

### **BLA Clinical Review Memorandum**

Application Type	Original BLA
STN	BLA 125772/0
CBER Received Date	March 24, 2022
PDUFA Goal Date	November 22, 2022
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Megha Kaushal, MD (Clinical Efficacy) Courtney Johnson, MD (Clinical Safety) Leah Crisafi (Clinical Safety)
Review Completion Date / Stamped Date	11/22/22
Supervisory Concurrence	
Applicant	CSL Behring LLC
Established Name	Etranacogene dezaparvovec
(Proposed) Trade Name	HEMGENIX
Pharmacologic Class	Gene therapy
Formulation(s), including Adjuvants, etc.	Adeno-associated virus vector-based
Dosage Form(s) and Route(s) of Administration	Single- Use Intravenous Infusion
Dosing Regimen	2 x 10 <sup>13</sup> genome copies (gc) per kg (2mL/kg) of body weight
Indication(s) and Intended Population(s)	Treatment of adults with Hemophilia B (congenital Factor IX deficiency)
Orphan Designated (Yes/No)	Yes

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## GLOSSARY

AAV	adeno-associated virus
AAV5	adeno-associated virus- serotype 5
ABR	annualized bleeding rate
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BTB	breakthrough therapy designation
BU	Bethesda unit
CAP	controlled attenuation parameter
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
CPK	creatinine phosphokinase
CSLB	CSL Behring
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
eCTD	Electronic Common Technical Document
EEP	efficacy evaluation period
FIX	Factor nine (IX)
HBV	hepatitis B
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
Hem-A QoL	Hemophilia Specific Quality of Life Index
HIV	human immunodeficiency virus
IMP	investigational medicinal product
IND	Investigational New Drug
IR	information request
ISS	integrated summary of safety
IU/L	international units
IV	intravenous
LTFU	long-term follow-up
NAb	neutralizing antibody
NI	noninferiority
OIR	Office of In Vitro Diagnostics and Radiological Health
PK	pharmacokinetic
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
RP	routine prophylaxis
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
ULN	upper limit of normal
WGS	whole genome sequencing

## 1. EXECUTIVE SUMMARY

Factor IX (FIX) deficiency (hemophilia B, Christmas disease) is the second most common coagulation factor deficiency. Deficiency of the essential blood coagulation FIX results in impaired hemostasis and increased bleeding tendency. Hemophilia B is divided into groups based on factor levels that correlate with the disease pattern. A goal of modern hemophilia management is to prevent spontaneous bleeds by supplying replacement factor that will maintain higher FIX activity levels.

Etranacogene dezaparvovec (AMT-061; AAV5-hFIXco-Padua; Hemgenix) is a gene therapy product that consists of a codon-optimized coding DNA sequence of the gain-of-function Padua variant of human FIX, under control of a liver-specific LP1 promoter and encapsulated in a nonreplicating recombinant adeno-associated viral vector of serotype 5 (AAV5). Following single intravenous (IV) administration, AMT-061 preferentially targets liver cells for transduction and results in expression of FIX-Padua protein.

This Applicant seeks the an indication for treatment of adult patients with hemophilia B with a (b) (4)

The primary basis to support licensure for the proposed indication for AMT-061 comes from a single, adequate and well controlled trial, Study CT-AMT-061-02 supported by an earlier safety study, Study CT-AMT -061-01.

Study CT-AMT-061-01 was a Phase 2b, open-label, single-dose, single-arm, multicenter trial to confirm the FIX activity level of the AAV5 containing the Padua variant of a codon-optimized human FIX gene (AAV5-hFIXco-Padua, AMT-061) administered to 3 adult subjects with severe or moderately severe hemophilia B.

Study CT-AMT-061-02 was a Phase 3, open-label, single-dose, multicenter, multinational trial investigating AMT-061 administered to adult subjects with severe or moderately severe hemophilia B. Subjects completed a lead-in period of at least six months prior to receiving FIX prophylaxis therapy. Fifty-four subjects received a single dose of AMT-061 and were followed up to 18 months post treatment.

