

Application Type	Original BLA
STN	125786/0
CBER Received Date	April 28, 2023
PDUFA Goal Date	April 27, 2024
Division / Office	BHB/DCEH/OTP
Committee Chair	Ronit Mazor, PhD
Clinical Reviewer(s)	Kavita Natrajan, MD
Project Manager	Cecilia (Maria) Crowley
Priority Review	No
Reviewer Name(s)	Yuqun Abigail Luo, PhD
Review Completion Date / Stamped Date	April 22, 2024 / April 26, 2024
Supervisory Concurrence	Lihan Yan, PhD, Branch Chief, TEB2/DB/OBPV
	John Scott, PhD, Director, DB/OBPV
Applicant	Pfizer Inc.
Established Name	fidanacogene elaparvovec
(Proposed) Trade Name	BEQVEZ
Pharmacologic Class	Adeno-associated virus vector-based gene therapy
Dosage Form(s) and Route(s) of Administration	Solution for intravenous infusion
Dosing Regimen	One-time treatment at a recommended dose of 5×10^{11} vector genomes per kilogram of body weight
Indication(s) and Intended Population(s)	Treatment of hemophilia B patients ≥ 18 years of age

Table of Contents

Glossary 3

1. Executive Summary 4

2. Clinical and Regulatory Background 6

 2.1 Disease or Health-Related Condition(s) Studied 7

 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 7

 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 8

3. Submission Quality and Good Clinical Practices 8

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines..... 8

 4.5 Clinical 8

 4.6 Pharmacovigilance 9

5. Sources of Clinical Data and Other Information Considered in the Review 9

 5.1 Review Strategy 9

 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 9

 5.3 Table of Studies/Clinical Trials..... 10

6. Discussion of Individual Studies/Clinical Trials 13

 6.1 Trial #1 13

 6.1.1 Objectives (Primary, Secondary, etc)..... 14

 6.1.2 Design Overview..... 15

 6.1.3 Population 16

 6.1.4 Study Treatments or Agents Mandated by the Protocol..... 17

 6.1.6 Sites and Centers 17

 6.1.7 Surveillance/Monitoring..... 18

 6.1.8 Endpoints and Criteria for Study Success 19

 6.1.9 Statistical Considerations & Statistical Analysis Plan 21

 6.1.10 Study Population and Disposition 25

 6.1.10.1.1 Demographics 25

 6.1.11 Efficacy Analyses..... 26

8. Integrated Overview of Safety 33

 8.2 Safety Database 33

 8.2.1 Studies/Clinical Trials Used to Evaluate Safety..... 33

 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations 33

 8.4.1 Deaths..... 35

 8.4.2 Nonfatal Serious Adverse Events..... 35

 8.4.8 Adverse Events of Special Interest..... 37

10. Conclusions 38

 10.1 Statistical Issues and Collective Evidence..... 38

 10.2 Conclusions and Recommendations 39

GLOSSARY

4MSU	4 Month Safety Update
AAV	Adeno-associated virus
ABR	Annualized bleeding rate. It means ABR for total bleeds, including both treated and untreated bleeds, if not otherwise indicated in this review memo.
ABR _{treated}	Annualized bleeding rate counting only treated bleeds
ABR _{total}	Annualized bleeding rate for total bleeds, counting both treated and untreated bleeds
AE	Adverse event
AIR	Annualized infusion rate of exogenous FIX products after BEQVEZ infusion
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CI	Confidence interval
CM	Concomitant medication
CMC	Chemistry, Manufacturing, and Controls
CRF	Case report form
CS	Corticosteroids
CSR	Clinical Study Report
DCOD	Data Cut-off Date
DNA	Deoxyribonucleic Acid
eCTD	Electronic Common Technical Document
eDiary	Electronic diary
DAS	Dosed analysis set
EEP	Efficacy evaluation period for ABR
FDA	Food and Drug Administration
FIX	Factor IX
FSFV	First subject first visit
FU	Follow-up

GLM	Generalized linear model
HB	Hemophilia B
ID	Identifier
IND	Investigational New Drug
IR	Information request
IU	International Unit
IU/mL	International unit/milliliter
IV	Intravenous
LSLV	Last subject last visit
mL	Milliliter
nAb	Neutralizing antibodies
NI	Non-inferiority
kg	Kilogram
PCD	Primary completion date for Study 1002
RP	Routine Prophylaxis
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
US	United States
vg	Vector genomes
vg/kg	Vector genomes per kilogram of body weight

1. Executive Summary

The original Biologics License Application (BLA) 125786/0 is a marketing application for BEQVEZ for the proposed indication of treatment of adults with moderate to severe Hemophilia B (HB).

The data package reviewed in this memo consisted of the data from 60 BEQVEZ-treated participants, 15 from Study 1005 (an early phase study) and 45 from Study 1002 (the main study). Both studies contributed to the safety database while Study 1002 contributed to the efficacy evaluation.

Efficacy results

Study 1002 was an ongoing, single-arm, multi-national Phase 3 study. The study enrolled 45 adult male patients with moderately severe to severe hemophilia B (factor IX activity ≤ 2 IU/dL). All patients completed a prospective lead-in study of at least six months for baseline data collection while they received routine factor IX prophylaxis in the usual care setting before entering Study 1002. Enrolled patients then received a single intravenous infusion of BEQVEZ at a dose of 5×10^{11} vg/kg of body weight and entered a follow-up (FU) period of 6 years. Only patients who were negative for pre-existing neutralizing antibodies to AAVRh74var capsid were eligible.

The primary efficacy outcome in Study 1002 was a non-inferiority (NI) test of the difference between the mean efficacy evaluation period (EEP) annualized bleeding rate (ABR) and the mean baseline ABR, with an NI margin of 3 bleeds/year. The EEP started from Day 82 (Week 12) after BEQVEZ treatment and ended on the data cut-off date. Of the 45 participants, 41 had at least 15 months of FU. The median EEP was 1.8 years (range: 0.2, 3.0 years), for a total EEP of 83 person-years. The model-derived mean baseline and EEP ABRs were 4.5 (95% confidence interval (CI): 1.9, 7.2) bleeds/year and 2.5 (95% CI: 1.0, 3.9) bleeds/year, respectively. The difference between the mean EEP ABR and the mean baseline ABR was -2.1 (95% CI: -4.8, 0.7) bleeds/year, meeting the NI study success criterion.

Six (13%) participants resumed routine prophylaxis (RP) during their EEPs, starting from 0.4 to 1.7 years after BEQVEZ treatment. An additional participant used exogenous factor IX replacement products in a prophylaxis-like manner for 78 days during the EEP. One participant who resumed RP also used replacement products in a prophylaxis-like manner for another 81 days during the EEP prior to resuming RP. To isolate the BEQVEZ treatment effect from the confounding by the prophylactic use of replacement products during these confounded EEPs, an ABR of 20 bleeds/year was imputed for these periods to approximate the hypothetical bleeding frequency in the absence of prophylactic use of replacement products in the primary analysis.

There are additional uncertainties associated with the treatment effect estimate. First, it is unknown whether an ABR of 20 bleeds/year approximates the hypothetical bleeding frequency closely. I conducted supplemental analyses which show that the imputed ABR would need to be at least 40 bleeds/year in order for the upper bound of the 95% CI of the difference in mean ABRs to be greater 3 bleeds/year, i.e., NI no longer holds. This analysis demonstrates the robustness of the NI conclusion to the magnitude of the imputed ABR. A second source of uncertainty is due to the disproportionate influence on the treatment effect estimate from a participant with a baseline ABR of 53.9 bleeds/year and an EEP ABR of 4.7 bleeds/year. A post-hoc analysis excluding this subject still meets the NI study success criterion. A third source of uncertainty is due to one-time preventive use of replacement products without documented reasons in several participants. It is unknown whether some of these uses were for treatment of undocumented bleeds or bleeds not adjudicated to be new bleeds. I did not identify a reasonable approach to address these one-time preventive uses in the primary analysis. However, the occurrences were few and I concluded that they do not affect the NI

conclusion. Taken together, these considerations add to quantitative uncertainty in the treatment effect estimate. However, based on supplementary analyses and the magnitude of the treatment effect, there is no meaningful uncertainty regarding the qualitative conclusion that mean ABR in patients treated with BEQVEZ is within 3.0 of mean ABR in patients on routine prophylaxis. That is, non-inferiority was unambiguously met, outweighing the uncertainties described above.

Twenty-eight (62%) participants received corticosteroids (CS) due to transaminase elevation and/or decline in factor IX activity. The mean time to CS initiation was 45 days. The mean duration of CS treatment was 113 days (range: 41 to 276 days). All six participants who resumed RP were on CS. It appears that CS use should be considered an integral component of the BEQVEZ treatment regimen as needed.

Safety results

There were no deaths due to any cause. I defer detailed safety review to the clinical review team.

Conclusions and recommendations

BEQVEZ is non-inferior to routine prophylaxis in reducing annualized bleeding rate in hemophilia B patients. I recommend approval of BEQVEZ.

2. Clinical and Regulatory Background

The original Biologics License Application (BLA) 125786/0 is a marketing application for fidanacogene elaparvovec (BEQVEZ) for the proposed indication of treatment of adults (aged 18 years or older) with Hemophilia B (HB).

BEQVEZ is an adeno-associated virus vector-based gene therapy. It consists of a recombinant viral capsid (AAVRh74var) containing the human coagulation factor IX (FIX) transgene FIX-R338L (Padua), a variant producing a protein with specific FIX activity higher than those produced by wild type FIX gene variants. The FIX transgene is designed to reside as episomal deoxyribonucleic acids in the nuclei of transduced liver cells. A one-time BEQVEZ treatment is intended to lead to long-term hepatic expression of FIX, replacing the deficient FIX activity in HB patients.

