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Applicant	CSL Behring LLC
Established Name	etranacogene dezaparvovec
(Proposed) Trade Name	HEMEGENIX
Dosage Form(s) and Route(s) of Administration	Sterile solution with a nominal concentration of $1 \times 10^{13}$ genome copies/mL, and each vial contains an

	extractable volume of not less than 10 mL
Dosing Regimen	$2 \times 10^{13}$ genome copies per kilogram of body weight, single intravenous infusion
Indication(s) and Intended Population(s)	<p>HEMGENIX is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:</p> <ul style="list-style-type: none"> <li>▪ Currently use Factor IX prophylaxis therapy, or</li> <li>▪ Have current or historical life-threatening hemorrhage, or</li> <li>▪ Have repeated, serious spontaneous bleeding episodes</li> </ul>

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## GLOSSARY

AAV5	Adeno-associated virus serotype 5
ABR	Annualized Bleeding Rate
AE	Adverse Event
AOM	Application Orientation Meeting
aPTT	Activated Partial Thromboplastin Time
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDx	Companion Diagnostics
CI	Confidence interval
CMC	Chemistry, Manufacturing, and Controls
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DCO	Data Cut-off Date
DNA	Deoxyribonucleic Acid
eCTD	electronic Common Technical Document
e-diary	Electronic diary
EEP	(ABR) efficacy evaluation period
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIX	Factor IX
FU	Follow-up
gc	Genome copies
GEE	Generalized estimating equations
HB	Hemophilia B
IA	Interim Analysis
IND	Investigational New Drug

IAP	Interim Analysis Plan
IP	Investigational product
ITT	Intent-to-Treat
IU	International Unit
IV	Intravenous
LoD	Limit of Detection
LS	Least squares
MI	Multiple Imputation
mITT	Modified Intent-to-Treat
NAb	Neutralizing Antibodies
NI	Non-inferiority
kg	Kilogram
PMA	Premarket Approval
PP	Per Protocol
RP	Routine Prophylaxis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
UK	United Kingdom
US	United States
vg	Vector genomes
vg/kg	Vector genomes per kilogram

## 1. Executive Summary

The applicant has developed AMT-061, an adeno-associated virus serotype 5 vector-based gene therapy intended to express the Padua variant of the human factor IX gene, for the treatment of adults with severe or moderately severe hemophilia B.

The biologics license application (BLA) data package includes data from three clinical trials. Two of these trials treated subject with AMT-061 at the proposed labeling dose of  $2 \times 10^{13}$  gc/kg (genome copies per kilogram of body weight): trial CT-AMT-061-01 (n=3) for dose confirmation and phase 3 trial CT-AMT-061-02 (also called “HOPE B”, n=54).

AMT-061 has a predecessor product AMT-060 which differs from AMT-061 at (b) (4) and instead codes for the wildtype variant of the human FIX gene. (b) (4) 10 subjects were treated in the AMT-060 dose-ascending trial CT-AMT-060-01.

The efficacy database consists of the 54 subjects treated in CT-AMT-061-02, and the safety database includes the 57 subjects treated in trials CT-AMT-061-01 and CT-AMT-061-02. Safety summary about the 10 AMT-060 treated subjects in the 5-year clinical study report of CT-AMT-060-01 has also been briefly reviewed to identify adverse events of death or malignancies.

Study CT-AMT-061-02 was an open-label, single-dose, multi-center, multinational trial with a planned sample size of at least 50 subjects with severe or moderately severe congenital hemophilia B who were on standard of care routine prophylaxis (RP). Eligible subjects were to start with a lead-in phase/period with a duration of at least 6 months wherein their baseline data including bleeding episodes and exogenous factor IX (FIX) replacement product use would be prospectively collected. Subjects who continued to be eligible would receive a single-dose of AMT-061 and then be followed up at least monthly during the first 12 months and every 6 months during the next 4 years wherein bleeding episodes, FIX activity levels, and exogenous FIX replacement product use would be collected.

The primary objective was to demonstrate the non-inferiority (NI) of the efficacy of a single-dose of  $2 \times 10^{13}$  gc/kg of AMT-061 in patients with severe or moderately severe congenital hemophilia B, in terms of annualized bleeding rate (ABR), during the 52-week period starting on Month 7 after AMT-061 treatment (i.e., Months 7 to 18) compared to standard of care continuous routine FIX prophylaxis during the lead-in period. The efficacy evaluation period (EEP, Months 7 to 18 post treatment) started from Month 7 in order to allow establishment of stable FIX expression after AMT-061 treatment. The primary efficacy analysis would be an NI comparison between the ABR during Months 7 to 18 post AMT-061 and that during the lead-in period, with an NI margin of 1.8 on the ABR rate ratio.

The primary efficacy analysis yielded an estimate of the ABR rate ratio (EEP/lead-in period) of 0.46 with a 95% confidence interval (CI) of (0.26, 0.81), therefore it met the NI success criterion which required the upper bound of the CI to be less than 1.8. The adjusted ABR was 4.1 bleeds/year with a 95% CI of (3.2, 5.4) for the lead-in period, and was 1.9 bleeds/year with a 95% CI of (1.0, 3.4) for the EEP period (Months 7 to 18 post AMT-061 treatment period). The results reported here reflect an update in an imputation algorithm in the primary analysis, which is described below.

The planned primary analysis used an imputation approach that defined the “at-risk” for bleed time with an intention to isolate the AMT-061 treatment effect from the confounding effect of FIX replacement product use during the EEP. This approach

excluded the period within 5 half-lives following a FIX replacement product use from the “at-risk” time. This approach was appropriate for the majority of subjects, who received FIX replacement products for at most a few times during the EEP. However, three subjects never stopped or resumed RP during EEP, therefore the approach described above did not incorporate their data in the analysis model appropriately.

After AMT-061 treatment, two subjects had to continue RP with exogenous FIX replacement products. One of them had the highest baseline anti-AAV5 NAb titer observed in the study, 1: 3212.3. This subject had a total of five bleeds, four spontaneous and one unknown, during EEP (Months 7 to 18) despite being on RP. The other subject received only around 10% of the intended AMT-061 dose due to hypersensitivity at the time of administration. This subject had one bleed during EEP. In addition, a third subject resumed RP on Day 396 post AMT-061 treatment. For these three subjects who continued or resumed RP, the planned imputation approach (for the primary analysis) described above was incoherent, giving a nonsensical imputed ABR of 1675 for one subject. For these three subjects, FDA and the applicant agreed to update the imputation approach to use a hypothetical imputation algorithm instead, where an ABR of 20 bleeds/year was imputed as the hypothetical ABR the subject would have experienced had they not used RP during the EEP. The primary NI analysis result reported above used this updated imputation algorithm for these three subjects. Sensitivity analyses reveal that the hypothetical ABR for these three subjects need to be at least 53 bleeds/year for the NI conclusion to no longer hold, demonstrating the robustness of the NI conclusion to the imputation algorithm for these three subjects.

Several issues complicated the interpretation of the study results. The first issue was that some subjects did not receive adequate routine prophylaxis during the lead-in period, potentially leading to a bias favoring AMT-061 in the NI comparison. However, the estimated mean ABR of 1.9 (95% CI: 1.0, 3.4) during the EEP was within the range of mean ABR reported for RP in various studies, providing some reassurance that the NI conclusion is robust to potential biases introduced by some degree of inadequacy of baseline RP regimens. The second issue is that there was a numerical difference between the estimated mean ABR during EEP between the US and non-US regions, with the mean ABR for US being almost twice that for non-US regions (2.7 vs. 1.4). There was a positive correlation of 0.73 between the ABRs before and after treatment in the US subjects, while there is no correlation for these two sets of ABRs in the non-US subjects. Nevertheless, the NI conclusion holds in both geographical regions analyzed separately, confirming the robustness of the NI conclusion despite this numerical difference in efficacy between the two regions.

For safety evaluation, one death occurred in Study CT-AMT-061-02 due to cardiogenic shock on Study Day 464. In addition, hepatocellular carcinoma was diagnosed in a subject around one year after AMT-061 treatment. For the predecessor product AMT-060, one death was reported of a subject treated in Study CT-AMT-060-01, determined to be due to natural but unknown causes. The investigators and the applicant determined



that all these three AEs were unrelated to or unlikely to be related to the investigational products. Further analysis of safety data is deferred to the clinical team.

In summary, the efficacy results of Study CT-AMT-061-02 provided sufficient statistical evidence to support the non-inferiority of AMT-061 treatment to standard of care routine prophylaxis in terms of ABR for the efficacy evaluation period of Months 7 to 18 after AMT-061 treatment.

## 2. Clinical and Regulatory Background

The investigational product under consideration, AMT-061 (AAV5-hFIXco-Padua, etranacogene dezaparvovec), is a single-dose gene therapy intended for the long-term treatment of congenital hemophilia B (HB) via sustained restoration of factor IX (FIX) activity. It is comprised of a non-replicating, recombinant, adeno-associated virus (AAV)-based vector with an expression cassette encoding a codon-optimized coding Deoxyribonucleic Acid (DNA) sequence for the gain-of-function Padua variant (R338L) of the human FIX gene (hFIXco-Padua) under the control of a liver specific promoter. Following intravenous (IV) infusion, AMT-061 preferentially transduces liver cells.

### 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 the essential blood coagulation factor IX.

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. It is less prevalent than hemophilia A which occurs in approximately 1 in 5,000 male births. HB primarily affects males. Female carriers are typically asymptomatic, but 10% to 25% will develop mild symptoms and, rarely, reported severe symptoms of bleeding.

The classification of the severity of HB has been based on either clinical bleeding symptoms or plasma FIX activity 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 [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 patients with factor IX levels of less than 1% occasionally have little or no spontaneous bleeding and appear to have clinically moderate or mild hemophilia. Furthermore, the reverse is true for patients with procoagulant activities of 1-5%, who may present with symptoms of clinically severe disease.

## 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s)

There is no cure for HB. The primary goals of hemophilia B therapy are the prevention of bleeding episodes, rapid and definitive treatment of bleeding episodes (breakthrough bleeding episodes) that occur even while on a regular prophylactic regimen, and provision of adequate hemostasis during surgery and emergencies. Currently, these goals are essentially met for HB subjects by intravenous (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.

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

Clinical development of AMT-061 was preceded by AMT-060, an investigational product similar to AMT-061, but which contains the wide-type variant of the human FIX gene instead of the gain-of-function Padua variant as in AMT-061. The Investigational New Drug application (IND) 16248 that contains the clinical protocols and statistical analysis plans (SAP) of the studies supporting this Biologics License Application (BLA) (b) (4).

### Pre-Submission Regulatory Activities and Interactions

1. Dec 22, 2011. Food and Drug Administration (FDA) granted Orphan Drug Designation for AMT-060, adeno-associated viral vector serotype 5 containing a codon-optimized human factor IX gene (AAV5-hFIXco), for treatment of hemophilia B.
2. Dec 12, 2013. Pre-IND meeting. CRMTS 9176. PTS 002296. Meeting minutes dated Jan 06, 2014.
3. Nov 14, 2014. Original IND (b) (4) submitted.
4. Jan 25, 2017. FDA granted Breakthrough Therapy designation for AMT-060, recombinant adeno-associated viral vector serotype 5 containing human coagulation factor IX cDNA (AAV5-hFIX), for treatment of severe Hemophilia B.
5. Jan 31, 2017. End-of-Phase 2 meeting for AMT-060. CRMTS 10559. Meeting minutes dated Mar 1, 2017.
6. Oct 06, 2017. Initial Comprehensive Breakthrough meeting for AMT-060. CRMTS 10863. Meeting minutes dated Nov 03, 2017.

