the safety and effectiveness of BEQVEZ, of which one study was used to assess efficacy; both studies were considered for evaluation of safety separately. • The main efficacy outcome was a non-inferiority test of mean ABR during Week 12 to data cutoff after BEQVEZ treatment compared with mean ABR during the pretreatment lead-in period. The model derived mean ABR was 2.5 (92% CI 1.0, 3.9) versus the mean ABR of 4.5 (95% CI: 1.9, 7.2) during the baseline period The difference in the mean ABR between the baseline period and post-BEQVEZ EEP is -2.1 (95% CI: -4.8, 0.7), which meets the NI margin as upper bound of the 95% CI is <3.0 bleeds/year.	• The evidence of clinical benefit of ABR was demonstrated by reduction of bleeds in the efficacy evaluable period post treatment. • ABR represents an appropriate clinical benefit endpoint for subjects with hemophilia B.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most common TEAE related to BEQVEZ was transaminase elevation in 24 subjects in Phase 3 study. • 28 (62%) received corticosteroids for elevated transaminases and/or decline in FIX activity for a mean (SD) duration of 113 (67) days.	• BEQVEZ has an acceptable safety profile and the risks are addressed in the package insert.
Risk Management	• The most substantial risks of treatment are hepatotoxicity, potential for malignancy including hepatocellular carcinoma, and infusion reactions. Risk management plans include the warnings and precautions and common adverse events listed in the prescribing information.	• The risks can be mitigated through routine medical management, adequate PI, and routine pharmacovigilance. Subjects in clinical studies of BEQVEZ will be followed up in a long-term study for 15 years. Subjects receiving BEQVEZ in the postmarketing setting will be followed in hemophilia registries for at least 20 years. • The data do not support the need for a risk evaluation and mitigation strategy (REMS).

Abbreviations: AAV5, adeno-associated virus serotype 5; ABR, annualized bleeding rate; CI, confidence interval; EEP, efficacy evaluation period; FIX, clotting factor IX; NI, non-inferiority; PI, package insert; SD, standard deviation; TEAE, treatment-emergent adverse event

11.2 Risk-Benefit Summary and Assessment

BEQVEZ has demonstrated efficacy with reduction in ABRs during the EEP compared to baseline ABRs and increased FIX expression. The mean ABR during Week 12 to data cutoff was 2.5 (92% CI 1.0, 3.9) versus the mean ABR of 4.5 (95% CI: 1.9, 7.2) during the baseline period The difference in the mean ABR between the baseline period and post-BEQVEZ EEP is -2.0 (95% CI: -4.8, -0.7), which meets the NI margin as upper bound of the 95% CI is <3.0 bleeds/year.

The mean (SD) FIX activity at Month 15 by the SynthASil, chromogenic, and Actin-FSL assays was 27 (25.7)%, 16 (17)%, and 13 (12.8)%, respectively. The FIX activity was maintained at Month 24 (N=22 subjects with longer follow-up), and mean (SD) FIX activity by the SynthASil, chromogenic, and Actin-FSL assays was 25 (22.6)%, 15 (18.8)%, and 13 (11.9)%, respectively.

The most common TEAE related to BEQVEZ treatment was an increase in hepatic transaminases. The duration and risk of immunosuppression required for addressing elevated hepatic transaminases and/or decline in FIX activity are within the scope of routine medical practice and can be mitigated through careful patient selection and close monitoring. The safety profile is acceptable. There were no deaths, malignancies, thromboembolism, FIX inhibitors, or infusion reactions reported.

The benefit risk profile of BEQVEZ is favorable.

11.3 Discussion of Regulatory Options

The available data support regular approval for the indication of BEQVEZ in patients with hemophilia B for the treatment of adults with moderate to severe hemophilia B (congenital FIX 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. In the clinical studies with BEQVEZ, subjects with preexisting nAbs to AAVRh74var were excluded from receiving the product. These data have been reviewed by (b) (4), and a companion diagnostic for (b) (4) BEQVEZ. ABR (total bleeds) is a clinical benefit endpoint and reduction in the same post-treatment meeting the prespecified NI margin is the basis for the regular approval of BEQVEZ. Since there is increased risk of bleeding with declining FIX activity levels, and occurrence of bleeding is not an event at a timepoint far removed from a decline in FIX activity levels, use of FIX activity as a surrogate endpoint is not warranted.

11.4 Recommendations on Regulatory Actions

The clinical team considered the magnitude of benefit observed in the ABR when considering granting/traditional approval to BEQVEZ in adults with moderately severe and severe hemophilia B.

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well-controlled clinical study, with supportive evidence from the initial clinical investigation. The compelling evidence of treatment effect in the single adequate and well-controlled study is based on a persuasive, clinically meaningful, and statistically significant benefit in ABRs in a sufficient number of subjects utilizing the subjects' own ABRs in the lead-in period prior to BEQVEZ administration as the control, which is appropriate. Although six subjects have resumed RP and one additional subject has had an increased ABR post-treatment compared to

baseline coupled with FIX activity <5%, 84% of subjects continue to benefit from the treatment. For subjects continuing to benefit, durability of FIX activity expression has also been demonstrated. The safety profile is acceptable and favors a positive benefit-risk profile.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends regular approval of BEQVEZ, an AAV vector-based gene therapy indicated for the treatment of adults with moderate to severe hemophilia B (congenital FIX 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.

Based on the available data, the clinical reviewer recommends regular approval of BEQVEZ.

11.5 Labeling Review and Recommendations

The draft label has been modified to reflect the efficacy and safety data presented in this memo. The key change made to the draft label were the following:

1) Revision of the indication statement to reflect the study population that served as the basis of this approval
2) Exclusion of efficacy data from Study C0371005 (Phase 1/2a) from section 14
3) Removal of treated bleeds, annual infusion rate from section 14 as is consistent with other labels and ABR (total bleeds) is the primary efficacy endpoint
4) Removal of claim of superiority by Applicant in section 14 since the FDA does not agree to this claim and was not supported by the study demonstrating NI
5) Inclusion of subjects who were considered to have lost response to BEQVEZ treatment over time in section 14
6) Revision of the ABR table to include imputation for those subjects who resumed RP and additional footnotes
7) Addition of infusion reactions, malignancy and monitoring of laboratory tests to the highlight section despite not having occurrence of these reactions given that they are important safety considerations
8) Addition of limited and no data in subjects with HIV and without active or prior history of FIX inhibitors respectively to the Highlights section and full PI under section 8 since these are populations relevant to hemophilia
9) Presentation of safety data from the Phase 3 and Phase 1/2 studies separately in section 6
10) Revision of section 2 to present a sequential, concise description of dose, administration, and post-administration instructions to the end user

11.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance will be done. There are no PMRs. There is one PMC from CMC. Subjects dosed in the clinical studies and commercially will be followed in LTFU studies and hemophilia registries as outlined in Section 4.6. A REMS was deemed not to be necessary. The USPI captures all the important established and potential risks of BEQVEZ.