BEQVEZ is to be administered as a single intravenous (IV) infusion at a dose of 5×10^{11} vector genomes per kilogram of body weight (vg/kg). Patients should test negative for anti-AAVRh74var neutralizing antibodies (nAb) prior to dosing. The nAb assay was developed in collaboration with (b) (4) as a companion diagnostic and (b) (4)

During development, investigational names of BEQVEZ include (b) (4) PF-06838435, among others.

2.1 Disease or Health-Related Condition(s) Studied

Congenital HB is an X-linked recessive genetic disorder characterized by a tendency for prolonged bleeding due to a partial or complete deficiency of FIX, an essential blood coagulation protein.

The number of people with HB is approximately 32,000 worldwide and approximately 6,000 in the United States (US) alone. HB occurs in approximately 1 in 25,000 male births. HB primarily affects males. Female carriers are typically asymptomatic, but 10% to 25% will develop mild symptoms and, rarely, report severe symptoms of bleeding.

The classification of the severity of HB has been based on either clinical bleeding symptoms or plasma FIX activity (FIX:C) levels, with the latter being the most widely used criteria. A person's HB is classified as severe, moderate, or mild if their FIX activity level is < 1% of normal (< 0.01 international unit/milliliter [IU/mL]), 1-5% of normal (0.01-0.05 IU/mL), >5% but <40% of normal (> 0.05 to < 0.40 IU/mL), respectively. In mild cases, bleeding symptoms may occur only after surgery, trauma, or a dental procedure. In some moderate and most severe cases, bleeding symptoms may occur after a minor injury or spontaneously.

Clinical bleeding symptom criteria have also been used because some patients with FIX levels of less than 1% occasionally have little or no spontaneous bleeding and appear to have clinically moderate or mild hemophilia. The converse holds for some patients with FIX activities of 1-5%, who may present with symptoms of clinically severe disease.

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

There is no cure for HB. The primary goals of HB therapies are the prevention of bleeding episodes, rapid and definitive treatment of bleeding episodes and breakthrough bleeding episodes that occur while patients are on a regular prophylactic regimen, and provision of adequate hemostasis during surgery and emergencies. Currently, these goals are essentially met for HB patients by IV injections of commercially available recombinant- or plasma-derived FIX replacement products, either at the time of a bleeding episode (on-demand/episodic) or by regular infusions up to several times a week (prophylactically). The recent approvals of extended half-life FIX products allow for a reduced frequency of factor administration (once every 7 to 14 days) and maintenance of a higher FIX trough level.

However, optimal management of HB patients is complex. Treating patients with hemophilia is highly individualized and takes into consideration various factors including the patient's medical history, FIX activity level, the severity of the clinical bleeding phenotype (regardless of baseline circulating FIX activity level), personal treatment preferences, and lifestyle activities. Adherence to the prescribed regimen is required to ensure efficacy.

On November 2022, the Food and Drug Administration (FDA) approved HEMGENIX, the first AAV-based gene therapy indicated for the treatment of adults with HB. HEMGENIX used a different viral capsid from that used by BEQVEZ.

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

Designations granted by the FDA

- Orphan Drug Designation (#15-4907) for treatment of HB. September 21, 2015.
- Breakthrough Therapy Designation for treatment of HB. July 15, 2016.
- Regenerative Medicine Advanced Therapy Designation. January 16, 2018.

Milestones and important interactions

- Pre-IND Meeting (PS 002434). July 15, 2014. Minutes dated August 5, 2014.
- The original submission under Investigational New Drug (IND) 16437, the IND supporting this BLA. April 10, 2015.
- Pre-BLA Meeting. February 10, 2023. Minutes dated March 10, 2023.
- Submission of BLA 125786/0/0. April 28, 2023.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

4.5 Clinical

(b) (4) dosing

Prior to the submission of the BLA, the Applicant initiated discussion with FDA regarding labeling with dosage calculations based on **(b) (4)** while the primary data supporting the BLA is from participants treated with BEQVEZ using dosage calculations based on actual, lot specific concentrations.

To support this change, the Applicant proposed to treat ^{(b) (4)} additional HB participants with BEQVEZ based on **(b) (4)** from June 2023 to October 2023, and submitted the data on these ^{(b) (4)} participants on January 2024, three months prior to the action due date of this BLA. With an October 2023 data cutoff date, approximately ^{(b) (4)} participants would have around 12 weeks of follow-up (FU). FDA reviewers in the

clinical and clinical pharmacology disciplines, and possibly the CMC (Chemistry, Manufacturing, and Controls) discipline, will evaluate the (b) (4) dosing data.

4.6 Pharmacovigilance

Longer term follow-up (LTFU) studies

To collect longer-term data, two LTFU studies are planned.

- Study C0371017 is an extended LTFU study for patients who received BEQVEZ in a clinical trial which will follow up patients for a total of 15 years post-infusion.
- Study C0371007 is a post-approval LTFU study to collect data on patients who receive BEQVEZ post FDA approval from existing international hemophilia registries and national registries. It is estimated that the BEQVEZ cohort will have around 220 patients while the control cohort will have around 1320 patients. The study will take 20 years to complete, from 2024 to 2044, including an enrollment period of 5 years and a FU period of 15 years.

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

5.1 Review Strategy

BEQVEZ, at the dose of 5×10^{11} vg/kg, was administered to HB participants in two clinical trials: the dose-escalation study 1005 (N=15) and the main study 1002 (N=45). For brevity, I retain only the last 4 digits for study identifier (ID) as all study IDs start with “C037”. For example, I will refer to Study C0371005 as Study 1005.

The efficacy database consists of the 45 participants from trial 1002. The safety database consists of the 60 participants from the two trials, including any long-term follow-up (LTFU) data on these participants in additional trials.

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

The basis of this statistical review includes documents in IND 16437, the original BLA 125786, information requests (IRs) from the FDA, IR responses from the Applicant, and the 4 Month Safety Update (4MSU) submitted to BLA 125786/0/14. When documents were available in both the IND and the BLA, I reviewed the IND versions. Main documents reviewed are listed below. Documents are BLA documents submitted to the original submission, unless explicitly noted otherwise.

- Protocols and Statistical Analysis Plans (SAPs) for Study 1002 under IND 16437
- Meeting minutes under IND 16437

- Applicant’s meeting minutes and slides for the Application Orientation Meeting (AOM) and the Dataset Walkthrough Meeting (held on June 5, 2023) submitted to BLA 125786/0/5
- Module 1.14 Draft Labeling
- Module 1.2 Information for Reviewer
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 2.7.6 Synopses of Individual Studies
- Module 5.2 Tabular Listing of all Clinical Studies
- Module 5.3.5.2 Study 1002 Clinical Study Report (CSR) and supporting documents and datasets

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the studies in the clinical development program of BEQVEZ that contributes to this BLA. Other BEQVEZ clinical studies not contributing data to this BLA are not listed. For example, the non-interventional 15-year extended LTFU study C0371017 does not contribute any data to this BLA and therefore is not listed in Table 1.

- Study 1004 is a lead-in study for BEQVEZ treatment studies, i.e., Study 1003 and Study 1002. It prospectively collects baseline data for at least 6 months when participants are on their usual HB care for comparison with post-BEQVEZ-treatment data. Study 1004 also enrolls Hemophilia A participants as a lead-in study for the (b) (4) [REDACTED]. This latter component is not relevant to this BLA and will not be included in this review.
- Study 1005 was intended to be a dose-escalation study but eventually all 15 participants were treated at the 5×10^{11} vg/kg dose. Participants were followed up for one year, and then followed up for an additional five years as Study 1003 Cohort 1. The product was manufactured by a process different from that for the product used in the main study (Study 1002). The reported efficacy outcome of Study 1005 participants was notably better than that of the main study. Because the study was not designed as an adequate and well-controlled trial and because of the manufacturing difference, the efficacy database of this BLA does not include Study 1005 data.
- Study 1003 consists of Cohort 1 (additional FU for Study 1005 participants) and a dose-escalation sub-study. Participants treated in the dose-escalation sub-study

would have prospectively collected baseline data from Study 1004, while Cohort 1 participants do not have these data (Table 1).

- Cohort 1 follows up participants treated in Study 1005 for an additional 5 years, for a total of 6 years post-BEQVEZ-treatment.
- The dose-escalation sub-study was added late into the clinical development, i.e., after the main study was underway using the 5×10^{11} vg/kg dose. It will investigate up to 4 additional higher dose levels. The sub-study will be conducted outside of the US. In response to FDA's inquiry about the reason to conduct a dose-escalation study after a phase 3 trial, the Applicant stated that the purpose was to investigate whether a higher dose level will lead to a higher FIX level safely, and therefore a higher dose level may be used in additional populations, e.g., pediatric patients and patients with low levels of nAbs to AAVRh74var.
- Study 1002 is the main study. Baseline data were prospectively collected in Study 1004. Participants will be followed-up for 6 years, but the main analyses will be based on a data cut-off date (DCOD) aimed to result in at least 15 months of data for around 40 treated participants.

Table 1. Summary of BEQVEZ clinical studies.