- a. (b) (4), which was thought to be more efficacious. FDA agreed that AMT-061 could be developed under the Breakthrough Therapy Designation granted for AMT-060.
  - b. At the time, CT-AMT-060-01, the dose-ascending trial of AMT-060, had treated 10 subjects, 5 at each of two dose levels.
  - c. For the AMT-061 clinical development, FDA agreed with the sponsor's plan to conduct a dose confirmation study (Study CT-AMT-061-01) on three subjects before initiating treatment in the phase 3 trial (Study CT-AMT-061-02).
7. Apr 17, 2019. FDA granted Orphan Drug Designation for AMT-061, adeno associated viral vector containing the Padua derivative of the human coagulation factor IX cDNA, for treatment of Hemophilia B.
  8. Dec 16, 2020. FDA notified the sponsor by email that IND 16248 had been placed on **clinical hold** following FDA's review of the Dec 11, 2020 IND amendment for the reason "**Clinical – unreasonable risks due to nature of SAE (Serious adverse event)**".
    - a. By this time, all planned subjects had already received their AMT-061 treatment.
    - b. The SAE was hepatocellular carcinoma diagnosed on (b) (6) based on histological biopsy in Subject (b) (6) who received AMT-061 in Study CT-AMT-061-02 on (b) (6).
    - c. Formal clinical hold letter was issued on Jan 15, 2021.
    - d. Clinical hold was removed on Apr 23, 2021.
  9. Jun 4, 2021. Pre-BLA meeting. CRMTS 13296. Meeting minutes dated Jul 2, 2021.

#### Protocol and Statistical Analysis Plan (SAP)

Study CT-AMT-061-02 forms the primary basis for this BLA. The original version (Version 1.0) of the protocol was dated Feb 16, 2018, and went through several revisions to arrive at the final version (Version 7.0, Amendment 6.0) dated Jun 28, 2021. Version 7.0 of the protocol, together with the corresponding SAP (Version 4.0, dated Jun 10, 2021), were submitted to IND 16248 on Aug 12, 2021. Early in the clinical development of AMT-061, discussions between FDA and the applicant on the (b) (4) after AMT-061 as a surrogate endpoint to support a marketing application for accelerated approval took place. However, due to lack of a sound basis for and consequent difficulties with choosing a threshold for the factor IX activity level after AMT-061 treatment to be used as the surrogate endpoint, the sponsor eventually (late 2020) adopted FDA's recommendation to focus on using the clinical endpoint annualized bleeding rate (ABR) to support a BLA for traditional approval.

Interactions had led to substantive and substantial revisions in the protocol and SAP throughout the AMT-061 development, with some FDA recommendations adopted by the sponsor after several rounds of interactions. The final versions of protocol and SAP had been revised substantially to incorporate FDA recommendations, which were partly based on evolving understanding of this class of therapy in general and also included clarification of expectations communicated earlier. The major revisions relevant to this statistical review include the following:

1. The non-inferiority (NI) comparison of the ABR between the period of 52 weeks following establishment of stable FIX expression (months 7 to 18 after AMT-061 treatment) and the lead-in period became the sole primary objective and endpoint. The other primary endpoints in earlier protocol versions related to endogenous FIX activity at 6 months and 12 months were designated as secondary endpoints instead.
2. It was clarified that the full analysis set (FAS) population would be used for all efficacy statistical analyses, including the ABR NI comparison, with the per protocol (PP) population used for sensitivity analyses.
3. Changed the data cutoff for the main clinical study report (CSR) to be 52 weeks after stable FIX expression (18 months post-treatment) from the initial proposal of 52 weeks post-treatment. However, the quality of the extra 26 weeks of data may not be the same as that in the first 52 weeks. Subjects had monthly follow-up during the first 52 weeks and used an e-diary to record factor IX use and bleeding episodes, while after the first 52 weeks the long-term follow-up schedule was every 6 months and subject recorded data using a paper diary.

### 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

#### 4.2 Assay Validation

There have been discussions regarding a companion diagnostic (CDx) assay for (b) (4) submitted (b) (4) of their Premarket Approval (PMA) submission, containing analytical study data to support approval of such a CDx to etranacogene dezaparvovec to the Center for Devices and Radiological Health (CDRH). On (b) (4) CDRH issued a deficiency letter for (b) (4) CDRH determined that the assay in its current form is not appropriate for its intended use. CDRH defers the ultimate decision regarding the use of the CDx for this product to the Center for Biologics Evaluation and Research (CBER). Further consideration of the AAV5-NAb issue is deferred to the clinical review discipline.

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

### 5.1 Review Strategy

AMT-061, at a single IV dose of  $2 \times 10^{13}$  genome copies per kilogram of body weight (gc/kg), was administered to HB subjects in two clinical trials: the dose confirmation trial CT-AMT-061-01 (n=3) and the phase 3 trial CT-AMT-061-02 (also called the HOPE B trial, n=54).

The efficacy database consists of the 54 subjects from trial CT-AMT-061-02. The safety database consists of the 57 subjects from the two AMT-061 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 16248, the original BLA 125772, information requests (IRs) from the FDA, and IR responses from the applicant. When documents were available in both the IND and the BLA, I reviewed the IND versions. Documents reviewed are listed below. Documents are BLA documents, unless explicitly noted otherwise.

- Protocols and SAPs for Study CT-AMT-061-02 (HOPE B) under IND 16248
- Meeting minutes under IND 16248
- Application Orientation Meeting (AOM) slides, presented by the applicant on April 29, 2022
- Module 1.14 Labeling
- Module 1.2 Reviewer's Guide
- 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 CT-AMT-061-02 Clinical Study Report (CSR) and supporting documents and datasets

### 5.3 Table of Studies/Clinical Trials

[Table 1](#) summarizes the two AMT-061 trials and the one AMT-060 trial.

The efficacy database consists of the 54 subjects from trial CT-AMT-061-02, with a data cutoff date of 18 months post treatment for subjects. The safety database includes all the subjects as in the efficacy database, and in addition includes data with a 2.5-year cutoff date for the 3 subjects treated in trial CT-AMT-061-01.

The primary objective of the CT-AMT-061-01 trial was to determine, based on FIX activity levels 6 weeks after AMT-061 treatment in the 3 subjects, whether the  $2 \times 10^{13}$

dose should be used for the phase 3 trial CT-AMT-061-02. It was determined that this dose should be used for the phase 3 trial.

Study CT-AMT-061-02 was titled “Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco- Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B study.” It met its primary efficacy endpoint.

AMT-060 is a predecessor to AMT-061 that differs from it at (b) (4). The CT-AMT-060-01 trial is included in Table 1 for completeness, and I will briefly review the safety descriptions in the 5-year CSR to identify any major additional safety issues (e.g., malignancy or death) that may be relevant to the entire class of hemophilia gene therapy products.

**Table 1. Summary of AMT-060 and AMT-061 Clinical Trials**

<b>Study Identifier</b>	<b>Phase</b>	<b>Objectives</b>	<b>Study Design and Type of Control</b>	<b>Test Product, Dosage Regimen, and Route of Administration</b>	<b>Number of Subjects</b>	<b>Study Subjects</b>	<b>Duration of Follow up</b>	<b>Study Status and Report</b>
CT-AMT-060-01	1/2	To investigate the safety of systemic administration of AMT-060 to adult patients with severe or moderately severe HB	Open-label, uncontrolled, single-dose, dose-ascending	AMT-060  Cohort 1: 5 subjects received $5 \times 10^{12}$ gc/kg  Cohort 2: 5 subjects received $2 \times 10^{13}$ gc/kg  Single IV dose	10  Country: NL DE DK	Adult subjects with severe or moderately severe HB	After AMT-061 treatment, 1 year FU and then 4 years of Long-term FU	Completed  Final CSR (5 years): 06 January 2022
CT-AMT-061-01	2b	To confirm the FIX activity level 6 weeks after AMT-061 treatment in adult subjects with severe or moderately severe HB	Open-label, uncontrolled, single-dose, single-arm	AMT-061  3 subjects received $2 \times 10^{13}$ gc/kg  Single IV dose	3  Country: US	Adult subjects with severe or moderately severe HB	After AMT-061 treatment, 1 year FU and then 4 years of Long-term FU	Ongoing  Interim CSR (2.5 years): 07 December 2021

								Final CSR expected: December 2023
CT-AMT-061-02	3	To demonstrate Non-inferiority of AMT-061 during the 52 weeks of stable FIX expression (Months 7 to 18) after treatment in adult subjects with severe or moderately HB, compared with standard of care continuous routine FIX prophylaxis during the Lead-in Phase, as measured by ABR	Open-label, uncontrolled, single-dose, single-arm	AMT-061 53 subjects received $2 \times 10^{13}$ gc/kg  1 subject received approximately 10% of the intended $2 \times 10^{13}$ gc/kg dose  Single IV dose	54  Country: US, 20 subjects  Non-US, 34 subjects	Adult subjects with severe or moderately severe HB	Before AMT-061 treatment, $\geq 6$ -month Lead-in Period with standard of care FIX prophylaxis  After AMT-061 treatment, 1 year FU and then 4 years of Long-term FU	Ongoing  Interim CSR (18 months): 21 February 2022  Final CSR expected: July 2025

AAV = adeno-associated virus; AAV5 = adeno-associated virus serotype 5; ABR = annualized bleeding rate; CSR = Clinical Study Report; FIX = factor IX; IV = intravenous; FU = follow up; gc/kg = genome copies per kilogram; HB = Hemophilia B; DE=Germany; DK=Denmark; NL= Netherlands.  
Source: Adapted from Original BLA 125772/0/0, Module 5.2. Tabular Listing of all Clinical Studies.



## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study CT-AMT-061-02

Study CT-AMT-061-02 (Health Outcomes with Padua Gene; Evaluation in Hemophilia B [HOPE B]) is the sole phase 3 trial forming the efficacy database for this BLA. It is reviewed in this section.

#### 6.1.1 Objectives

The primary objective was to demonstrate the non-inferiority of the efficacy of a single-dose of  $2 \times 10^{13}$  gc/kg of AMT-061 in patients with severe or moderately severe congenital hemophilia B, in terms of ABR, during the 52-week period starting on Month 7 after AMT-061 treatment (i.e., Months 7 to 18) compared to standard of care continuous routine FIX prophylaxis during the lead-in period. The efficacy evaluation period (EEP) starts from Month 7 in order to allow establishment of stable Factor IX (FIX) expression after AMT-061 treatment.

Secondary objectives were to demonstrate efficacy in additional endpoints, e.g., endogenous FIX activity and FIX replacement product usage, and evaluate safety aspects.