Efficacy was based on annualized bleeding rate (ABR) during Months 7-18 after treatment with AMT-061 compared with the ABR during the lead-in period. The mean ABR during Months 7-18 was 1.9 bleeds/year [95% confidence interval (CI): 1.0, 3.4], compared with a mean ABR of 4.1 bleeds/year [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio (Months 7-18 post-treatment/lead-in) was 0.46 bleeds/year [95% CI: 0.26, 0.81], demonstrating noninferiority (NI) of ABR during Months 7-18 compared with the lead-in period. The mean FIX activity levels over time, as measured by a one-stage [activated partial thromboplastin time (aPTT)-based] assay, were 39% ( $\pm 18.7\%$ ), 41.5% ( $\pm 21.7\%$ ), 36.9% ( $\pm 21.4\%$ ), and 36.7 ( $\pm 19.0\%$ ) of normal, respectively, at 6, 12, 18, and 24 months.

The safety population consists of 57 subjects who received AMT-061, to include 3 subjects treated in the Phase 2b trial - CT-AMT-061-01, and 54 subjects treated in the Phase 3 trial- CT-AMT-061-02. In the Phase 2b trial, all 3 subjects received the planned dose of AMT-061. In the Phase 3 trial, 53 subjects received the planned dose of AMT-061 and 1 subject received a partial (10%) dose of AMT-061 due to a hypersensitivity

reaction. In Study CT-CMT-061-01, no deaths, treatment-emergent adverse events (TEAEs) leading to premature treatment discontinuation, or TEAEs of special notification, were reported. Transient mild increases in ALT levels post-AMT-061 administration were reported in 2 subjects who did not receive treatment with steroids and were not associated with loss of FIX activity. No subjects experienced clinically significant increases in ALT levels post-AMT-061 administration.

In Study CT-CMT-061-02 (n = 54), Fifty-three subjects received AMT-061 at  $2 \times 10^{13}$  gc/kg. One subject received approximately 10% of the  $2 \times 10^{13}$ -gc/kg dose due to a related hypersensitivity reaction. Overall, AMT-061 was safe and well tolerated. One death was reported and assessed by the Investigator as not treatment-related; this subject experienced cardiogenic shock that resulted in death on Study Day 464 (approximately 15 months post-treatment). Reported SAES were not considered treatment-related SAEs. The most common adverse reactions (incidence  $\geq 5\%$ ) were elevated ALT/AST, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, malaise and fatigue. The TEAE and SAE profile was comparable between subjects who were positive or negative for baseline anti-AAV5 NABs, with infusion-related reactions more prevalent in those who were positive. One subject developed a lesion consistent with hepatocellular carcinoma (HCC). After a comprehensive investigation, it was assessed by the Investigator and Sponsor to unlikely be a result of vector integration.

Note that the trial utilized a clinical trial assay to assess pre-existing anti-AAV5 neutralizing antibodies (Nab). Twenty-one subjects were positive for the neutralizing anti-AAV5 antibody titers, with a range from 1:8.7 – 1:3212. The subject with the highest neutralizing antibody (NAb) titer did not express the transgene and continued to have multiple bleeding events post treatment. A parallel review of the companion diagnostic by Center for Devices and Radiological Health (CDRH) concluded that the assay was neither valid or reliable. Due to the limited data and unreliability of this assay, it is unknown if higher pre-existing NAb titers will result in increased risk of bleeding due to lack of pharmacologic effect. A postmarketing requirement (PMR) for a safety study will evaluate the correlation of NABs to bleeding and other safety signals based on a validated assay. The indication statement for this product has been revised to remove the NAb titer threshold statement and all references made in the label, as there is no validated or reliable assay, at the time of approval.

The applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical investigation and preclinical studies. The overall benefit risk assessment is favorable and the clinical review team recommends regular approval of AMT-061 for the treatment of hemophilia B in adults who currently use FIX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or repeated, serious spontaneous bleeding episodes.