Study ID	Study description	Subject disposition as of DCOD
1004	<p>Lead-in study for the two BEQVEZ treatment studies 1002 and 1003. Also called BeneGene-1.</p> <p>Ongoing.</p> <p>The study collects prospective data on adult male HB participants (FIX:C\leq2%) who remain on their current FIX prophylaxis replacement therapy in the usual care setting to serve as baseline data for comparison with data collected after BEQVEZ treatment in Study 1002 (main study) and Study 1003. Participants are negative for nAbs to AAVRh74var.</p> <p>FSFV: July 26, 2018.</p> <p>DCOD: November 02, 2022.</p> <p>Planned FU: Minimum of 6 months.</p> <p>As of the DCOD, the median duration of FU is 1.2 years.</p> <p>Countries and Regions: Australia, Belgium, Brazil, Canada, France, Germany, Greece, Israel, Italy, Japan, Korea, Saudi Arabia, Spain, Sweden, Taiwan, Turkey, United Kingdom, United States (US).</p>	<p>102 enrolled 59 completed 40 ongoing</p>
1005	Dose escalation study.	22 enrolled

Study ID	Study description	Subject disposition as of DCOD
	<p>Completed.</p> <p>Adult male HB participants (FIX:C≤2%).</p> <p>FSFV: November 18, 2015</p> <p>LSLV: April 08, 2019</p> <p>Planned dose levels of single IV infusion of BEQVEZ: 5×10^{11}, 1×10^{12}, or 2×10^{12} vg/kg.</p> <p>Actual dose: All 15 participants received the 5×10^{11} dose.</p> <p>Duration of FU (planned and actual): One year.</p> <p>Countries and Regions: Australia and US.</p>	15 completed
1003	<p>LTFU study (Cohort 1) of 5 additional years for participants who received BEQVEZ in Study 1005, and dose-escalation sub-study (additional cohorts).</p> <p>Ongoing.</p> <p>Countries and Regions: Australia, Canada, Turkey, and US.</p> <p><u>Cohort 1</u></p> <p>FSFV: June 22, 2017.</p> <p>DCOD: November 02, 2022.</p> <p>14 enrolled after completing Study 1005: 5 completed, 7 ongoing, 1 withdrew consent, 1 lost to FU.</p> <p>FU duration: 36 to 75 months post BEQVEZ infusion.</p> <p><u>Dose-escalation sub-study</u></p> <p>Added in protocol amendment 2 (September 16, 2020).</p> <p>Up to 4 additional higher doses: 7.5×10^{11}, 1×10^{12}, 1.5×10^{12}, and 2×10^{12} vg/kg.</p> <p>Planned duration: 1 year FU with an additional 5 years of LTFU in the same study.</p> <p>Cohort 2 (1×10^{12}vg/kg): n=2 treated</p> <p>Cohort 3 (2×10^{12}vg/kg): n=1 treated</p> <p>FU duration: 7 to 108 days post BEQVEZ infusion.</p>	See left
1002	<p>Main study for this BLA. Also called BeneGene-2.</p> <p>Ongoing.</p> <p>Phase 3 single-arm study to evaluate the efficacy and safety of BEQVEZ, at a single IV infusion of 5×10^{11} vg/kg, in adult male participants with moderately severe to severe HB (FIX:C≤2%).</p> <p>FSFV: July 29, 2019.</p>	51 enrolled 45 treated

Study ID	Study description	Subject disposition as of DCOD
	DCOD: November 16, 2022. Planned: 6 years. Year 1: short-term FU. Years 2-6: LTFU. Median FU: 2.1 years. Countries and Regions: Australia, Brazil, Canada, France, Germany, Greece, Japan, Saudi Arabia, Sweden, Taiwan, Turkey, United Kingdom, US.	

Abbreviations. FIX: coagulation factor IX; FIX:C: FIX activity; IV: intravenous; LSLV: Last subject last visit; LTFU, long-term follow-up; nAbs: neutralizing antibodies; n: number of participants in a cohort; DCOD: Data cutoff date; FSFV: First subject first visit; FU: Follow-up.

Source: Adapted from - BLA 125786/0/0, Module 5.2, Table 1.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The efficacy database consists of efficacy data from Study 1002 with a DCOD of November 16, 2022. The baseline data for Study 1002 participants were prospectively collected in Study 1004, the lead-in study for Study 1002. Brief description of Study 1004 will be incorporated into the review of Study 1002 in this section. The safety database consists of data from Study 1002, Study 1005, and Study 1003 Cohort 1. This Section covers efficacy review, while Section 8 covers safety review.

6.1 Trial #1

Study 1002, the main study, was titled “Phase 3, open-label, single-arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2).”

Reviewer Comment #1: Document versions and analysis update

Prior to the BLA submission, the last protocol and SAP versions of Study 1002 submitted to IND 16437 were protocol amendment 3 (June 29, 2022) and SAP version 6 (July 7, 2022), respectively. These two versions of the documents were the ones included in the initial BLA submission.

However, I will base this review memo primarily on the newer versions submitted to the IND shortly after the BLA submission: protocol amendment 5 (May 9, 2023) and SAP version 7 (May 12, 2023). The sponsor/Applicant stated that the purpose of these two versions were primarily to add (b) (4) participants to receive BEQVEZ based on (b) (4) dosing to support this dosing regimen (Section 4.5), with additional revisions (e.g., exclusion criteria) and substantial clarifications. I defer the review of (b) (4) dosing to other review disciplines and will not cover this further in what follows. I choose to base my review on these two newer versions assuming the expositions are much improved

after the substantial clarification, and some of the FDA recommendations and queries would have been addressed. However, the summary of changes does not include information on whether some revisions in protocol version 5 introduced discrepancies between the protocol and how the trial was actually conducted based on earlier versions of the protocol, and whether there were revisions that FDA might not agree with. I will address this potential concern when I encounter such revisions relevant to this review memo.

Protocol amendment 4 (January 12, 2023) was not submitted to the IND and was revised to add 10 participants to receive BEQVEZ based on nominal dosing in several countries not including the US. This plan was subsequently superseded by protocol amendment 5, a global amendment.

The protocol and SAP for Study 1002 underwent substantial revisions throughout the clinical development, often to reflect accumulated knowledge in AAV-based gene therapy products for treatment of hemophilia A and hemophilia B. Some of the revisions were requested by the FDA and implemented by the Applicant in the IND. Some revisions to critical statistical analyses were not included in the protocol and SAP to avoid revisions close to the time of the BLA submission, but were instead included in the BLA submission as additional analyses and through Applicant responses to FDA information requests (IRs). In addition, some proposals in the protocol and the SAP may be acceptable to other regulatory authorities to which the Applicant submitted the documents but did not receive agreement from the FDA. This review memo reflects analyses included in the FDA labeling or otherwise support the FDA labeling and regulatory decision. To be concise, I do not include in this memo details of the interactions and discussions between the Applicant and the FDA leading to the final analyses.

For clarity and consistency, I replace developmental names of the product, e.g., PF-06838435, with BEQVEZ in what follows as needed.

End of Reviewer Comment #1

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective

To demonstrate the efficacy of a single infusion of BEQVEZ in male patients ≥ 18 years of age with moderately severe to severe hemophilia B (FIX:C $\leq 2\%$) in terms of annualized bleeding rate for total bleeds (ABR_{total}), which counts both treated and untreated bleeds.

Secondary Objectives

To demonstrate the efficacy of BEQVEZ in terms of the use of exogenous FIX products, ABR counting treated bleed only ($ABR_{treated}$), and FIX:C.

Reviewer Comment #2: Secondary objectives and endpoints

The secondary efficacy objectives and endpoints, proposed by the Applicant, are relevant considerations in assessing the efficacy of BEQVEZ. However, they were proposed to be considered and analyzed as stand-alone endpoints, disconnected from other efficacy endpoints. FDA established the following considerations in its review of BEQVEZ' effectiveness:

- $ABR_{treated}$ would not be considered in the labeling. In what follows, I may refer to ABR_{total} simply as ABR in discussing the primary efficacy endpoint when no ambiguity can arise. Except for in the discussion of the non-inferiority (NI) margin, $ABR_{treated}$ will not be considered further.
- Use of exogenous FIX products will be considered as a potential confounding factor in the assessment of ABR after BEQVEZ infusion, and will not be included in the labeling as a stand-alone endpoint.
- Use of exogenous FIX products and FIX:C will be considered together with bleeding pattern to identify participants for whom the treatment effect of BEQVEZ may decrease over time.
- Pattern in individual FIX:C time course will be used to assess durability of treatment effect in a descriptive way without performing statistical hypothesis test against fixed thresholds.

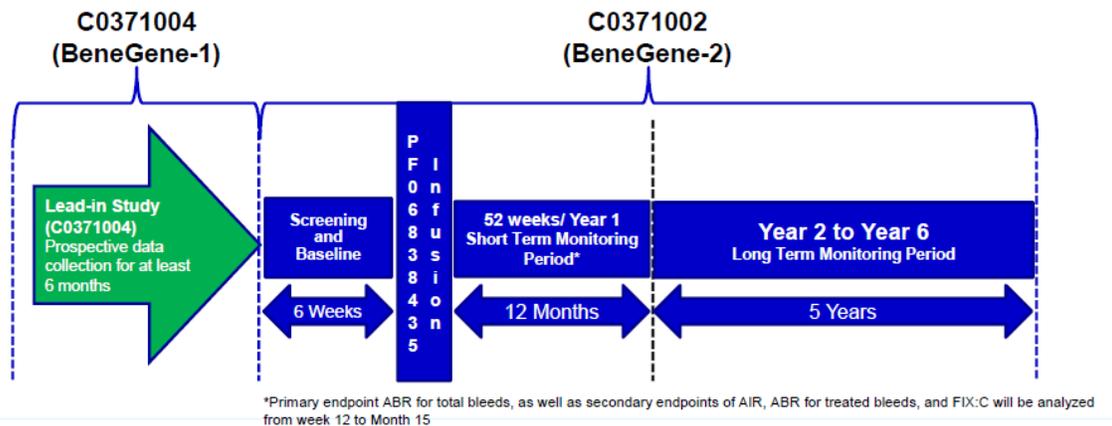
These considerations will be briefly discussed further in what follows for completeness as needed.