#### **Reviewer's Comment:**

*I have rephrased the primary objective considerably because the applicant's phrasing was difficult to read and did not describe the patient population. For the EEP, the applicant used Months 6 to 18 in the protocol but Months 7 to 18 in the clinical study report. Both refer to starting EEP on Day 183 as implemented in the analysis. This inconsistency was likely introduced unintentionally as the protocol went through several rounds of substantial revisions along the way, and when clarification to resolve misunderstandings regarding the start and end times of EEP came late in the development.*

*Here is the primary objective as given in the submission for comparison: To demonstrate the non-inferiority of AMT-061 ( $2 \times 10^{13}$  gc/kg) during the 52 weeks following establishment of stable FIX expression (Months 6 to 18) post-treatment (AMT-061) follow-up compared to standard of care continuous routine FIX prophylaxis during the lead-in phase, as measured by the ABR.*

#### 6.1.2 Design Overview

This is an open-label, single-dose, multi-center, multinational trial with a planned sample size of at least 50 subjects with severe or moderately severe congenital hemophilia B who were on standard of care routine prophylaxis. Eligible subjects were to start with a lead-in phase/period with a duration of at least 6 months wherein their baseline data including bleeding episodes and exogenous FIX replacement product use would be prospectively collected. Subject continued to be eligible would receive a single-dose of AMT-061 and then be followed-up at least monthly during the first 12 months and every 6 months during the next 4 years wherein bleeding episodes, FIX activity levels, and exogenous FIX replacement product use would be collected. The primary efficacy analysis would be

a non-inferiority (NI) comparison between the ABR post AMT-061 and that during the lead-in period, with an NI margin of 1.8 on the ABR rate ratio.

### 6.1.3 Population

Subjects were adult males aged  $\geq 18$  years with congenital HB with known severe or moderately severe FIX deficiency ( $\leq 2\%$  of normal circulating FIX) for which the subject was on continuous routine FIX prophylaxis. Continuous routine prophylaxis was defined as the **intent** of treating with an a priori defined frequency of infusions (e.g., twice weekly, once every two weeks, etc.) as documented in the medical records. Subjects were also required to have had 150 previous exposure days of treatment with FIX protein, and to have been on stable prophylaxis for at least 2 months prior to screening. Subjects with a history of FIX inhibitor were excluded, as well as those with a positive inhibitor test at screening or the last visit of the lead-in period.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were to receive a single IV infusion of  $2 \times 10^{13}$  gc/kg of AMT-061.

The reference therapy was the standard of care continuous routine FIX prophylaxis replacement therapy used during the lead-in phase prior to treatment with AMT-061.

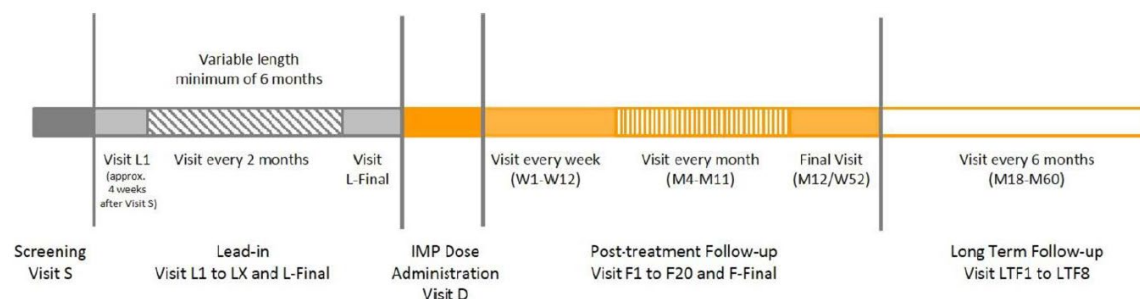
### 6.1.6 Sites and Centers

Among the 54 treated subjects, 29 subjects were from 11 European Union (EU) sites, 5 subjects from 3 United Kingdom (UK) sites, and 20 subjects from 14 US sites.

### 6.1.7 Surveillance/Monitoring

Each subject's study schedule consisted of a screening period, a lead-in phase/period (at least 6 months), a treatment + post-treatment follow-up phase/period (12 months), and a long-term follow-up phase (an additional 48 months). See [Figure 1](#) for details.

**Figure 1. Study Schedule**



Source: IND 16248 amendment 82, CT-AMT-061-02 Protocol (Version 7.0, Amendment 6.0, 28 Jun 2021), p.23, Figure 2.

### 6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint is ABR comparison for non-inferiority between AMT-061 (EEP of Months 7 to 18 following AMT-061 treatment) and prophylaxis (lead-in phase).

Secondary efficacy endpoints include endogenous factor IX activity at 6, 12, and 18 months after AMT-061 dosing, consumption of factor IX replacement therapy during the EEP, and various types of bleeds, among others.

The trial would be considered a success if the upper bound of the 95% confidence interval (CI) on the rate ratio of ABR is below the non-inferiority margin of 1.8.

**Reviewer's Comment:**

*I have rephrased the primary endpoint considerably because the applicant's phrasing was difficult to read. Here is the primary endpoint as given in the submission for comparison: ABR comparison between AMT-061 and prophylaxis for non-inferiority between the lead-in phase and the 52 weeks following stable FIX expression (Months 6 to 18 post-treatment).*

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

#### Non-inferiority Margin

The sponsor proposed, and FDA accepted, an NI margin of 1.8 on the rate ratio of ABR. The selection of this margin is based on both statistical reasoning and clinical judgment. For statistical reasoning, the applicant quoted ABR results from three recent trials in [Table 2](#), and also a 95% CI of (0.051, 0.238) on the rate ratio from the Idelvion trial. Using two different effect metrics, the NI margin of 1.8 represents a preservation of 75% or 59% of the effect on ABR of Idelvion prophylaxis compared to on-demand (i.e., no prophylaxis) regimens. From a clinical perspective, it was recognized that currently used routine prophylaxis regimens would results in a mean ABR of around 2 to 3 bleeds/year. Applying an NI margin to these results means AMT-061 could have a mean ABR of around 3.6 to 5.4 to be declared to be NI to routine prophylaxis. However, the constraint of what sample size is feasible for the trial (around n=50) means only an effect size with the AMT-061 mean ABR being lower than that of the baseline would have an adequate statistical power to meet the non-inferiority success criterion.

**Table 2. Recent ABR Results of Prophylaxis Compared to On-Demand Regimens**

Publication	ABR On-demand	ABR Prophylaxis	Rate Ratio
Alprolix (Powell, 2013)	18.67 (N=27)	3.12 (N=61)	0.17
Idelvion (Santagostino, 2016)	20.09 (N=19)	2.22 (N=19)	0.11
Nonacog (Collins, 2014)	15.58 (N=15)	40 IU: 2.51 (N=29)	0.16

Source: Adapted from - IND 16248 amendment 82, CT-AMT-061-02 SAP (Version 4.0, 10 Jun 2021), p.37, Table 1.

#### Sample Size

The study was planned to have a minimum of 50 analyzable subjects based on a statistical power simulation on the NI analysis of the ABR endpoint. Assuming a mean ABR of 2.4 bleeds/year during lead-in and of 1.9 bleeds/year post-treatment, with a

Pearson correlation of 0.05 between the number of events between the two periods, and both bleeding counts following a negative binomial distribution with a common dispersion parameter of 1.5, a sample size of  $n=50$  will demonstrate NI with an NI margin of 1.8 on the ABR rate ratio with a statistical power of 82.0%.

#### Analysis populations/sets

The Full Analysis Set (FAS) includes all subjects who were enrolled, entered the lead-in phase, were dosed with AMT-061, and provided at least one efficacy endpoint assessment after AMT-061 dosing.

The FAS population is the primary population for all efficacy analyses.

The Per Protocol (PP) population includes all subjects from the FAS population who adhere to a stable and adequate prophylaxis use during the lead-in phase, who complete at least 18 months of efficacy assessments for the 18-month data cutoff analysis, who complete at least a full year of efficacy assessments for the 12-month data cutoff analysis, or who complete at least 6 months of efficacy assessments for the 6-month data cutoff analysis, and who have no major protocol deviations that impact the interpretation of efficacy.

The PP population will be used for sensitivity analyses.

The lead-in safety population includes all subjects who were enrolled into the lead-in period.

The post-treatment safety population includes all subjects who received AMT-061, irrespective of any protocol deviations.

#### Primary analysis for the primary efficacy endpoint: NI comparison of ABR

The primary analysis of the primary endpoint will analyze the number of bleeding events using a repeated measures generalized estimating equations (GEE) negative binomial regression model accounting for the paired design of the trial, and with an offset parameter to account for the differential collection periods. An unstructured covariance matrix will be employed. The model will include the treatment (i.e., period) as a categorical variable.

The estimated rate ratio and one-sided 97.5% Wald CI and the corresponding p-value will be determined. The upper limit of the resultant CI of the rate ratio will be compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.

Events from the entire lead-in period will be counted, and the entire lead-in period is considered to be time at risk for bleeding.

In the analysis, any person-time during the post-treatment period within 5 half-lives immediately following exogenous factor IX use will not be counted in the time at risk for having a bleeding event. This approach excluded time periods “contaminated” by FIX product use to separate the AMT-061 effect from the “contamination” effect of FIX products. Nevertheless, any bleeds occurring on or after stable FIX expression (post-

treatment Month 7) will still be counted as events, even if they occurred during a time interval of “contamination”.

**Reviewer’s Comment:**

Primary analysis with imputation of hypothetical ABR for subjects on RP during EEP

*The trial would monitor each subject’s FIX activity levels after AMT-061 treatment and would consider or mandate continuation or re-initiation of continuous routine FIX prophylaxis based on their activity level (between 2 and 5%, and <2%, respectively). Subjects had used FIX products to treat bleeds, before or during invasive procedures, or for one-time prophylaxis (sometimes without documented reasons).*

*In the primary analysis of the NI comparison of ABR described above, periods within 5 half-lives immediately following FIX product use were excluded from the “at-risk” time for the bleed counts in the statistical model, while all bleed episodes would be counted regardless of whether they happen during FIX product “contaminated” or “uncontaminated” periods.*

*This is a reasonable approach to try to isolate the effect on ABR of AMT-061 from the confounding of FIX products when FIX products had been used for only a few times during the Months 7 to 18 EEP. However, when a subject continued or resumed routine prophylaxis after AMT-061 treatment, this approach to addressing the confounding effect of use of FIX products is not reasonable. For example, if a subject continued RP after AMT-061 treatment and as a result had zero at-risk time, this subject’s data of using RP would not contribute to the statistical model. For subjects using RP for part of or the entire EEP after AMT-061 treatment, the pertinent question for the NI comparison of ABR is “what the subject’s bleeding count would have been during EEP had the subject not received routine prophylaxis during EEP?” That is, one should impute a hypothetical bleed count for this subject assuming he received no FIX product treatment. Some possible values are the mean ABRs for similar patients not receiving routine prophylaxis (i.e., on-demand) as reported in Table 2, i.e., ABR of 16 to 20. While multiple imputation (MI) can also be considered, it is difficult to come up with a statistical distribution on the hypothetical ABR, and MI will not result in materially different conclusions given the relative magnitudes of effect of the various factors under consideration. Therefore, I suggest imputing ABR of 20 for the periods during EEPs when subjects were on routine prophylaxis in this trial. See Section 6.1.10 for more details. For future trials, imputation using hypothetical ABRs for subjects receiving routine prophylaxis during the EEP should be considered at the trial planning stage.*