## 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

**Table 1. Demographics Information**

Parameter	Efficacy Population n=54
Sex, n (%)	54 (100)
Age	
Mean (SD)	41.5 (15.8)
Median (min, max)	37 (19, 75)
Race, n (%)	
White	40 (74.1)
Black	1 (1.9)
Asian	2 (3.7)
Other	6 (11.1)
Ethnicity, n (%)	
Non-Hispanic or Latino	45 (83.3)

Source: Adapted from Original BLA 125772/0 Clinical Study Report, page 79

### Reviewer Comments:

*This demographic table is based on Study CT-AMT-061-02 and the 54 male subjects who were treated (1 subject received a partial dose) and completed follow up.*

*The limited sample size in Blacks, Asians, and Hispanics makes it challenging to reach conclusions about the efficacy of AMT-061 in these racial groups. Since the predilection for clinical bleeding is primarily dependent on the degree of FIX deficiency, race-related differences in efficacy of AMT-061 are usually expected to be minimal. Therefore, it is reasonable to extrapolate the efficacy data from Whites to other ethnic groups. However, in this trial there were 14 subjects that were Non-White. These subjects had higher ABRs (during Months 7-18 compared with the lead-in period) compared to subjects who were White [White: 0.9 (0.5, 1.9) vs Non-white 4.5 (2.0, 10)]. The Non-White subjects include subjects who failed the therapy and continued on routine prophylaxis.*

*There were eight subjects above the age of 60. These subjects had higher ABRs during Months 7 to 18 [3.3 (0.8, 13.4)]. These include subjects who failed the therapy and continued on routine prophylaxis.*

## 1.2 Patient Experience Data

### Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Patient-reported outcome	6.1.11.2
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	



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

## 2. CLINICAL AND REGULATORY BACKGROUND

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

Hemophilia B is a recessive X-linked congenital bleeding disorder, caused by mutations in the FIX gene. It is the second most common coagulation factor deficiency. Most FIX deficiency occurs in males as expected for an X-linked disease, but females comprise 3% of affected persons. More than 50% of all patients with hemophilia B have no known family history of the disease, and these are called sporadic cases. Deficiency or absence of FIX results in impaired hemostasis, prolonged bleeding, and rebleeding.

Hemophilia B is often characterized as severe, moderate, or mild based on factor level correlating with the disease pattern. Subjects with FIX activity level <1% of normal are called severe and have at least monthly bleeds, most frequently in joints without preceding trauma. A FIX activity level of 1%-5% is designated as moderate. These subjects have bleeds associated with mild trauma, and their bleeding frequency is less often than severe subjects. Subjects with mild deficiency of FIX activity levels of ≥5%-40% have prolonged bleeding with worse than mild trauma, surgery, and, since females are almost exclusively in this group, menstruation.

A goal of modern hemophilia management is to prevent spontaneous bleeds by supplying replacement factor that will maintain FIX activity levels to a value of >1%-5%, i.e., in the range of subjects with the moderate form of the disease. This approach is known as routine prophylaxis. This treatment option has limitations including regular IV injections and risk of infection. Periodic infusion resulting in variable FIX activity may result in breakthrough bleeding episodes.

The most serious complication of replacement therapy is inhibitor development. FIX inhibitors are allogenic antibodies to FIX that reduce or eliminate the activity of FIX. The

magnitude of the inhibitor response can be quantified through the performance of a functional inhibitor assay from which a Bethesda unit (BU) inhibitor titer can be reported. The definitions are  $\geq 0.6$ -5 BU for a 'low responding inhibitor' and  $\geq 5$  BU for a 'high responding inhibitor'.

Approximately 1%-3% of patients with hemophilia B develop inhibitors following exposure to FIX replacement therapy. Among patients with severe hemophilia B, the percentage has, however, been reported to be as high as 9%.

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

Treatments for hemophilia B require replacement with exogenous FIX. FIX formulations include human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. FIX products, either plasma derived or recombinant, are commercially available. Recombinant FIX preparations are the mainstay of therapy. Bypassing agents are available in the instance of inhibitor formation, but these are not first-line therapy.