End of Reviewer Comment #2

6.1.2 Design Overview

Study 1002 is a phase 3, single-arm, multi-site study to compare the efficacy of a single intravenous (IV) infusion of BEQVEZ with FIX prophylaxis replacement therapy in the usual care setting in adult male patients with moderately severe to severe hemophilia B ($FIX:C \leq 2\%$). Eligible study participants will have completed at least 6 months of routine FIX prophylaxis replacement therapy in the lead-in study (Study 1004) for prospective baseline data collection. The study duration for each participant in Study 1002 will be 312 weeks, i.e., 6 years. Approximately 50 participants will be screened to achieve at least 40 evaluable participants at the time of primary completion date (PCD), when at least 40 participants have completed 15 months of FU after BEQVEZ infusion. Figure 1 depicts the study schematic.

Figure 1. Study 1002 schematic.



Abbreviations. ABR: Annualized bleeding rate; AIR: Annualized infusion rate of exogenous FIX products after BEQVEZ infusion; FIX:C: FIX activity.

Source: BLA 125786/0/5, Application Orientation Meeting slides, p.21.

6.1.3 Population

Key inclusion criteria:

- Participants must have completed at least 6 months of prospective data collection while receiving FIX prophylaxis replacement therapy as per their usual care in the lead-in study (Study 1004) prior to providing consent at the screening visit for this study (Study 1002). The duration of each patient's participation in Study1004 may be longer than 6 months as it will be dictated by the timing of their enrollment into Study 1002.
- Participants who have documented moderately severe to severe hemophilia B, defined as FIX:C $\leq 2\%$.
- Participants who have previous experience with FIX therapy (≥ 50 documented exposure days to a FIX protein product such as recombinant, plasma-derived, or extended half-life FIX product).
- Participants must agree to suspend prophylaxis therapy for hemophilia B after administration of the BEQVEZ. FIX replacement therapy is allowed as needed.

Key exclusion criteria:

- Anti-AAVRh74var nAb titer above the established threshold (i.e., positive for nAb), performed by a central laboratory during screening.
- Prior history of inhibitor to FIX or positive inhibitor testing as measured by the central laboratory ≥ 0.6 Bethesda Units during screening, clinical signs or symptoms of decreased response to FIX.

- Any participant with a planned surgical procedure requiring FIX surgical prophylactic factor treatment in the next 15 months.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatment, a single infusion of 5×10^{11} vg/kg of BEQVEZ, will be administered on Day 1.

A participant may resume FIX prophylaxis if the BEQVEZ treatment is not efficacious, defined for this study as:

- FIX activity after 12 weeks of $\leq 2\%$ (in the absence of a confirmed FIX inhibitor) as determined by the central laboratory on 2 consecutive samples collected within a 2-week period;
and/or
- Over a 4-week period (in the absence of a confirmed FIX inhibitor),
 - 2 or more spontaneous bleeds into a major joint and/or target joint;
or
 - 3 or more spontaneous bleeds (consisting of joint bleeds and/or significant soft tissue/muscle or other site bleeds).

Significant spontaneous bleeds are defined as those that lead to a transient or persistent loss of function.

The investigator is to inform the sponsor's medical monitor prior to resumption of prophylaxis or if prophylaxis has been resumed. A participant who resumes prophylaxis may choose to discontinue it. In such cases, the investigator should inform the sponsor for awareness.

In addition, a substantial number of participants received corticosteroids (CS) for an extended time, to address immune response to vector capsids leading to a rise in liver function tests, or a decline in FIX activity levels, or both.

6.1.6 Sites and Centers

A total of 27 sites in 13 countries treated at least one participant (Table 2). US treated the largest number of participants (9/45, 20%), followed by Turkey (7/45, 16%) and Taiwan (5/45, 11%). No single site contributes disproportionately to the data package; the largest number of participants treated at any site was 4, at one site each in France, Turkey and the US, respectively.

Table 2. Study 1002: Distribution of participants treated with BEQVEZ by countries.

Country	Number of Participants	Number of Sites
Australia	2	2
Brazil	3	2
Canada	3	2
Germany	3	2
France	5	2
United Kingdom	1	1
Greece	2	1
Japan	1	1
Saudi Arabia	2	1
Sweden	2	1
Turkey	7	4
Taiwan	5	3
United States	9	5
Total	45	27

Source: FDA reviewer analysis.

6.1.7 Surveillance/Monitoring

In Study 1002, the day of BEQVEZ will be designated Study Day 1. Each treated participant is expected to be followed-up for 6 years in the study. The first 52 weeks (Year 1) post-infusion is the short-term monitoring period while Years 2 to 6 is the long-term monitoring period. During the short-term monitoring period, study visits will occur on Weeks 1, 2, 4, 8, 12, 18, 24, 32, 42, and 52. During the long-term monitoring period, study visits will occur every 6 months for Years 2 and 3 (i.e., on Weeks 78, 104, 130, and 156), and yearly for Years 3 to 6 (i.e., on Weeks 208, 260, and 312). FU time in months is calculated as Study Day/30.4375 (365/12=30.4375). FU time in years is calculated as 12 months per year, i.e., 365 days.

An eDiary, a handheld device, will be provided to all participants on Visit 1. The participants are required to enter any occurrence of hemophilic bleeding episodes (including date, time, location, and etiology) and any exogenous FIX replacement (including date, time, reason, and dose) required to treat the bleeds in the eDiary.

In the event that a participant may have to resume FIX prophylaxis treatment at some point after BEQVEZ infusion, prophylaxis FIX infusion data will not have to be reported on the eDiary (or conveyed to the study site staff on contemporaneous basis) after Week

78 (Visit 14, Month 18). However, bleeds and non-prophylactic infusions (e.g., On-demand and Preventative) would continue to be reported for these participants throughout the course of the study. Prescribed FIX prophylaxis replacement therapy will continue to be captured (e.g., particularly any change in regimen), by the site staff, using the “FIX Replacement (Prescribed Dose)” case report form (CRF).

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint: Annualized bleeding rate for total bleeds (ABR_{total})

The primary efficacy endpoint is a non-inferiority (NI) comparison of ABR_{total} during the efficacy evaluation period (EEP: from Week 12 [Day 82] to DCOD) versus that during the baseline period where participants receive FIX prophylaxis in the usual care setting. The baseline ABR is obtained from data in the lead-in study (Study 1004) and the pre-infusion period in Study 1002 (period prior to BEQVEZ infusion in Study 1002). Bleeding episodes associated with a surgical procedure (perioperative and/or during the surgical rehabilitation period) will not be included in the ABR_{total} calculation.

The trial would be considered a success if the upper bound of the 95% confidence interval (CI) on the mean difference of ABR is less than the NI margin of 3.0 bleeds/year.

Reviewer Comment #3: Efficacy evaluation period and other primary endpoint considerations

The Applicant initially proposed the EEP to be from Week 12 [Week 12 ± 2 days of visit window, Day 82] to Month 15 [Week 65 ± 2 weeks of visit window, Day 469].

EEP is to start from Week 12 to allow BEQVEZ to take effect, i.e., in the Applicant’s words, to reach a “steady state.” Though it is reasonable to start EEP from Week 12, steady state can be a misnomer as participants may experience rapid decline in FIX:C during the FU period.

For the end of EEP, the FDA advised the Applicant to revise it from Month 15 to data cut-off date (DCOD), for the following considerations:

- BEQVEZ is a one-time treatment intended to have a long-lasting effect, compared to chronic treatment with FIX prophylaxis. As such, it is important to characterize the treatment effect of BEQVEZ over a FU period of adequate duration for the benefit-risk assessment of BEQVEZ versus standard-of-care FIX prophylaxis, considering the risk profile of both treatment regimens. While it is reasonable to have the primary completion date (PCD) be when at least 40 participants had completed the 15-month FU, we should include all data that are already available at PCD, including those data past the 15-month FU for some participants, to maximize information content for the comparison. These data are already available so there is no good reason to exclude them.
- FU included in the primary analysis should also be adequate to allow characterization of use and effect of important concomitant medications (CMs).

Corticosteroids (CSs) are commonly used in AAV-based gene therapy products for hemophilia A and B.

- In addition to the NI comparison of ABR during EEP with baseline ABR, it is important to summarize durability of the treatment effect over time. We will include this analysis in this memo and the labeling.

End of Reviewer Comment #3

Key secondary efficacy endpoint: FIX activity

Pattern in FIX:C time course will be used to assess durability of treatment effect in a descriptive way without performing statistical hypothesis test against fixed thresholds.

In addition, characterization of bleeding episodes, e.g., joint and spontaneous bleeds, will be summarized descriptively.

Reviewer Comment #4: Secondary endpoints

As described in *Section 6.1.1 Objectives (Primary, Secondary, etc)*, I considered the secondary efficacy endpoints proposed by the Applicant and decided to treat them in a way similar to how the information is incorporated into the treatment effect evaluation in approved AAV-based hemophilia gene therapy products. In this reviewer comment, I will describe in some detail the considerations behind my alternative analysis approach for FIX:C.

The Applicant defined the FIX:C key secondary endpoint as the geometric mean of all valid measurements of FIX:C following steady state (Week 12 weeks [Day 82]) to Month 15 [Day 469], inclusive, which is to be compared to a fixed threshold of 5%. This definition is not clinically meaningful and can be difficult to interpret for the following reasons.

In Study 1002, FIX:C was measured by three assays simultaneously: the one-stage Actin-FSL assay, the one-stage SynthASil assay, and the Chromogenic assay. The one-stage Actin-FSL and Chromogenic assays gave lower readings than the one-stage SynthASil assay; the reading by the latter can sometimes be twice as much as the former two. Furthermore, it is unknown whether BEQVEZ-derived FIX:C with the same reading by the same assay as that given by an exogenous replacement product would have the same clinical effect in the same patient. As such, while FIX:C thresholds such as 5% may be familiar to the hemophilia community in the context of replacement products, BEQVEZ-derived FIX:C readings do not translate to the expected clinical effect based on past experiences from plasma-derived or recombinant FIX replacement products.