Additional statistical considerations regarding efficacy evaluation

- 1. Early in the clinical development stage, FDA had considered the choice between a randomized controlled trial and a single-arm trial, and chose the latter based on practicality constraints and the clinical context. There had been a good amount of data on the efficacy of routine FIX product prophylaxis vs no prophylaxis (i.e., on-demand or episodic treatments) to orient the design of this NI trial. AMT-061 was expected to provide effects (during the given follow-up period) similar to routine prophylaxis (RP), and given the large effect size of RP vs no treatment, a properly designed single-arm NI should be interpretable*

*despite some extra uncertainty generally associated with single-arm trials. FDA recommends collecting baseline data prospectively to further improve the validity of trial results. Nonetheless, trial results should be examined with the care generally afforded to single-arm trials to evaluate potential biases and extra uncertainties.*

2. *Adequacy of baseline RP regimen. FDA had repeatedly advised the IND sponsor to ensure baseline RP regimens received by the subjects were adequate to ensure valid NI comparison.*
3. *Efficacy data, including information on bleeding episodes, were collected using e-diary and subjects visits were monthly within the first 12 months after AMT-061 treatment. Month 13 to 18 data were collected on paper diary and subject visits, after entering long-term follow-up phase starting Month 13, were every six months. It is unknown whether the latter data collection form and the low visit frequency might have an effect on the accuracy of data recording.*
4. *The SAP listed 16 secondary endpoints, 12 of which would be analyzed using hypothesis testing and have type 1 error rate controlled by hierarchical testing. However, hypothesis testing is not logical for several of them, and instead, descriptive summaries would be more informative. Two examples are given below.*
  - a. *The SAP proposed to test that, compared to baseline, FIX activity levels increased at Months 6, 12, and 18, respectively. Descriptive summaries about the trend on decrease of FIX activity level over time, after achieving their maximum in the early months after AMT-061 treatment, together with inter-subject variability, is more relevant.*
  - b. *The SAP proposed to test the decrease in FIX product use after AMT-061 treatment compared to baseline. This is illogical in a sense, because FIX product use should be expected to be close to zero post AMT-061 treatment as FIX product RP use was the baseline to which AMT-061 is compared. Also, multiple different FIX replacement products are in current use, making summing the consumption together not informative. Information on FIX product use post AMT-061 treatment should have been approximately captured in the NI ABR comparison, together with information on how many subjects had continued or resumed RP post AMT-061 treatment.*
5. *The SAP listed testing for superiority in ABR as the 8<sup>th</sup> secondary endpoint. This claim will be evaluated in Section 6.1.10 below.*

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

###### 6.1.10.1.1 Demographics

The demographic characteristics of the enrolled subjects are summarized in [Table 3](#). Among the 54 subjects who had been treated with AMT-061 (FAS population), the mean

(standard deviation [SD]) age at enrollment for the FAS population was 41.5 (15.8) years; the oldest subject was 75 years old.

**Table 3. Demographics**

Characteristic	Lead-in Safety Population Incl. Lead-in Discontinuers (N=67)	Post-treatment Safety Population/FAS (N=54)	PP Population (N=53)
<b>Age (years), n<sup>1</sup></b>	67	54	53
Mean (SD)	42.8 (16.2)	41.5 (15.8)	40.9 (15.5)
Median (Q1-Q3)	38.0 (31.0-55.0)	37.0 (30.0-53.0)	37.0 (30.0-50.0)
Min, Max	19,78	19,75	19,75
<b>Sex, n (%)</b>			
Male	67(100.0)	54 (100.0)	53 (100.0)
<b>Race, n (%)</b>			
White	50 (74.6)	40 (74.1)	40 (75.5)
Other	7 (10.4)	6 (11.1)	5 (9.4)
Missing	5 (7.5)	5 (9.3)	5 (9.4)
Asian	3 (4.5)	2 (3.7)	2 (3.8)
Black or African American	2 (3.0)	1 (1.9)	1 (1.9)
<b>Ethnicity, n (%)</b>			
Non-Hispanic or Latino	56 (83.6)	45 (83.3)	44 (83.0)
Hispanic or Latino	6 (9.0)	4 (7.4)	4 (7.5)
Missing	5 (7.5)	5 (9.3)	5 (9.4)
<b>Height (cm), n</b>	66	54	53
Mean (SD)	176.9 (7.9)	176.5 (8.2)	176.8 (8.0)
Median (Q1-Q3)	176.5 (172.0-182.0)	176.5 (172.0-182.0)	177.0 (172.0-182.0)
Min, Max	153, 197	153, 197	153, 197
<b>Weight (kg), n</b>	66	54	53
Mean (SD)	87.2 (20.0)	85.1 (19.3)	85.5 (19.3)
Median (Q1-Q3)	85.5 (74.0-96.0)	84.0 (74.0-93.0)	84.0 (75.0-93.0)
Min, Max	58, 169	58, 169	58, 169
<b>BMI (kg/m<sup>2</sup>), n</b>	66	54	53
Mean (SD)	27.7 (5.4)	27.2 (5.1)	27.2 (5.1)
Median (Q1-Q3)	26.7 (23.8-30.1)	26.2 (23.8-29.1)	26.3 (23.8-29.1)
Min, Max	21, 51	21, 51	21, 51

Abbreviations: BMI = body mass index; FAS = Full Analysis Set; Incl. = including; Max = maximum; Min = minimum; PP = Per-Protocol; Q = quartile, SD = standard deviation.

<sup>1</sup> Age was the age at the time of Informed consent

Source: Original BLA 125772/0/0, Study 061-02 CSR, p.79, Table 10.

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The medical history related to HB for the FAS population, as well as two other analysis populations, are summarized in [Table 4](#). At the time of their diagnosis, 44/54 (81.5%) subjects had severe hemophilia B (i.e., FIX levels <1% of normal) and 10/54 (18.5%) subjects had moderately severe hemophilia B (i.e., FIX levels ≥1% and ≤2% of normal). In the year prior to screening, 5/54 (9.3%) subjects had more than 10 bleeds. All subjects used prophylactic treatment while 4 (7.4%) of them also used on-demand treatment.

**Table 4. Summary of Medical History Relating to Hemophilia B**

Characteristic	Lead-in Safety Population Incl. Lead-in Discontinuers (N = 67)	Post-treatment Safety Population/FAS (N = 54)	PP (N = 53)
<b>Duration of Hemophilia B (years), n<sup>1</sup></b>	65	53	52
Mean (SD)	40.8 (15.7)	39.7 (15.0)	39.5 (15.1)
Median (Q1-Q3)	36.4 (30.1-50.6)	34.3 (30.1-48.9)	34.2 (29.8-49.6)
Min, Max	18, 78	18, 74	18, 74
<b>Severity of Hemophilia B at Time of Diagnosis, n (%)</b>			
Severe <sup>2</sup>	56 (83.6)	44 (81.5)	43 (81.1)
Moderately Severe FIX <sup>3</sup>	11 (16.4)	10 (18.5)	10 (18.9)
<b>Bleeding Episodes in Year Prior to Screening, n (%) [# of Episodes]</b>			
Any Bleeding Episodes	53 (79.1) [258]	44 (81.5) [215]	43 (81.1) [214]
Joint Bleeding Episodes	33 (49.3) [155]	30 (55.6) [132]	29 (54.7) [131]
Spontaneous Bleeding Episodes	36 (53.7) [141]	32 (59.3) [118]	31 (58.5) [117]
Traumatic Bleeding Episodes	26 (38.8) [72]	20 (37.0) [64]	20 (37.7) [64]
Unknown	14 (20.9) [45]	11 (20.4) [33]	11 (20.8) [33]
<b>Bleeding Episodes in Year Prior to Screening, n (%)</b>			
0 Bleeding Episodes	14 (20.9)	10 (18.5)	10 (18.9)
1 Bleeding Episodes	11 (16.4)	9 (16.7)	8 (15.1)
2 Bleeding Episodes	14 (20.9)	10 (18.5)	10 (18.9)
3 Bleeding Episodes	8 (11.9)	8 (14.8)	8 (15.1)
4 Bleeding Episodes	4 (6.0)	4 (7.4)	4 (7.5)
5 Bleeding Episodes	2 (3.0)	2 (3.7)	2 (3.8)
6 Bleeding Episodes	2 (3.0)	2 (3.7)	2 (3.8)
7 Bleeding Episodes	2 (3.0)	2 (3.7)	2 (3.8)



Characteristic	Lead-in Safety Population Incl. Lead-in Discontinuers (N = 67)	Post-treatment Safety Population/FAS (N = 54)	PP (N = 53)
<b>Duration of Hemophilia B (years), n<sup>1</sup></b>	65	53	52
Mean (SD)	40.8 (15.7)	39.7 (15.0)	39.5 (15.1)
Median (Q1-Q3)	36.4 (30.1-50.6)	34.3 (30.1-48.9)	34.2 (29.8-49.6)
8 Bleeding Episodes	3 (4.5)	2 (3.7)	2 (3.8)
10 Bleeding Episodes	1 (1.5)	0	0
11-15 Bleeding Episodes	4 (6.0)	3 (5.6)	3 (5.7)
>20 Bleeding Episodes	2 (3.0)	2 (3.7)	2 (3.8)
<b>FIX Replacement Therapy Type, n (%)</b>			
Prophylactic	67 (100.0)	54 (100.0)	53 (100.0)
On-demand	5 (7.5)	4 (7.4)	4 (7.5)
<b>FIX Replacement Therapy Type, n (%)</b>			
Extended Half-life	40 (59.7)	31 (57.4)	30(56.6)
Standard Half-Life	27 (40.3)	23 (42.6)	23 (43.4)
<b>HIV Status, n (%)</b>			
Negative	63 (94.0)	51 (94.4)	50 (94.3)
Positive	4 (6.0)	3 (5.6)	3 (5.7)
<b>Hepatitis B Infection, n (%)</b>			
Prior Resolved <sup>4</sup>	13 (19.4)	9 (16.7)	9 (17.0)
<b>Hepatitis C Infection, n (%)</b>			
Prior or Ongoing <sup>4</sup>	38 (56.7)	31 (57.4)	30 (56.6)
Prior Resolved	34 (50.7)	28 (51.9)	27 (50.9)
Ongoing	4 (6.0)	3 (5.6)	3 (5.7)
Positive at Screening <sup>5</sup>	1 (1.5)	1 (1.9)	1 (1.9)

Abbreviations: FAS = Full Analysis Set; FIX = Factor IX; HIV = human immunodeficiency virus; Incl. = including; PP = Per Protocol; SD = standard deviation.

<sup>1</sup>. Duration was calculated based on the date the subject was initially diagnosed with hemophilia B according to the Case Report Form.

<sup>2</sup>. FIX plasma level <1%.

<sup>3</sup>. FIX plasma level ≥1% and ≤2%.

<sup>4</sup>. Prior or ongoing per reported medical history. All subjects tested negative pre-dose.

<sup>5</sup>. Subjects positive at screening had “Hepatitis C Virus RNA = Detected” for Hepatitis C. Subject was positive at screening and negative at L-Final visit.

Source: Original BLA 125772/0/0, Study 061-02 CSR, pp.80-82, Table 11.

### 6.1.10.1.3 Subject Disposition

A total of 75 subjects were screened and 67/75 (89.3%) subjects entered the lead-in period (see Table 5). Of the subjects who entered the lead-in period, 13/67 (19.4%) subjects discontinued prior to dosing. There were 54/67 (80.6%) subjects treated with AMT-061, of which 53/54 (98.1%) subjects completed treatment. One subject prematurely discontinued treatment infusion due to an AE of hypersensitivity and received a partial dose (10%); the subject continued in the study for follow-up. One subject who received full treatment died 464 days (approximately 15 months) post-treatment due to cardiogenic shock. Overall, 53/54 subjects completed 18 months of follow-up post AMT-061 administration.

**Table 5. Subject Disposition**

	<b>Total (N=75) n (%)</b>
Screen Failures <sup>1</sup>	8/75 (10.7)
Entered Lead-in Period	67/75 (89.3)
Lead-in Discontinuers (i.e., Not Treated with AMT-061)	13/67 (19.4)
Treated with AMT-061	54/67 (80.6)
Prematurely Discontinued from Treatment due to Adverse Event (Received Partial Dose)	1/54 (1.9)
Completed Treatment (Received Full Dose)	53/54 (98.1)
Early Withdrawal from Study (Post-treatment; due to Adverse Event)	1/54 (1.9)
Completed Study	0

<sup>1</sup>. The Screen Failure Population included screened subjects who never entered the lead-in period.

Source: Original BLA 125772/0/0, Study 061-02 CSR, p.76, Table 8.

### 6.1.11 Efficacy Analyses

The initial database lock for the study was on 18 October 2021 and included all subject-specific Month 18 visits, as well as visits beyond Month 18 if they occurred (or the events/exposures began) before 31 August 2021. The final database lock occurred on 25 January 2022 following an update to correct inaccurate raw laboratory data points related to FIX activity and anti-AAV5 NABs.

#### 6.1.11.1 Analyses of Primary Endpoint(s)

##### Applicant's initial primary analysis on ABR

The applicant's initial primary analysis on ABR, using the repeated measures GEE negative binomial regression model with at-risk (for bleed) time excluding periods within 5 half-lives of FIX replacement product use, reported an ABR rate ratio (month 7-18 post-treatment/lead-in period) estimate of 0.36 with a 95% CI of (0.20, 0.63). The upper limit of the 95% CI is less than the NI margin of 1.8, therefore meeting the non-inferiority success criterion. Lead-in period mean ABR was estimated at 4.2 bleeds/year with a 95% CI of (3.2 5.5). EEP (Month 7-18 post-treatment) mean ABR was estimated at 1.5 bleeds/year with a 95% CI of (0.8, 2.8).

However, for the three subjects who did not stop or resumed RP during their EEPs post AMT-061 treatment, this approach to address confounding by excluding periods contaminated by FIX product use (the 5 half-lives) from the at-risk period is not reasonable, even though it is reasonable for the remaining subjects for whom FIX products were used at most a few times per subject. I illustrate below the problem with this approach:

1. Subject (b) (6) continued RP post AMT-061 treatment. He received 30 FIX injections during Months 7 to 18. Removing time within 5 half-lives of a FIX product injection from at-risk time results in 1.09 days at risk. During this time, this subject had a total of five bleeds, four spontaneous and one unknown, thus the ABR with this adjusted at-risk time would be  $5/(1.09/365.25) = 1675$  bleeds/year. It seems then the estimate of the mean ABR, even if all the other subjects had zero bleeds post-treatment, would be at least 31 (1675/54) bleeds/year, vastly different from the 1.5 bleeds/year given by the applicant's primary analysis. The reason for these seemingly conflicting results is that the data of this subject has very little weight compared to most of the other subjects, i.e., 1.09 day vs. ~365 days. Thus, this "imputation" of ABR seriously downplays the role of subjects who continued RP. On the other hand, it would not be reasonable to impute an ABR of 1675 with an at-risk time of 365 days to make this subject having the same weight as the others. As a side note, this subject had the highest pre-dose NAb titer of 1:3212.3.
2. Subject (b) (6) also continued RP post AMT-061 treatment. He did not have "uncontaminated" at-risk time during Months 7 to 18. The applicant imputed at-risk time using data in Months 0-6 and Months 19-24, and gave an at-risk time of 20 days and 2 bleeds, resulting in an "imputed" ABR of 36. In addition to issues similar to that with Subject (b) (6) as described above, borrowing at-risk time from the neighboring time intervals created further incongruence for this subject's data. As a sided note, this subject received only ~10% of the intended dose due to hypersensitivity at the time of administration.
3. Subject (b) (6). In addition to the two subjects described above who were reported by the applicant as the only subjects using RP during the EEP of Months 7 to 18, I identified Subject (b) (6) as resuming RP on Day 396 post-treatment and for the remaining 149 days during EEP. The applicant confirmed this in responding to my information request (IR). For this subject, the algorithm as used in the initial primary analysis to recalculate at-risk time again is not a reasonable way to address the confounding effect of RP during the period when he was on RP.

#### Updated primary analysis on ABR with imputation of hypothetical ABRs for subjects on RP during EEP

As described above, alternative, more reasonable approaches should be used to impute the ABRs for those subjects receiving RP post treatment during EEP (Months 7 to 18). The clinical question of interest regarding the sole effect of AMT-061 is "How many

bleeds will the subject likely experience in the absence of RP?” for these three subjects. There may be multiple reasonable ways to impute a bleeding count for these subjects. One way is to count each FIX product use post treatment as a bleed, which in the case of Subject (b) (6) would be 30 bleeds. Another reasonable imputation would be the subject’s expected ABR while receiving on-demand treatment prior to receiving AMT-061. From Table 2, mean ABRs for similar populations while receiving on-demand treatment were 15.6 to 20.1.

Therefore, I have decided to use a single imputation method to stipulate that, for the period when a subject was receiving RP during EEP post AMT-061 treatment, the ABR be imputed as 20. This is likely an underestimate for Subject (b) (6), given that he had 5 bleeds, including 4 spontaneous bleeds, despite receiving RP post-treatment, while he had no bleeds during the lead-in period. For Subject (b) (6), this is also unlikely to be an overestimate given that his ABR during the lead-in period was 12.6, and he was identified as receiving inadequate prophylaxis during lead-in (see later discussion on baseline RP adequacy for more details). For Subject (b) (6), imputing an ABR of 20 for the 149 days he was on RP results in a total of 9 bleeds for the entire EEP, during which he also had one recorded bleed. All three subjects would have at-risk time equal to their follow-up time during EEP. I have decided not to use multiple imputation given that (1) there is no good basis to develop a distribution for the imputation; and (2) no extra precision is needed in this context given the relative degree of uncertainties of various factors.

Table 6 reported the results of the updated primary analysis with an ABR of 20 imputed for the three subjects receiving RP during the EEP for the period when they were on RP. The upper limit of the 95% CI on the ABR rate ratio is less than the NI margin of 1.8, therefore the non-inferiority criterion for the primary endpoint has also been met using the updated primary analysis.

**Table 6. Result of updated primary analysis on ABR (point estimates and 95% CI)**

Lead-in Period Adjusted Mean ABR	EEP (Months 7 to18 Post-treatment) Adjusted Mean ABR	ABR Rate Ratio (EEP/ Lead-in Period)
4.1 (3.2, 5.4)	1.9 (1.0, 3.4)	0.46 (0.26, 0.81)

Note: An ABR of 20 is imputed for Subjects (b) (6) for the time when they were on RP during the EEP.

Source: Reviewer’s analysis.

I have also assessed the impact on the upper limit of the 95% CI on the ABR rate ratio of varying imputed ABR. When imputed ABR is at least 26, the upper limit is greater 1, meaning that AMT-061 is no longer “superior” to the lead-in period treatment. When imputed ABR is at least 53, the upper limit is greater 1.8, meaning that AMT-061 is no longer “non inferior” to the lead-in treatment. From this analysis, the non-inferiority claim is quite robust to the imputed ABR values. On the other hand, the “superiority” claim no longer holds when ABR is at least 26, which might still be a reasonable

imputation. It is also worth noting that “superiority” is being used here in a purely statistical sense; a single non-randomized study is not adequate to show clinical superiority of the gene therapy modality to routine prophylaxis; see further discussion below.

***Reviewer’s comment:***

*All analyses below use the updated ABR imputation for the three subjects using RP during the EEP.*

Assessment of adequacy of RP regimens received during the lead-in period

Throughout the development of the CT-AMT-061-02 protocol and SAP, the FDA had advised the sponsor to ensure the RP regimens the subjects receive during the lead-in period are adequate. This is important as otherwise it is not clear to what AMT-061 is compared, and the NI margin was derived assuming AMT-061 would be compared to adequate RP regimens. My review revealed that some subjects might have received FIX products at lower frequency than adequate RP regimens. In response to my IR, the applicant had conducted an extensive analysis. I summarized some salient features of the findings below.

1. Overall, there were six subjects that may not have had an adequate prophylaxis regimen in the lead-in period. The subject IDs are (b) (6). Their lead-in ABRs were 5.1, 12.7, 7.0, 5.8, 10.7, and 11.4, respectively. A sensitivity analysis excluding these 6 subjects gives an ABR rate ratio estimate of 0.44 with a 95% CI of (0.23, 0.84). The lead-in period adjusted mean ABR is 3.5 with a 95% CI of (2.6, 4.8) and the Months 7-18 ABR is 1.6 with a 95% CI of (0.8, 3.0).
2. Using a metric for evaluating baseline prophylaxis regimen compliance defined as (Actual number of days subject received prophylaxis FIX infusion excluding FIX use for other purposes/Total number of days subject should receive prophylaxis FIX as prescribed), 13/54 (24.1%) subjects were < 80% compliant, and 9/54 (16.7%) were < 70% compliant.

It might be puzzling that only six subjects were identified as not receiving adequate RP while 13 subjects were < 80% compliant. Recognizing there is wide inter-individual variability in tendency to bleed, this might suggest that some lead-in subjects do not tend to bleed even without receiving RP as prescribed. These subjects would not be as informative to assess the AMT-061 effect, as a low ABR post AMT-061 treatment might reflect their innate low tendency to bleed, rather than the effect of AMT-061.

Nonetheless, given that several sensitivity analyses have shown that the upper limits of the 95% CIs on the ABR rate ratio are well below the NI margin of 1.8, and some degree of variability in compliance with prescribed RP is to be expected, I conclude that the NI comparison of the ABR endpoint is met.

Assessment of a superiority claim of AMT-061 over standard of care RP

The applicant claims superiority of AMT-061 over standard of care continuous routine Factor IX prophylaxis in the draft labeling and the CSR, based on the result that the upper

limit of the 95% CI on ABR rate ratio is less than 1 and a p-value < 0.05 for the test of the null hypothesis that the rate ratio is  $\geq 1$ . The review team have determined that the study results do not support such a superiority claim based on the following observations and considerations.