Another consideration is that BEQVEZ is a one-time treatment, in contrast to the chronic nature of existing replacement products. Therefore, it is of critical importance to examine the durability (constancy) of the treatment effect over time, instead of the average effect over time assuming constancy which may not hold.

Due to these considerations, instead of the proposed FIX:C endpoint definition, we prioritize investigating the time course of FIX:C in participants treated with BEQVEZ to address the durability question of the treatment effect. FDA recommended this approach to the Applicant prior to the BLA submission and the Applicant agreed to include descriptive statistics in the BLA submission.

I have decided to use the one-stage Actin-FSL assay FIX:C reading in the remainder of this review, as this is sufficient to address the durability question and it is what the Applicant used for reporting primary assay results.

End of Reviewer Comment #4

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary analysis is planned when 40 participants have completed 15 months of follow up after BEQVEZ infusion. The final analysis will be conducted when all treated participants have completed the entire study, i.e., 6-year FU, or discontinued.

Non-inferiority margin

The Applicant set the NI margin at 3.0 bleeds/year in mean difference between the EEP ABR and the baseline ABR (while participants are on prophylaxis during usual care). To support this choice, they stated that when comparing ABR_{treat} between on-demand and prophylaxis regimens in clinical trials, mean ABR_{treat} from on-demand regimen is higher than that from prophylaxis by at least 24.5 bleeds/year based on the lower bound of a 95% confidence interval (CI). They further assumed that the mean difference in ABR_{total} was increased by a factor of 1.17, resulting in 28.7 bleeds/year ($1.17 \times 24.5 = 28.7$). They then proposed an NI margin of 3.0 bleeds/year, preserving 89.5% of the prophylaxis treatment effect in clinical trials, based on considerations on clinical meaningfulness and feasible sample size. FDA accepted the proposed NI margin.

Reviewer Comment #5: NI margin

In setting the NI margin, the Applicant recognized that there were several sources of uncertainties: there could be a difference of around 4 bleeds/year in ABR between real-world and clinical trial settings, and ABR would depend on the specific prophylaxis product/regimen and patient population.

Given that Study 1002 is a single-arm international study with a multitude of prophylaxis products/regimens observed in a usual care setting instead of in a clinical trial setting, it is important to also consider the absolute magnitude of EEP ABR and baseline ABR in the context of the participants actually included in the trial when interpreting the trial results.

End of Reviewer Comment #5

Sample size

The Applicant stated that with 40 participants, under the assumption of a baseline ABR of 5.0 bleeds/year and an EEP ABR of 1.5, respectively, there is a >90% statistical power to demonstrate NI with a margin of 3.0, for a one-sided test with a significance level of 0.025.

Analysis sets

- Enrolled. All participants who signed the informed consent form and met all inclusion/exclusion criteria.
- Dosed. All participants enrolled in the study who received BEQVEZ infusion.
- Evaluable. All participants enrolled in the study who received BEQVEZ infusion and have no significant interruption of efficacy measurement.
 - The Evaluable analysis set would exclude participants with significant interruption of efficacy measurement, or participants who do not have or have not yet completed 15 months of FU post BEQVEZ infusion. Significant interruption will be assessed after discussion between the investigator and the medical monitor, e.g., if a participant requires a major surgery, this will be a significant interruption of measurement.

Reviewer Comment #6: Analysis set

While the Applicant initially proposed to use the Evaluable analysis set for the primary analysis of the primary efficacy endpoint. FDA and the Applicant reached agreement to use the Dosed analysis set (DAS) instead for improved efficiency.

End of Reviewer Comment #6

Reviewer Comment #7: Testing for superiority

The Applicant proposed to further test for superiority of BEQVEZ over FIX factor prophylaxis, if the statistical test for NI in ABR is significant. FDA has determined that this BLA does not present statistically highly persuasive evidence to base a conclusion of superiority on a single adequate and well-controlled trial.

End of Reviewer Comment #7

Primary analysis on the primary efficacy endpoint ABR_{total}

ABR_{total}, the primary efficacy endpoint, will be analyzed using a repeated measures generalized linear model (GLM) with a negative binomial distribution and the identity link function. The model will include treatment (baseline or EEP) as a factor, participant as a random effect, and duration (the elapsed time in years of each treatment period).

Reviewer Comment #8: Confounding by use of FIX replacement products and related issues

For participants who resumed FIX prophylaxis after BEQVEZ infusion, as defined by the protocol, the Applicant proposed to exclude the data after the resumption from the primary analysis. This approach is biased because it excludes all the data that are unfavorable to BEQVEZ in the NI comparison. Instead, I recommended to address the confounding on ABR caused by post-infusion FIX prophylaxis in a way similar to those used in the labeling of approved AAV-based gene therapies for hemophilia B or hemophilia A, i.e., Hemgenix and Biomarin. Specifically, an ABR of 20 bleeds/year, if determined to be appropriate in the BEQVEZ setting, could be imputed for the EEPs confounded by use of prophylaxis FIX, including those not meeting the protocol-defined prophylaxis criterion. Some considerations and caveats are below.

- One possible approach to imputing an ABR for the confounded EEPs is through a hypothetical strategy in handling an intercurrent event in the estimand framework. This imputed ABR is intended to be the hypothetical ABR a participant would experience in the absence of the rescue FIX products. Although not receiving the rescue medication may not happen often in developed countries, in the absence of concurrent controls, the hypothetical strategy serves to isolate the effect of BEQVEZ from the RP comparator to an extent, which is important because the duration of effectiveness of BEQVEZ without RP is a key clinical consideration. The treatment policy would have confounded the effect of BEQVEZ with that of FIX prophylaxes, the comparator, invalidating the NI comparison. Furthermore, there exists considerable historical data on ABR for patients similar to those treated with BEQVEZ in Study 1002, while they received on-demand or RP treatment regimens, to inform the hypothetical ABR choice.
- It is difficult to predict what ABR any particular participant would experience in the absence of the rescue FIX products. Assuming that it is close to what a participant might experience when receiving only on-demand treatment is probably a conservative assumption that provides confidence in the overall conclusion of non-inferiority.
- After arriving at the decision to impute a single unconfounded ABR that reflects the mean ABR confounded participants/EEPs would have experienced if they received only on-demand treatment, there are two sources of information to support the choice of this imputed unconfounded ABR.
 - One source of information is the reported mean on-demand ABR for similar HB patients from literature. The Hemgenix file reported mean on-demand ABR from several clinical trials, all less than or around 20 bleeds/year (See <https://www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix> for the public posted statistical review memo in the approval related documents). On the other hand, the BEQVEZ IND reported a mean ABR difference between RP and on-demand of 28.7 bleeds/year, indicating a mean on-demand ABR being greater 28.7 bleeds/year. This difference reflects different but reasonable selections of literature. For the purpose of setting the single unconfounded ABR to be imputed, it is reasonable to use the same tentative 20 bleeds/year for

consistency across submissions, as both should reflect the same historical data.

- On FDA's request, the applicant performed a tipping point analysis examining when the NI conclusion would no longer hold, given that there is considerable uncertainty associated with the choice of the imputed ABR.

On a related note, the Applicant proposed not to impute for any missing data caused by loss to follow up. This is also potentially biased in favor of BEQVEZ, as it is possible loss-to-FU may be due to lack of efficacy. In practice, this issue did not arise in the application.

From experience and discussion with the clinical review teams for similar gene therapy products, there were uses of FIX products during the EEPs without clearly documented reasons. While I will designate some of these periods as confounded EEPs and impute bleed counts accordingly, this is an intractable issue and the imputation is likely an underestimate as some of the uses might have been treatment for subclinical bleeds.

End of Reviewer Comment #8

Reviewer Comment #9: Additional efficacy evaluation: Diminishing treatment effect over time, corticosteroids use, and FIX:C time course

While the SAP included multiple secondary endpoints for hypothesis testing, I have discussed in *Section 6.1.8 Endpoints and Criteria for Study Success* that these endpoints should not be considered in univariate analyses and statistical tests are not interpretable. In what follows I describe three statistical analyses that will provide further characterization of the BEQVEZ treatment effect.

Diminishing treatment effect over time. The Applicant reported the proportion of participants resuming routine prophylaxis (RP) per protocol definition to assess the durability of the BEQVEZ treatment effect. This approach does not capture all the diminished effectiveness, as some participants might not have resumed RP (immediately) despite increased bleeding and negligible FIX:C and some participants might have used FIX product in a prophylactic manner without meeting the protocol definition of RP.

Corticosteroids (CS) use. A substantial number of Study 1002 participants used CS to manage transaminase elevations and potential loss of transgene expression. CS use also confounds the treatment effect of BEQVEZ. However, due to the extensive use, I view CS use as an integral component of the BEQVEZ treatment regimen and will not attempt to isolate the treatment effect of BEQVEZ in the absence of such CS use. I will describe the extent of CS use in the results section.

FIX:C time course. I will summarize the FIX:C data to highlight the time course, instead of testing whether the mean FIX:C was greater than some threshold at some time points, as discussed in *Section 6.1.8 Endpoints and Criteria for Study Success*. The SAP includes several imputation rules when FIX:C were missing or confounded by FIX product use. For example, it proposed to impute FIX:C post RP resumption based on baseline

hemophilia B severity: 0.9% for severe HB and 1.9% for moderately severe HB, respectively. It also proposed to impute missing Week 65 (Month 15) FIX:C as the average of the preceding and following valid assessments.