1. As described above, a substantial proportion of subjects had not received an adequate routine prophylaxis regimen or had not complied with the prescribed RP regimen during the lead-in period, and as a result the baseline comparator was not well-characterized standard of care RP regimens, and therefore could not support a meaningful assessment on superiority.
2. The trial had only evaluated the efficacy of AMT-061 over a limited period of 12 months (Months 7 to 18) following AMT-061 treatment. There is no data at this time to enable assessment of AMT-061 efficacy beyond this period, while routine prophylaxis can generally be used indefinitely. AMT-061 may also carry more risk than RP, including potential longer-term risk that cannot be adequately evaluated at this time due to limited AMT-061 exposure in follow-up duration and number of subjects treated. This latter point is deferred to other review disciplines with the expertise in this area.
3. In this trial, 3/54 (5.6%) of the subjects continued or resumed RP after AMT-061 treatment. Subjects had also used factor IX replacement products to prevent bleeding for invasive procedures or for other precautions, and for treatment of bleeds. Using replacement products after AMT-061 treatment as rescue medicines complicates any superiority claim over these products.
4. Given the single-arm open-label nature of the trial, robustness of study results should be assessed by taking into account some degree of extra uncertainty introduced by potential biases. While the NI conclusion with an NI margin of 1.8 appears to be robust to imputation of hypothetical ABR for subjects using RP post AMT-061 treatment, the superiority conclusion is not (see analysis following Table 6 above).

#### 6.1.11.2 Analyses of Secondary Endpoints

##### **Reviewer's Comment:**

*The SAP specified a list of 16 secondary endpoints and planned to test 12 of them hierarchically to control type 1 error rate. However, this approach does not align with clinical questions of relevance or interest. Two examples are given below.*

1. *The applicant tests for reduction in use of exogenous replacement products after AMT-061 treatment compared to the amount used during the lead-in period. This is not relevant to efficacy evaluation, as exogenous replacement products **was** the control products and we expect subjects to use little or no exogenous replacement products after AMT-061 treatment. In addition, the information on their use post AMT-061 treatment is already approximately captured in the overall bleed counts in all subjects and the number of subjects who continued or resumed RP after AMT-061 treatment. The review team recommended the applicant to remove results on this comparison from the draft labeling. I do not include these analyses in this review memo.*

2. *The applicant tests the hypotheses that FIX activity level increases at several timepoints, compared to baseline, after AMT-061 treatment. We already expect the activity levels at these timepoints would be higher than baseline, so a statistical test is of no interest. What is of interest is the trend of FIX activity level over time and the inter-subject variability, which are best addressed with descriptive summaries.*

In this section on secondary endpoints, I provided informative descriptive summaries on FIX activity levels post AMT-061 treatment.

#### FIX activity level after AMT-061 treatment

Different assays give different readings of FIX activity level on the same subject's blood sample after AMT-061 treatment. It is also unknown whether a particular reading, say 40%, from any assay on a post gene therapy sample, would have the same prognostics for this treated subject as the untreated population with the same numerical reading (40%) on their FIX activity level. The evaluation and interpretation of the implication of the magnitude of the FIX activity level is deferred to other review disciplines.

Table 7 and Figure 2 summarize the time trend of factor IX activity level, measured by a one-stage aPTT assay at central labs, at Months 6, 12, and 18 after AMT-061 treatment. While there is wide variability across individuals, most subjects appear to maintain their level within this time frame, with slight decrease at Month 18.

**Table 7. Summary statistics of factor IX activity level (%) by one-stage aPTT assay at central labs at Months 6, 12, and 18 after AMT-061 treatment**

Timepoint	Number of Subjects	Number of Subjects with Contaminated <sup>c</sup> FIX Levels	Min <sup>d</sup>	25% Percentile	Median	75% Percentile	Max
Month 6	54	3	8.2	26.2	36.3	48.6	97.1
Month 12	53 <sup>a</sup>	3	5.9	28.7	38.8	49.8	113.0
Month 18	53 <sup>b</sup>	3	4.5	24.1	32.0	44.0	122.9

Max = maximum; Min = minimum

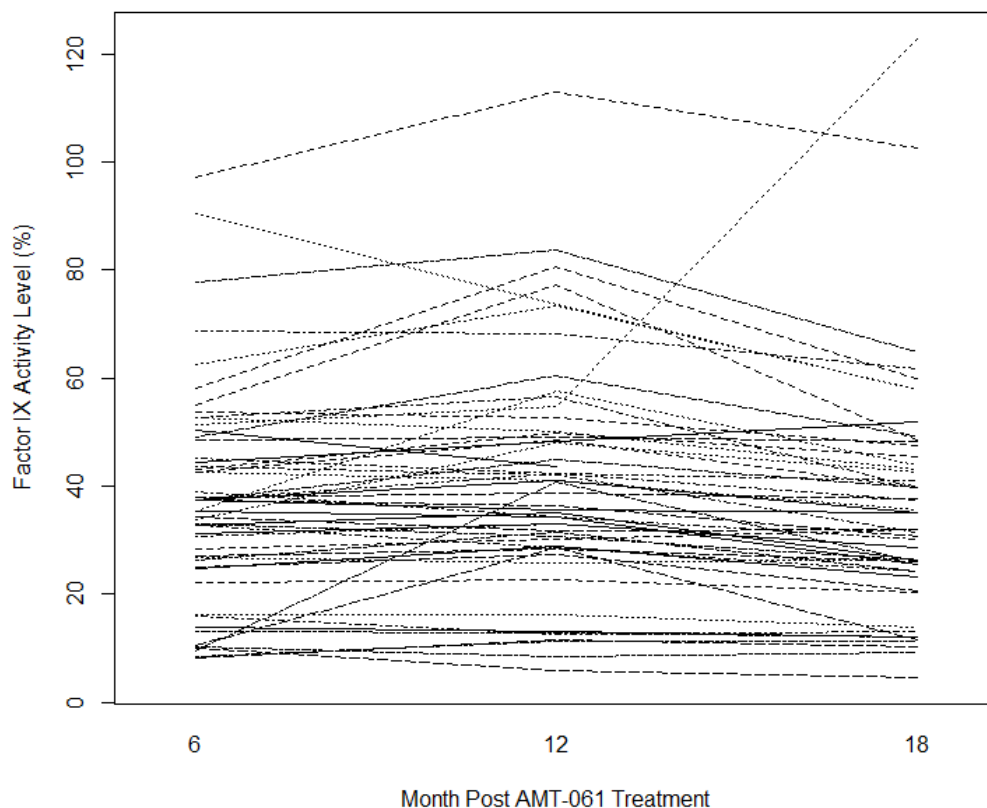
<sup>a</sup> Subject (b) (6) missed Month 12 visit. His two adjacent visits were at Month 7 (Day 202) and Month 18 (Day 575).

<sup>b</sup> (b) (6) did not have Month 18 visit due to death.

<sup>c,d</sup> At each timepoint, there were three subjects whose FIX activity level measurement were taken within 5 half-lives of the last FIX replacement product use. So the minimum (min), in the absence of replacement product use, might be lower. No imputation is implemented.

Source: Reviewer's analysis.

**Figure 2. Factor IX activity level (%) by one-stage aPTT assay at central labs vs. time at Months 6, 12, and 18 after AMT-061 treatment**



Source: Reviewer's analysis.

#### Additional descriptive summaries on bleeding episodes and related endpoints

At dosing, two subjects had pre-existing target joints, which resolved during the post-treatment period. One subject had a new target joint that occurred during the post-treatment period and was not resolved at the time of the data cutoff for this report. [Table 8](#) summarizes the number of observed joint and spontaneous bleeds during the lead-in and the EEP. During lead-in, 57% (77/136) of the observed bleeds were joint bleeds, compared to 35% (19/54) of the observed bleeds during EEP. Note that these numbers do not consider the subjects who were on RP during the EEP by imputing the hypothetical bleeds of these types, as there is no good basis to support such imputation. Therefore, these proportions are likely an underestimate for the EEP.



**Table 8. Number of joint and spontaneous bleeds during the lead-in period and the EEP**

	<b>At-Risk Time (Person-Year)</b>	<b>Imputed Number of Bleeds</b>	<b>Observed Number of Bleeds</b>	<b>Observed Number of Joint Bleeds (% of Total)</b>	<b>Observed Number of Spontaneous Bleeds (% of Total)</b>
<b>Lead-in Period</b>	33.1	136	136	77 (57%)	50 (37%)
<b>Months 7 to 18 after AMT-061 Treatment</b>	51.9	96	54	19 (35%) <sup>a</sup>	14 (26%) <sup>a</sup>

<sup>a</sup> The proportion of the type of bleeds is relative to the total observed bleeds. For example, 19/54 = 35%.  
Source: Reviewer's analysis.

#### 6.1.11.3 Subpopulation Analyses

**Table 9** summarizes the subgroup analysis results, using the updated imputation of hypothetical ABRs for subjects on RP during EEP, based on age, race, ethnicity, baseline anti-AAV5 NAb titer, and geographical region. For most subgroups, the upper limit of the 95% CI on the rate ratio is less than the NI margin of 1.8. The two subgroups with an upper limit of the CI greater than the NI margin are those  $\geq 60$  years of age (n=8), and those of “non-white or not specified” race (n=14); their relatively small sample sizes led to consequently wider confidence intervals.

##### Baseline anti-AAV5 NAb titer

Initially, FDA and the applicant would like to assess whether higher baseline anti-AAV5 NAb titer would reduce the efficacy of AMT-061 and to identify a titer cut-off based on the ABR outcome. However, the anti-AAV5 assay has not yet been validated and this question cannot be addressed at this time. Furthermore, given the small sample size, it would be difficult to identify such a cut-off. For example, 13 of the 21 subjects positive for anti-AAV5 NAb at baseline had titer readings below 1:100, while the remaining 8 subjects had titer readings covering a wide range (1:111.5 to 1:3212.3) sparsely. It would be difficult to identify a cut-off above 1:100 even if the assay is validated. Using the current assay readings, the subgroup with positive titer appears to be less effective than those with negative titers, though the former group still meets the NI margin of 1.8.

**Table 9. Subgroup analysis results on ABR using the updated imputation of hypothetical ABRs for subjects on routine prophylaxis during EEP**

Subgroup	N	Lead-in Period Adjusted ABR (95% CI)	EEP (Months 7 to 18) Adjusted ABR (95% CI)	ABR Rate Ratio (EEP/ Lead-in) (95% CI)
<b>Age (Years)</b>	-	-	-	-
< 40	31	3.9 (2.7, 5.6)	1.8 (0.8, 4.0)	0.47 (0.21, 1.03)
40 to < 60	15	4.9 (3.2, 7.6)	1.3 (0.5, 3.7)	0.27 (0.10, 0.69)
≥ 60	8	3.5 (1.4, 8.3)	3.3 (0.8, 13.4)	0.95 (0.42, 2.15)
<b>Race</b>	-	-	-	-
White	40	3.6 (2.5, 5.1)	0.9 (0.5, 1.9)	0.26 (0.15, 0.47)
Non-White or Not Specified	14	5.6 (3.9, 8.1)	4.5 (2.0, 10.0)	0.81 (0.36, 1.82)
<b>Ethnicity</b>	-	-	-	-
Not Hispanic or Latino	45	3.9 (2.8, 5.4)	1.7 (0.8, 3.6)	0.45 (0.22, 0.90)
Hispanic or Not Specified	9	5.5 (4.5, 6.7)	2.7 (1.2, 6.1)	0.49 (0.22, 1.08)
<b>Baseline anti-AAV5 NAb Titer</b>	-	-	-	-
Negative	33	3.8 (2.6, 5.6)	1.2 (0.6, 2.4)	0.31 (0.17, 0.56)
Positive	21	4.7 (3.3, 6.5)	3.0 (1.3, 7.0)	0.65 (0.29, 1.50)
<b>Geographical Region</b>	-	-	-	-
US	20	4.2 (2.5, 7.0)	2.7 (1.2, 5.9)	0.65 (0.38, 1.10)
Non-US	34	4.1 (3.0, 5.5)	1.4 (0.6, 3.5)	0.34 (0.13, 0.90)
Netherlands	15	5.3 (3.7, 7.5)	1.5 (0.6, 3.7)	0.28 (0.12, 0.63)

Source: Reviewer's analysis.

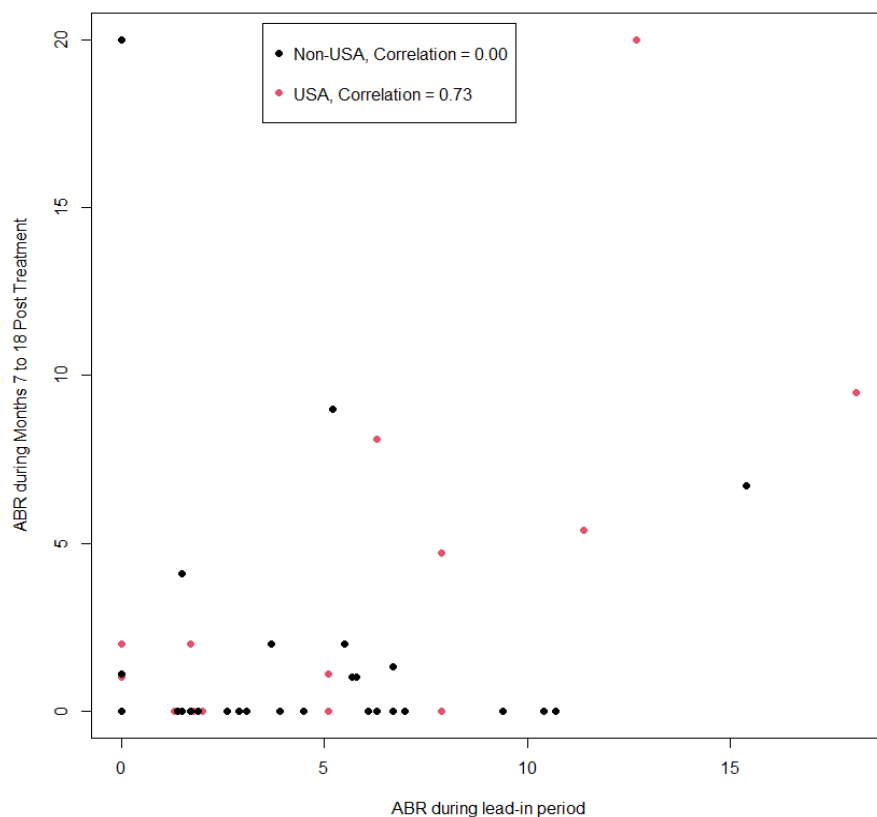
#### Subgroup analysis by geographical region

While US subjects and non-US subjects had similar adjusted mean ABRs during the lead-in period, the adjusted mean ABR during Months 7 to 18 in the US subgroup is almost twice that in the non-US group, 2.7 vs. 1.4 bleeds/year (Table 9). Netherlands had the

most subjects (15 out of 34) in the non-US group. Of note, for US sites, 20 out of 31 screened subjects (65%) eventually received AMT-061 treatment while 15 of the 16 (94%) screened subjects in Netherlands received AMT-061 treatment. There is a positive correlation of 0.73 between the ABRs before and after treatment in the US subjects, while there is no correlation for these two sets of ABRs in the non-US subjects (Figure 3). This lack of correlation between ABRs prior to and after AMT-061 treatment in the non-US subjects is also evident from Table 10. Of the eight US subjects with a lead-in ABR of > 4 bleeds/year, five of them (62.5%) still had ABR > 4 during the EEP; while for non-US subjects only 13.3% (2/15) of those with a lead-in ABR > 4 still had ABR > 4 during the EEP.

Though there seems to be some difference in the effect size between the two subgroups, both met the non-inferiority success criterion by having the upper limit of the 95% CI on the ABR rate ratio being less than 1.8 (Table 9).

**Figure 3. ABR during lead-in vs. ABR during Months 7 to 18 post-treatment by geographical regions**



Source: Reviewer's analysis.

**Table 10. Cross tabulation of ABR by period with a cut-off of 4 bleeds/year**

	Lead-in Period ABR $\leq$ 4	Lead-in Period ABR > 4
<b>EEP (Month 7 to 18 after AMT-061 Treatment)</b>	-	-
<b>FAS (n=54)</b>	-	-
ABR $\leq$ 4	29	16
ABR > 4	2	7
<b>USA (n=20)</b>	-	-
ABR $\leq$ 4	12	3
ABR > 4	0	5
<b>Non-USA (n=34)</b>	-	-
ABR $\leq$ 4	17	13
ABR > 4	2	2

Source: Reviewer's analysis.

#### 6.1.11.4 Dropouts and/or Discontinuations

#### 6.1.11.5 Exploratory and Post Hoc Analyses

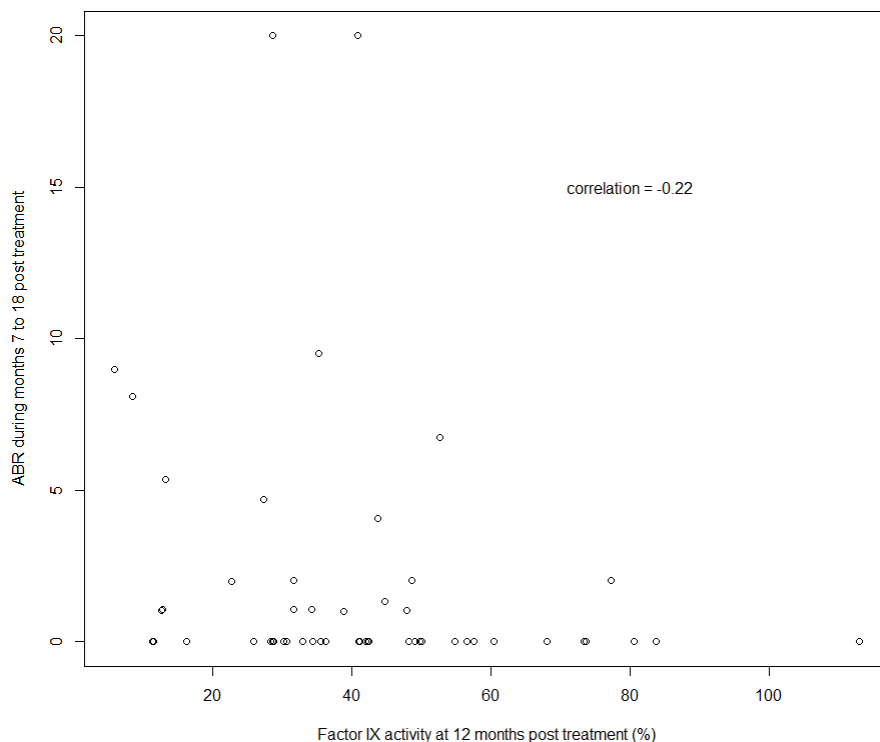
##### Use of systemic corticosteroids

A total of 9 subjects out of the 54 treated subjects (16.7%) used systemic corticosteroids for transaminase elevations after AMT-061 treatment in Study CT-AMT-061-02. The mean corticosteroid treatment duration for those subjects was 79.8 days, with a range of 51 to 130 days. As systemic corticosteroid use stopped before the EEPs started, they do not affect the efficacy evaluation.

##### Correlation between ABR during EEP and Month 12 FIX activity level

[Figure 4](#) examines the correlation between ABR during the EEP (Month 7 to 18 after AMT-061 treatment) and factor IX activity level at Month 12 post treatment. There is a negative correlation of -0.22. Note that ABRs during the EEP period were likely influenced by many factors, including lead-in period ABR and potentially geographical regions. Therefore, this negative correlation should be interpreted with caution and viewed as descriptive only.

**Figure 4. Correlation between ABR during the EEP and Factor IX activity at Month 12**



Source: Reviewer's analysis.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database includes all subjects treated in the two AMT-061 studies: the phase 3 study CT-AMT-061-02 (n=54) and the dose confirmation study CT-AMT-061-02 (n=3). In addition, the 5-year CSR on study CT-AMT-060-01, which was on the different predecessor investigational product AMT-060, will be briefly reviewed to identify any additional major safety issues (e.g., malignancy or death) that may be relevant to the entire class of hemophilia gene therapy products.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Of the 57 subjects in the safety database, 56 subjects received a single IV dose of  $2 \times 10^{13}$  gc/kg AMT-061. One subject in Study CT-AMT-061-02 received a partial dose (10%) of AMT-061 due to a hypersensitivity reaction and continued in the study. One subject in Study CT-AMT-061-02 died during the study. Across both studies, 56 subjects completed the 18-month Visit. Follow-up (FU) duration ranged from 12 to 36 months, with a total FU/exposure of 1,206.5 person-months ([Table 11](#)).

**Table 11. Follow-up/Exposure Duration of the AMT-061 Safety Database Subjects**

	Study CT-AMT-061-01 (N = 3)	Study CT-AMT-061-02 (N = 54)	Both Studies Combined (N = 57)
Exposure Duration <sup>b,c</sup>	n, Person-months <sup>a</sup>	n, Person-months <sup>a</sup>	n, Person-months <sup>a</sup>
12 to < 18 months		3, 50.6	3, 50.6
18 to < 24 months		47, 958.7	47, 958.7
24 to < 36 months	3, 91.2	4, 106.0	7, 197.2
Total person-months <sup>a</sup>	3, 91.2	54, 1115.3	57, 1206.5

<sup>a</sup> Person-months is the total number of months contributed to each exposure duration interval.

<sup>b</sup> Exposure duration is defined as time on study from treatment date to the minimum of End-of-study Visit date, early termination date, or data cutoff date.

<sup>c</sup> A protocol defined visit window of  $\pm 2$  weeks surrounding each scheduled visit resulted in 2 subjects' exposure of 17.7 months (instead of 18 months). A third subject had a < 18-month exposure duration due to death.

Source: Adapted from - Original BLA 125772/0/0, 2.7.4 Summary of Clinical Safety, p.12, Table 3.

All 57 subjects were male. Of the 52 subjects who self-reported race, 41 (78.8%) subjects identified as White, 3 (5.8%) subjects identified as Black, 2 (3.8%) subjects identified as Asian, and 6 (11.5%) subjects identified as other (Table 12). Of these, 48 (92.3%) subjects identified as non-Hispanic. The median age of subjects was 37 years and ages ranged from 19 to 75 years.