In the original submission to the BLA, for the analysis of FIX:C the Applicant used a washout period of 7 days for plasma-derived or standard recombinant FIX and 14 days for extended half-life recombinant FIX. FDA reviewers in the clinical and clinical pharmacology disciplines requested the Applicant to reanalyze FIX:C data using a washout period of 5 times the half-life of the exogenous FIX products, citing that “*These proposed washout periods are not adequate ... For example, some extended half-life recombinant FIX products have a half-life of over 4 days and [are] expected to have a trough level > 5% depending on the dosing regimen.*” The Applicant reported a range of 17 to 118 hours for half-life for replacement products, therefore the updated washout period of 5 times half-life has a range of 3.5 to 24.6 days. In BLA 125786/0/13 the Applicant updated FIX:C data with the new washout period definition. The Applicant concluded that the two definitions of washout period do not lead to material difference in the FIX:C results.

End of Reviewer Comment #9

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

The dosed analysis set (DAS) consists of the 45 participants who received a single dose of BEQVEZ. By the DCOD of November 16, 2022, 41 participants had at least 15 months (\pm 2 Weeks) of FU. Table 3 summarizes the demographics of these 45 participants. All participants were male and 62% of the participants were < 35 years of age. A majority of participants were White (33 [73%]) and not Hispanic or Latino or Spanish origin (35 [78%]).

Table 3. Study 1002: Demographics.

	BEQVEZ-treated Participants (N=45)
Age (Years), n (%)	
< 35	28 (62)
\geq 35	17 (38)
Median (Minimum, Maximum)	29 (18, 62)
Race, n (%)	
White	33 (73)
Black or African American	1 (2)

	BEQVEZ-treated Participants (N=45)
Asian	7 (16)
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Not reported	4 (9)
Ethnicity, n (%)	
Hispanic or Latino or Spanish origin 2 (4.4)	2 (4)
Not Hispanic or Latino or Spanish origin	35 (78)
Not reported	8 (18)

Source: Adapted from-BLA 125786/0/0, Study 1002 Clinical Study Report, p.43, Table 4.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Of the 45 participants who received BEQVEZ, 38 (84%) had FIX:C<1% and 7 (16%) had FIX:C from 1% to 2% (inclusive). A total of 15 (33%) participants were positive for hepatitis C virus, 13 (29%) were positive for hepatitis B virus and 3 (7%) for human immunodeficiency virus. All participants had a factor mutation. Target joints at baseline were identified in 13 (29%) participants. The most commonly reported significant medical history was musculoskeletal and connective tissue disorders (22 [49%] participants) and surgical and medical procedures (21 [47%] participants).

6.1.10.1.3 Subject Disposition

A total of 51 participants who completed the lead-in study (Study 1004) were screened in Study 1002, of which 45 received a single dose of BEQVEZ at the posed dose level of 5×10^{11} vg/kg. Five participants were screen failures, and a sixth participant discontinued for other reasons before receiving BEQVEZ.

6.1.11 Efficacy Analyses

The analysis set for this efficacy analyses section is the dosed analysis set (DAS) consisting of all 45 BEQVEZ treated participants.

6.1.11.1 Analyses of Primary Endpoint(s)

Efficacy evaluation periods confounded by factor replacement product use for extended prophylaxis

The efficacy evaluation period (EEP) for each subject was Week 12 (Day 82) to data cutoff following BEQVEZ treatment. The first 81 days after BEQVEZ treatment was not included in the EEP to allow BEQVEZ to take effect. The primary efficacy analysis is a NI test of EEP ABR compared to baseline ABR.

Some participants resumed routine prophylaxis (RP) after BEQVEZ treatment, or used factor replacement products for an extended period for prophylaxis. As previously discussed, prophylaxis use of factor products after BEQVEZ treatment confounded the treatment effect of BEQVEZ. We will attempt to isolate the BEQVEZ treatment effect by imputing a hypothetical bleed counts for the confounded EEPs. The hypothetical strategy attempts to approximate the number of bleeding events a participant who used prophylaxis during EEP would have experienced in the absence of the confounding prophylaxis products.

Table 4 summarizes the confounded EEPs for 8 participants. Six participants resumed RP starting from Day 155 to Day 623 (0.4 to 1.7 year) after BEQVEZ treatment; 5 due to FIX:C level and 1 due to bleed frequency. One participant (Subject ID (b) (6)) had used prophylaxis from Day 395 to Day 472, prior to resuming RP on Day 623. Two additional participants had used factor products in a prophylaxis-like manner for 81 and 8 days, respectively. Because imputation would not lead to any difference in analysis results for the participant with the 8-day confounded period, this participant will not be included in description of imputation in the primary ABR analysis.

Table 4. Study 1002: Confounded efficacy evaluation periods in 8 participants.

	Subject ID	Prophylaxis-like Period Start (Study Day)	Prophylaxis-like Period End (Study Day)	Routine Prophylaxis Resumption Start (Study Day)	Data Cut-off (Study Day)	Efficacy Evaluation Period (Days)
1	(b) (6)	-	-	155	791	710
2		-	-	198	555	474
3		-	-	275	799	718
4		-	-	365	1078	997
5		-	-	410	514	433
6		395	472	623	728	647
7		162	242	-	1024	943
8		803	810	-	1088	1007

Efficacy evaluation period (EEP) is from Day 82 to Data Cut-off.

Subject (b) (6) had only 8 days of confounded period during their EEP, which do not result in a difference in the primary analysis whether imputation is implement. This subject will not be included in the description of the imputation in the primary analysis.

Source: Adapted from - BLA 125786/0/20, Applicant's response to FDA's Information Request, p.4, Table 1.

Primary analysis of ABR, the primary efficacy endpoint (imputation of ABR=20 for confounded EEPs)

Table 5 summarizes the primary analysis of ABR, together with additional bleeding event related information deemed important to include in the package insert. The median

duration of EEP was 1.8 (range: 0.2 to 3.0) years, with a total of 83 person-years of EEP. The model-derived mean baseline ABR was 4.5 [95% confidence interval (CI): 1.9, 7.2] bleeds/year, and the model-derived mean EEP ABR was 2.5 [95% CI: 1.0, 3.9] bleeds/year, resulting in a difference between the mean EEP ABR and the mean baseline ABR of -2.1 (95% CI: -4.8, 0.7) bleeds/year. The upper bound of the 95% CI in the difference was less than 3.0 bleeds/year, meeting the NI study success criterion.

Table 5. Study 1002: Summary of annualized bleeding rate and bleeding events (N=45)

	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)	1.3 (0.0, 53.9) ^c	0.0 (0.0, 19.0) ^b
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 bleed (proportion of total bleeds)	157 (70%)	60 (61%)
Number of observed joint bleed (proportion of total bleeds)	184 (82%)	71 (72%)

Abbreviations. ABR: Annualized Bleeding Rate for all bleeds (treated and untreated with factor IX, excluding procedural bleeds); CI: confidence interval.

- 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 after BEQVEZ infusion. 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: Adapted from - BLA 125786/0, Draft Package Insert, Table 5.

Supplementary analyses

Two types of supplementary analyses were performed to assess the robustness of the conclusion of BEQVEZ effectiveness to imputation and influential data points.

First, a tipping point analysis was performed to evaluate when the NI conclusion would no longer hold. The minimum hypothetical ABR to be imputed for the NI study success

criterion to no longer be met is 40 bleeds/year, indicating reasonable robustness of the NI conclusion to the imputed hypothetical ABR.

In addition, a single participant, with a baseline ABR of 53.9 bleeds/year and an EEP ABR of 4.7 bleeds/year, disproportionately influenced the baseline ABR estimate. A supplementary analysis, excluding this participant, still met the NI study success criterion.

Corticosteroids use as a component of the treatment regimen

In Study 1002, transaminase elevations (defined as $\geq 1.5 \times$ baseline) occurred in 29 (64%) participants. Twenty-eight (62%) participants received corticosteroids (CS) for transaminase elevation and/or decline in factor IX activity. The mean time to CS initiation was 45 days. The mean duration of CS treatment was 113 days (range: 41 to 276 days). All 6 participants who resumed routine prophylaxis were on CS.

Decision for initiation of CS was at the discretion of the Investigator, though the protocol recommended criteria based on transaminase increase or FIX:C decrease in initial local lab results. The reason for investigator's decision to initiate CS was not explicitly collected in the case report form.

FDA was interested in whether participants who received CS would be able to stop CS and in the performance over time after cessation of CS. To that end, there was discussion of the need for at least 12 months of data after cessation of CS. During the BLA Application Orientation meeting, the Applicant provided the following information regarding FU after cessation of CS: *“Among the participants who received corticosteroid, 75% (21/28) had ≥ 12 months of follow-up post-corticosteroid cessation, 11% (3/28) had 10- <12 months of follow-up post-cessation. 14% (4/28) had less than 10 months of follow-up post-cessation, however, 3 out of these four participants had not reached 15 months of total follow-up by the data cutoff date.”* FDA considered the duration of FU adequate for the data package.

Reviewer Comment #10: Additional unquantifiable uncertainties in the estimate of treatment effect size

There are some additional uncertainties in the estimation of the treatment effect attributable to the BEQVEZ treatment regimen (BEQVEZ + corticosteroids), i.e., without confounding by preventive use of exogenous factor IX replacement products, beyond those quantified in the primary analysis.

- Single-arm studies often involve additional uncertainties and potential biases that may be difficult to quantify. In Study 1002, for example, the data from the high-baseline-ABR participant (baseline ABR at 53.9 bleeds/year) contribute disproportionately to the treatment effect estimate which may be less generalizable to the indicated population. However, I agree with the Applicant that it was important to include participants who experienced frequent bleeding despite being on RP.

- To isolate the effect of the BEQVEZ treatment regimen, a hypothetical ABR of 20 bleeds/year was imputed for the EEPs confounded by extended use of factor products for prophylaxis. While this choice of imputation is supported by some rationales, it is unknown how closely it approximates the hypothetical situation of no prophylactic use of FIX replacement products.
- There are additional occasional one-time uses of factor products for preventive purposes without documented reasons in several participants during their EEPs, including those who eventually resumed routine prophylaxis. It is unknown whether some of these might have been used to treat undocumented bleeds or bleeds adjudicated not to be new bleeds. I determined that such uses are not at a scale that will change the qualitative conclusion of the effectiveness of BEQVEZ, though they will affect the estimate of the treatment effect if incorporated into the analysis. I have not identified a reasonable approach to incorporate these uses into the analysis, and because the conclusion of effectiveness will not be affected, these uses have not been addressed in the primary analysis of ABR.

Through supplementary and sensitivity analyses, I conclude that these additional uncertainties do not affect the qualitative NI conclusion on the treatment effect of BEQVEZ. However, we should be aware that the treatment effect estimate is associated with additional unquantifiable uncertainties.

End of Reviewer Comment #10

6.1.11.2 Analyses of Secondary Endpoints

FIX:C over time

Table 6 summarizes the percentiles of FIX:C by three assays over time. I requested the Applicant to use an imputation addressing FIX:C measurements that were confounded by factor replacement product use or missing due to dropouts. This is intended to be a descriptive summary and not for formal statistical testing as discussed previously.

First, the three assays yielded quite different readings for the same sample, with One-Stage SynthASil Assay yielding readings 2 to 3 times that of the other two assays. The ratio of the reading by one assay over that by the other is not constant across samples, and the relative magnitude of those readings can reverse directions in two samples.

Table 6 includes information at 5 scheduled visits: Weeks 24, 52, 65, 104, and 156, corresponding roughly to Month 6, 12, 15, 24, and 36. There were only three participants having FU to Week 156, giving too little data to draw any conclusion. The time trend appears to confirm the observation in the ABR data:

- A small portion of participants (< 25%) had insignificant levels of FIX:C towards the end of the FU.
- The median FIX:C stabilized after the first year (Week 52), while experiencing some decline from Week 24 to Week 52.

Table 6. Study 1002: Percentiles of FIX:C by three assays over time.

Percentile	Week 24 (n=44)	Week 52 (n=43)	Week 65 (n=41)	Week 104 (n=23)	Week 156 (n=3)
One-Stage Actin-FSL Assay					
Minimum	0.0	0.0	0.0	0.0	5.0
10 th	2.1	0.5	0.0	0.0	-
25 th	6.9	2.7	3.5	3.6	-
Median	9.9	9.6	10.2	9.5	12.5
75 th	15.1	16.1	18.8	16.0	-
90 th	24.3	22.1	30.5	26.7	-
Maximum	55.0	59.7	63.5	46.6	22.0
One-Stage SynthASil Assay					
Minimum	0.0	0.0	0.0	0.0	10.2
10 th	6.1	2.0	0.0	0.0	-
25 th	16.2	8.1	9.2	7.2	-
Median	23.7	21.1	23.3	22.9	21.3
75 th	32.5	33.1	35.3	34.6	-
90 th	48.0	42.8	42.9	43.1	-
Maximum	99.7	105.4	119.0	95.3	35.3
Chromogenic Assay					
Minimum	0.0	0.0	0.0	0.0	4.4
10 th	3.5	1.0	0.0	0.0	-
25 th	5.3	2.8	4.0	3.6	-
Median	10.3	10.8	10.2	10.6	11.3
75 th	20.9	23.0	24.4	22.6	-
90 th	27.8	27.7	27.1	29.0	-
Maximum	57.7	65.0	74.2	80.3	18.3

If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the FIX activity assessments at the visits following withdrawal/dropout/resumption will be imputed as 0. If the FIX activity assessment was missing at a visit (except last visit prior the data cut-off), it was imputed with value from the following visit. If there was no unconfounded FIX:C after a timepoint, FIX:C was imputed as 0 from that timepoint onward. FIX activity assessment missing at the last visit prior the data cut-off was not imputed as there may be valid assessments after data cut-off in this ongoing study. Any samples taken within 7 days (14 days if extended-half-life product is used) of exogenous FIX replacement therapy are not included.

Source: Adapted from - BLA 125786/0/20, Applicant's response to FDA's Information Request, pp.9-10, Table 3.

Decreased treatment effect over time

At the time of writing of this memo, there is an ongoing discussion between the FDA clinical review team and the Applicant on whether, in addition to the 6 participants who resumed RP, there were additional subjects who no longer responded to BEQVEZ, as indicated by increased (spontaneous) bleeding frequency, (frequent) one-time preventive use of factor products, and declining FIX:C. I defer this to the clinical review team.

6.1.11.3 Subpopulation Analyses

Subgroup analyses on ABR were performed by age, race, ethnicity, and region (Table 7). The results are consistent. The upper bounds of the 95% CIs on the difference in the mean ABRs are less than the NI margin of 3.0 bleeds/year in all subgroups except for the subgroup of "Hispanic or Latino or unknown." This latter group has a sample size of 10 and an upper bound 3.6 bleeds/year, slightly above the NI margin. Given the small sample size in this subgroup, the multiplicity associated with multiple subgroup analyses, and the closeness of 3.6 bleeds/year to the NI margin, I conclude that BEQVEZ is effective in this subgroup as well.

Table 7. Study 1002: Subpopulation Analysis.

Subpopulation	n	Baseline ABR (95% CI) [bleeds/year]	EEP ABR (95% CI) [bleeds/year]	Difference in mean ABRs (95% CI) [bleeds/year]
Age				
18 to 29 years	24	5.9 (1.3, 10.6)	3.4 (1.0, 5.9)	-2.5 (-7.3, 2.3)
30 to 62 years	21	2.9 (0.9, 5.0)	1.3 (0.3, 2.3)	-1.6 (-3.9, 0.7)
Race				
White	33	4.0 (0.7, 7.2)	1.8 (0.4, 3.1)	-2.2 (-5.5, 1.2)
Not White or unknown	12	6.0 (1.5, 10.5)	4.4 (0.7, 8.0)	-1.7 (-6.2, 2.9)
Ethnicity				
Not "Hispanic or Latino"	35	4.4 (1.2, 7.6)	1.9 (0.6, 3.2)	-2.5 (-5.8, 0.8)
Hispanic or Latino or unknown	10	4.8 (0.4, 9.1)	4.4 (0.0, 8.8)	-0.3 (-4.2, 3.6)
Region				
United States	9	3.9 (-0.4, 8.2)	1.2 (-0.5, 2.9)	-2.7 (-7.2, 1.8)
Not United States	36	4.6 (1.5, 7.8)	2.8 (1.1, 4.5)	-1.9 (-5.1, 1.4)

Abbreviations. ABR: Annualized bleeding rate; EEP: Efficacy evaluation period; CI: Confidence interval. Age subpopulation is dichotomized by the median age of 29 years.

Groups of small sizes are aggregated into one subpopulation.
Estimates and CIs are derived from the same model used in the primary analysis for ABR.

Source: Reviewer’s analysis.

6.1.11.4 Dropouts and/or Discontinuations

One participant (Subject ID (b) (6), 2%) withdrew early from Study 1002 on June 1, 2022, prior to the DCOD of November 16, 2022. This subject was from a Turkey site, and had 2.5 years of FU by the time of withdrawal. He resumed RP on Day 368 (Year 1) given that “his FIX:C level had been < 2% for 7 months.”

8. INTEGRATED OVERVIEW OF SAFETY

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database consists of safety data on a total of 60 participants treated with the proposed dose of BEQVEZ, 45 participants in Study 1002 and 15 in Study 1005, respectively, with the FU period until the data cut-off dates (DCODs) of the 4MSU. Safety data on Study 1005 participants who were further followed up as Cohort 1 in its corresponding LTFU Study 1003 are included in this Safety Analysis Set (SAF) as well. Safety data from these three studies are pooled because participants had similar eligibility criteria and received the same dose of BEQVEZ.

In addition, four participants were treated in the dose-escalation substudy (Cohorts 2 and 3) in Study 1003 with doses different from the proposed dose and with limited FU (range: 119 to 246 days). The safety data on these 4 participants are not included in this review. LTFU Study 1017 had only one participant enrolled with no reported adverse events (AEs). This participant will not be mentioned further.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 8 summarizes the duration of FU for the 60 participants in the safety analysis set. The 45 Study 1002 participants had a total FU of 109 person-years (median: 2.4 years; range: 0.8 to 3.6 years). The 15 Study 1005 participants had a total FU of 77.5 person-years (median: 5.9 years; range: 1.0 to 6.7 years). Two and three participants in Study 1002 and Study 1005/1003 Cohort 1, respectively, discontinued early.

All participants in the SAF are males. Table 9 summarizes the demographics and baseline characteristics in the SAF.

Table 8. Number of participants in the Safety Analysis Set and their duration of follow-up by the 4-month safety update cut-off date.

	Study 1002	^a Study 1005 and	Pooled
--	------------	-----------------------------	--------

		Study 1003 Cohort 1	
Number of participants	45	15	60
Duration of follow-up (years)			
Median (Minimum, Maximum)	2.4 (0.8, 3.6)	5.9 (1.0, 6.7)	2.6 (0.8, 6.7)
(1 st quartile, 3 rd quartile)	(1.9, 3.0)	(4.9, 6.0)	(2.1, 3.4)
Total duration of follow-up (person-years)	109.0	77.5	186.5
Number of participants who discontinued early	2 ^b	3 ^c	5

^a Study 1005 participants were followed up for one year and then transitioned to Study 1003 Cohort 1 for a total follow-up of six years after BEQVEZ infusion.

^b Two participants discontinued Study 1002 early. Participant (b) (6) withdrew consent on Day 910 (Year 2.5). He resumed exogenous prophylactic FIX therapy on Day 368 (Year 1) given that his FIX level had been <2% for 7 months. Participant (b) (6) withdrew consent on Day 1009 (Year 2.8).