**Table 12. Demographic Characteristics of the AMT-061 Safety Database Subjects**

Characteristic	Study CT-AMT-061-01 (N = 3)	Study CT-AMT-061-02 (N = 54)	Total Etranacogene Dezaparvovec (N = 57)
<b>Sex, n (%)</b>			
Male	3 (100)	54 (100)	57 (100)
<b>Race, n (%)</b>			
N	3	49	52
American Indian or Alaska Native	0	0	0
Asian	0	2 (4.1)	2 (3.8)
Black or African American	2 (66.7)	1 (2.0)	3 (5.8)
Native Hawaiian or Other Pacific Islander	0	0	0
White	1 (33.3)	40 (81.6)	41 (78.8)
Other	0	6 (12.2) <sup>a</sup>	6 (11.5)
Missing	0	5	5

Characteristic	Study CT-AMT-061-01 (N = 3)	Study CT-AMT-061-02 (N = 54)	Total Etranacogene Dezaparvovec (N = 57)
<b>Ethnicity, n (%)</b>			
N	3	49	52
Hispanic or Latino	0	4 (8.2)	4 (7.7)
Not Hispanic or Latino	3 (100)	45 (91.8)	48 (92.3)
Missing	0	5	5
<b>Age (years)</b>			
N	3	54	57
Mean (SD)	46.7 (3.51)	41.5 (15.79)	41.7 (15.42)
Median	47.0	37.0	37.0
Min, Max	43, 50	19, 75	19, 75

Max = maximum; Min = minimum; N, n = number of subjects; SD = standard deviation.

<sup>a</sup> “Other” specified race in Study CT-AMT-061-02 are: 'IRANIAN' for 2 subjects, 'IRAQI' for 1 subject, 'SPANISH' for 1 subject, 'EAST INDIAN' for 1 subject, 'HISPANIC- PER SUBJECT' for 1 subject.

Source: Original BLA 125772/0/0, 2.7.4 Summary of Clinical Safety, p.14, Table 5.

## 8.4 Safety Results

### 8.4.1 Deaths

Two deaths were reported, one in Study CT-AMT-061-02 and the other in CT-AMT-060-01 (on the predecessor product).

Subject (b) (6), a 75-year-old White male with a medical history of atrial enlargement, atrial fibrillation, and atrial hypertension, experienced a fatal event of Cardiogenic Shock on Study Day 464, following a urinary tract infection. The investigator considered the event of Cardiogenic Shock as severe in intensity and unrelated to study medication. The applicant considered the event of Cardiogenic Shock as unrelated to study medication.

One death was reported (after database lock) from CT-AMT-060-01, the dose-escalation trial on the predecessor product AMT-060. Subject (b) (6) was a 69-year-old male with moderate/severe HB treated with the lower dose of the two dose levels at a Denmark site. The subject was treated with a single IV dose of  $5.0 \times 10^{12}$  gc/kg AMT-060 on (b) (6). He was found dead on (b) (6). The cause of death was not determined. The investigator assessed the relationship between AMT-060 and the death as being unlikely related.

#### 8.4.2 Nonfatal Serious Adverse Events

Of the 57 AMT-061 treated subjects, 14 (24.6%) subjects experienced 15 treatment-emergent serious adverse events (SAEs) (Table 13). All SAEs were assessed by the Investigators to be unlikely related or unrelated to AMT-061.

**Table 13, Treatment-emergent serious adverse events after AMT-061 treatment**

Subject ID	SAE Preferred Term	Severity	Outcome
<b>Study CT-AMT-061-01</b>	-	-	-
(b) (6)	Osteonecrosis	Moderate	Ongoing (not recovered)
<b>Study CT-AMT-061-02</b>	-	-	-
(b) (6)	Haemarthrosis	Moderate	Recovered/Resolved
(b) (6)	Jaw Fracture	Severe	Recovered/Resolved
(b) (6)	Complication associated with Device	Moderate	Recovered/Resolved
(b) (6)	Lower Gastrointestinal Haemorrhage	Moderate	Recovered/Resolved
(b) (6)	Nephrolithiasis	Mild	Recovered/Resolved
(b) (6)	Epilepsy	Moderate	Recovered/Resolved
(b) (6)	Covid-19	Severe	Recovered/Resolved
(b) (6)	Musculoskeletal Chest Pain	Mild	Recovered/Resolved
(b) (6)	Hepatocellular Carcinoma	Severe	Not recovered/Not resolved
(b) (6)	Transient Ischaemic Attack	Moderate	Recovered/Resolved
(b) (6)	Cellulitis	Severe	Recovered/Resolved
(b) (6)	Atrial Fibrillation	Moderate	Recovered/Resolved
(b) (6)	Cardiogenic Shock	Severe	Fatal
(b) (6)	Upper Gastrointestinal Haemorrhage	Severe	Recovered/Resolved

Source: Adapted from - Original BLA 125772/0/0, 2.7.4 Summary of Clinical Safety, p.28, Table 15.



## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

AMT-061 is an investigational single-dose gene therapy for congenital hemophilia B with an AAV5 vector coding for the Padua variant of the human FIX gene.

The clinical development program of AMT-061 consists of two clinical trials: trial CT-AMT-061-01 (n=3) for dose confirmation and phase 3 trial CT-AMT-061-02 (also called “HOPE B”, n=54). The efficacy database consists of the 54 subjects treated in CT-AMT-061-02, and the safety database includes the 57 subjects treated in trials CT-AMT-061-01 and CT-AMT-061-02. AMT-061 has a predecessor product AMT-060 which differs from AMT-061 (b) (4) and instead codes for the wildtype variant of the human FIX gene. (b) (4), 10 subjects were treated in the AMT-060 dose-ascending trial CT-AMT-060-01. Safety summary about these 10 AMT-060 treated subjects in the 5-year CSR has also been briefly reviewed to identify AEs of death or malignancies.

Study CT-AMT-061-02 was an open-label, single-dose ( $2 \times 10^{13}$  gc/kg of AMT-061), multi-center, multinational trial with a planned sample size of at least 50 subjects with severe or moderately severe congenital hemophilia B who were on standard of care routine prophylaxis. Eligible subjects were to start with a lead-in phase/period with a duration of at least 6 months wherein their baseline data including bleeding episodes and exogenous FIX replacement product use would be prospectively collected. Subject continued to be eligible would receive a single-dose of AMT-061 and then be followed up at least monthly during the first 12 months and every 6 months during the next 4 years wherein bleeding episodes, FIX activity levels, and exogenous FIX replacement product use would be collected.

The primary objective was to demonstrate the non-inferiority (NI) of the efficacy of a single-dose of  $2 \times 10^{13}$  gc/kg of AMT-061 in patients with severe or moderately severe congenital hemophilia B, in terms of annualized bleeding rate (ABR), during the 52-week period starting on Month 7 after AMT-061 treatment (i.e., Months 7 to 18) compared to standard of care continuous routine FIX prophylaxis during the lead-in period. The efficacy evaluation period (EEP, Months 7 to 18 post treatment) started from Month 7 in order to allow establishment of stable Factor IX (FIX) expression after AMT-061 treatment. The primary efficacy analysis would be an NI comparison between the ABR during Months 6 to 18 post AMT-061 and that during the lead-in period, with an NI margin of 1.8 on the ABR rate ratio.

The primary efficacy analysis yielded an estimate of the ABR rate ratio (EEP/lead-in period) of 0.46 with a 95% confidence interval (CI) of (0.26, 0.81), therefore meeting the NI success criterion which required the upper bound of the CI to be less than 1.8. The adjusted ABR was 4.1 bleeds/year with a 95% CI of (3.2, 5.4) for the lead-in period, and was 1.9 bleeds/year with a 95% CI of (1.0, 3.4) for the EEP period (Months 7 to 18 post AMT-061 treatment period). The results reported here reflect an update in an imputation algorithm in the primary analysis, which is described below.

The planned primary analysis used an imputation approach that defined the “at-risk” for bleed time with an intention to isolate the AMT-061 treatment effect from the confounding effect of FIX replacement product use during the EEP. This approach excluded the period within the 5 half-lives following a FIX replacement product use from the “at-risk” time. This approach was appropriate for the majority of subjects, who received FIX replacement products at most a few times during the EEP. However, three subjects never stopped or resumed RP during EEP, and the approach described above did not incorporate their data in the analysis model appropriately.

After AMT-061 treatment, two subjects had to continue RP with exogenous FIX replacement products. One of them had the highest baseline anti-AAV5 NAb titer at 1: 3212.3. This subject had a total of five bleeds, four spontaneous and one unknown, during EEP (Months 7 to 18) despite being on RP. The other subject received only around 10% of the intended AMT-061 dose due to hypersensitivity at the time of administration. This subject had one bleed during EEP. In addition, a third subject resumed RP on Day 396 post AMT-061 treatment. For these three subjects who continued or resumed RP, the planned imputation approach (for the primary analysis) described above broke down, giving a nonsensical imputed ABR of 1675 for one subject. For these three subjects, FDA and the applicant agreed to update the imputation approach to use a hypothetical imputation algorithm instead, where an ABR of 20 bleeds/year was imputed as the hypothetical ABR the subject would have experienced had they not used RP during the EEP. The primary NI analysis result reported above used this updated imputation algorithm for these three subjects. Sensitivity analyses reveal that the hypothetical ABR for these three subjects need to be at least 53 bleeds/year for the NI conclusion to no longer hold, demonstrating the robustness of the NI conclusion to the imputation algorithm for these three subjects.

Several issues complicated the interpretation of the study results. The first issue was that some subjects did not receive adequate routine prophylaxis during the lead-in period, potentially leading to a bias favoring AMT-061 in the NI comparison. However, the estimated mean ABR of 1.9 (95% CI: 1.0, 3.4) during the EEP was within the range of mean ABR reported for RP in various studies, providing some reassurance that the NI conclusion is robust to potential biases introduced by some degree of inadequacy of baseline RP regimens. The second issue is that there was a numerical difference between the estimated mean ABR during EEP between the US and non-US regions, with the mean ABR for US being almost twice as that for non-US regions (2.7 vs. 1.4). There was a positive correlation of 0.73 between the ABRs before and after treatment in the US subjects, while there is no correlation for these two sets of ABRs in the non-US subjects. Nevertheless, the NI conclusion holds in both geographical regions, confirming the robustness of the NI conclusion despite this numerical difference in efficacy between the two regions.

For safety evaluation, one death occurred in Study CT-AMT-061-02 due to cardiogenic shock on Study Day 464. In addition, hepatocellular carcinoma was diagnosed in a subject around one year after AMT-061 treatment. For the predecessor product AMT-

060, one death was reported of a subject treated in Study CT-AMT-060-01, determined to be due to natural but unknown causes. The investigators determined that all these three AEs were unrelated to or unlikely to be related to the investigational products. Further analysis of safety data is deferred to the clinical team.

## 10.2 Conclusions and Recommendations

The efficacy results of Study CT-AMT-061-02 provided sufficient statistical evidence to support the non-inferiority of AMT-061 treatment to standard of care routine prophylaxis in terms of ABR during the efficacy evaluation period of Months 7 to 18 after AMT-061 treatment.