^c Of the 15 participants treated in Study 1005, one (Participant (b) (6)) did not enter Study 1003 for additional follow-up. Of the 14 participants in Study 1003 Cohort 1, two discontinued early. Participant (b) (6) withdrew consent on Day 1101 (Year 3.0). Participant (b) (6) was lost to follow-up on Day 1648 (Year 4.5).

Source: Adapted from - Original BLA 125786/0/14, 4-Month Safety Update, Table 5, p.29.

Table 9. Summary of the demographics and baseline characteristics in the Safety Analysis Set.

Demographic and Baseline Characteristics	Study 1002 (N=45)	Study 1005 (N=15)
Age (Years)		
Median (Minimum, Maximum)	29 (18, 62)	42 (18, 61)
(1 st quartile, 3 rd quartile)	(25, 41)	(23, 52)
Race, n (%)		
White	33 (73)	12 (80)
Black or African American	1 (2)	1 (7)
Asian	7 (16)	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	1 (7)
Not reported	4 (9)	0
Multiracial	0	1 (7)

Demographic and Baseline Characteristics	Study 1002 (N=45)	Study 1005 (N=15)
Ethnicity, n (%)		
Hispanic or Latino	2 (4)	0
Not Hispanic or Latino	35 (78)	15 (100)
Not reported	8 (18)	0
Region, n (%)		
APAC (Asia-Pacific)	6 (13)	0
Australia	2 (4)	2 (13)
Europe	13 (29)	0
Middle East	9 (20)	0
North America	12 (27)	13 (87)
South America	3 (7)	0
Body mass index (BMI) (kg/m²)		
Median (Minimum, Maximum)	28 (18, 48)	27 (18, 33)
(1 st quartile, 3 rd quartile)	(24, 30)	(22, 30)
Hepatitis C virus (HCV), n (%)	15 (33)	10 (67)
Hepatitis B virus (HBV), n (%)	13 (29)	7 (47)
Human immunodeficiency virus (HIV), n (%)	3 (7)	2 (13)
Baseline FIX activity < 1%, n (%)	38 (84)	10 (67)
Target joints identified, n (%)	13 (29)	9 (60)

Source: Adapted from - Original BLA 125786/0/14, 4-Month Safety Update, Table 8, pp.34-35.

8.4.1 Deaths

There were no deaths due to any cause.

8.4.2 Nonfatal Serious Adverse Events

Treatment emergent serious adverse events (SAEs) reported during the entire follow-up period in the safety analysis set are summarized by System Organ Class and Preferred Term in Table 10. Eleven of the 60 participants (18.3%) in the safety analysis set

experienced 23 treatment-emergent SAEs. Two SAEs occurred in the same participant, duodenal ulcer hemorrhage and associated anemia, were initially reported by the Applicant as related to BEQVEZ treatment. In the 4MSU, the Applicant reported that these SAEs were no longer assessed by the investigator as related to BEQVEZ. The Applicant reported that no additional events of duodenal ulcer hemorrhage or associated anemia were reported after Study 1002 Protocol Amendment 1 introduced a recommendation that participants who were initiated on corticosteroid treatment be treated with a gastric acid reducer for the duration of the corticosteroid course.

Table 10. Treatment-emergent serious adverse events in the Safety Analysis Set by the 4-month safety update cut-off date.

Serious adverse events by System Organ Class and Preferred Term	Number (%) of participants with SAEs in the Safety Analysis Set (N=60)
Blood and lymphatic system disorders	2 (3.3)
Anemia	2 (3.3)
Gastrointestinal disorders	2 (3.3)
Duodenal ulcer	1 (1.7)
Duodenal ulcer hemorrhage	1 (1.7)
Upper gastrointestinal hemorrhage	1 (1.7)
Hepatobiliary disorders	1 (1.7)
Drug-induced liver injury	1 (1.7)
Infections and infestations	3 (5.0)
Appendicitis	1 (1.7)
COVID-19	1 (1.7)
COVID-19 pneumonia	1 (1.7)
Pilonidal disease	1 (1.7)
Injury, poisoning and procedural complications	3 (5.0)
Accident	1 (1.7)
Alcohol poisoning	1 (1.7)
Femoral neck fracture	1 (1.7)
Joint dislocation	1 (1.7)
Kidney contusion	1 (1.7)

Serious adverse events by System Organ Class and Preferred Term	Number (%) of participants with SAEs in the Safety Analysis Set (N=60)
Liver contusion	1 (1.7)
Rib fracture	1 (1.7)
Investigations	1 (1.7)
Coagulation factor IX level decreased	1 (1.7)
Metabolism and nutrition disorders	1 (1.7)
Hypokalemia	1 (1.7)
Musculoskeletal and connective tissue disorders	2 (3.3)
Hemarthrosis	1 (1.7)
Spinal stenosis	1 (1.7)
Nervous system disorders	1 (1.7)
Seizure	1 (1.7)
Vascular disorders	1 (1.7)
Aortic dissection	1 (1.7)
Total number of participants with SAEs	11 (18.3)

Source: Adapted from - Original BLA 125786/0/14, 4-Month Safety Update, Table 15, pp.72-75.

8.4.8 Adverse Events of Special Interest

The Applicant identified a list of Adverse Events of Special Interest (AESIs) based on the safety profile of BEQVEZ and other AAV-mediated gene therapy products, events of potential regulatory interest, and theoretical concerns related to the administration of gene therapies. These AESIs are listed below.

1. Hypersensitivity reactions (within scope of hypersensitivity standardized MedDRA queries).
2. Clinical embolic and thrombotic events.
3. FIX inhibitors.
4. Hepatic malignancies.
5. Drug related elevated hepatic transaminases that fail to improve or resolve through treatment with immunosuppressive regimens.

6. Malignancy assessed as having reasonable possibility of being related to study drug.

The Applicant reported that no AESIs of clinical thrombotic events, FIX inhibitors, malignancies (hepatic or any other type), drug related elevated hepatic transaminases that fail to improve or resolve through treatment with immunosuppressive regimens, have been observed up to the 4MSU DCOD. Please refer to the clinical review memo for more information.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The data package reviewed in this memo consisted of the data from 60 BEQVEZ-treated participants, 15 from Study 1005 (an early phase study) and 45 from Study 1002 (the main study). Both studies contributed to the safety database while Study 1002 contributed to the efficacy evaluation.

Efficacy results

The primary efficacy outcome in Study 1002 was a non-inferiority (NI) test of the difference between the mean efficacy evaluation period (EEP) annualized bleeding rate (ABR) and the mean baseline ABR, with an NI margin of 3.0 bleeds/year. The EEP started from Day 82 (Week 12) after BEQVEZ treatment and ended on the data cut-off date. Of the 45 participants, 41 had at least 15 months of FU. The median EEP was 1.8 years (range: 0.2, 3.0 years), for a total EEP of 83 person-years. The model-derived mean baseline and EEP ABRs were 4.5 (95% CI: 1.9, 7.2) bleeds/year and 2.5 (95% CI: 1.0, 3.9) bleeds/year, respectively. The difference between the mean EEP ABR and the mean baseline ABR was -2.1 (95% CI: -4.8, 0.7) bleeds/year, meeting the NI study success criterion.

Six (13%) participants resumed routine prophylaxis (RP) during their EEPs, starting from 0.4 to 1.7 year after BEQVEZ treatment. An additional participant used exogenous factor IX replacement products in a prophylaxis-like manner for 78 days during the EEP. One participant who resumed RP also used replacement products in a prophylaxis-like manner for another 81 days during the EEP prior to resuming RP. To isolate the BEQVEZ treatment effect from the confounding by the prophylactic use of replacement products during these confounded EEPs, an ABR of 20 bleeds/year was imputed for these periods to approximate the hypothetical bleeding frequency in the absence of prophylactic use of replacement products in the primary analysis.

There are additional uncertainties associated with the treatment effect estimate. First, it is unknown whether an ABR of 20 bleeds/year approximates the hypothetical bleeding frequency closely. I conducted supplemental analyses which show that the imputed ABR would need to be at least 40 bleeds/year in order for the upper bound of the 95% CI of the difference in mean ABRs to be greater 3.0 bleeds/year, i.e., NI no longer holds. This

analysis demonstrates the robustness of the NI conclusion to the magnitude of the imputed ABR. A second source of uncertainty is due to the disproportionate influence on the treatment effect estimate from a participant with a baseline ABR of 53.9 bleeds/year and EEP ABR of 4.7 bleeds/year. A post-hoc analysis excluding this subject still meets the NI study success criterion. A third source of uncertainty is due to one-time preventive use of replacement products without documented reasons in several participants. It is unknown whether some of these uses were for treatment of undocumented bleeds or bleeds not adjudicated to be new bleeds. I did not identify a reasonable approach to address these one-time preventive uses in the primary analysis. However, the occurrences were few and I concluded that they do not affect the NI conclusion.

Taken together, these considerations add to quantitative uncertainty in the treatment effect estimate. However, based on supplementary analyses and the magnitude of the treatment effect, there is no meaningful uncertainty regarding the qualitative conclusion that mean ABR in patients treated with BEQVEZ is within 3.0 of mean ABR in patients on routine prophylaxis. That is, non-inferiority was unambiguously met, outweighing the uncertainties described above.

Twenty-eight (62%) participants received corticosteroids (CS) due to transaminase elevation and/or decline in factor IX activity. The mean time to CS initiation was 45 days. The mean duration of CS treatment was 113 days (range: 41 to 276 days). All six participants who resumed RP were on CS. It appears that CS use should be considered an integral component of the BEQVEZ treatment regimen as needed.

Safety results

There were no deaths due to any cause. I defer detailed safety review to the clinical review team.

10.2 Conclusions and Recommendations

BEQVEZ is non-inferior to routine prophylaxis in reducing annualized bleeding rate in hemophilia B patients. I recommend approval of BEQVEZ.