The currently approved products for FIX replacement are shown in Table 2.

**Table 2. Approved FIX Products**

Product	Category	Half-life (hr)	Year Approved
Alphanine SD	Plasma derived	21	1990
Mononine	Plasma derived	23-31	1992
Benefix	Recombinant	18	1997
Rixubis	Recombinant	26.7	2013
Alprolix	Recombinant fusion protein	86.5	2014
Ixinity	Recombinant	17-31	2015
Idelvion	Recombinant, Albumin Fusion Protein	104	2016
Rebinyn	Recombinant	93	2017

Abbreviations: FIX, Factor IX.

All approved products are approved for the indications, control, and prevention of bleeding episodes and perioperative management. Rixubis, Alprolix, and Idelvion are approved for the additional indication of routine prophylaxis. The goal of maintaining FIX activity levels of at least 1% (routine prophylaxis) requires regularly scheduled FIX infusions. For routine prophylaxis, the labeled dosing frequency is twice a week for Rixubis, once every 7 to 10 days for Alprolix, and once every 7 days for Idelvion.

There are no approved gene therapy products for Hemophilia B.

## **2.3 Safety and Efficacy of Pharmacologically Related Products**

Currently, no other gene therapy-based products are approved for Hemophilia B subjects.

## 2.4 Previous Human Experience with the Product (Including Foreign Experience)

There is no previous human experience with an approved FIX gene therapy product. 2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

The FDA had the following meetings with UNIQURE (initial Sponsor) and CSL Behring (CSLB):

- December 22, 2011: Orphan Drug Designation (ODD) for AMT-060  
FDA granted a November 1, 2011, ODD request for adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIXco; AMT-060) for treatment of hemophilia B.
- October 10, 2013: Pre-Investigational New Drug (IND) meeting request  
UNIQURE requested a pre-IND meeting to discuss plans for initiating the clinical development program for AAV5-hFIX or AAV5-hFIXco; A Recombinant Adeno-Associated Viral Vector Containing the Codon-Optimized Human Coagulation Factor IX cDNA for treatment of patients with severe hemophilia B. FDA granted a face-to-face Type B Meeting for December 12, 2013.
- December 11, 2013: FDA pre-IND preliminary responses  
The FDA advised the Sponsor to exclude subjects with other coagulation disorders or thrombocytopenia and subjects with documented prior titers of FIX >0.6 BU/mL. FDA recommended that the Sponsor use clinical information and results of human studies of related products to help them determine the product's dose for the proposed study. FDA stated the proposed cohort of 2 subjects in each cohort is too small and that although the Sponsor's proposed staggered treatment approach is okay, they need to provide a rationale for proposed intra- and inter-cohort staggering periods. FDA recommended that the long-term follow-up (LTFU) should be included as an integral part of the trial and not designed as separate protocol. The Agency asked the Sponsor to correlate FIX activity with clinically meaningful parameters to help design later phase studies to demonstrate efficacy and to detect clinically important delayed AEs, extending post-treatment follow-up period to at least one year.
- January 6, 2014: FDA pre-IND meeting minutes  
FDA recommended an increase in the cohort size. FDA recommended that the Sponsor specify the bioactivity information (e.g., FIX activity) that will be considered when deciding on dose escalation and selection of dose for Part B of the study. In addition, FDA recommended that the Sponsor specify the target level of FIX activity that is intended to be reached.
- June 16, 2014: FDA confirmed a teleconference for a Type C meeting to discuss the manufacturing plans for the production of gene therapies using AAVbased vectors at large and commercial scale.

- July 10, 2014, and August 1, 2014: Type C Chemistry, Manufacturing, and Controls (CMC) meeting Preliminary Responses and meeting minutes provided to the Sponsor.
- January 25, 2017: FDA granted breakthrough therapy designation (BTD) for AMT-060.
- January 27, 2017: FDA provided preliminary responses to End-of-Phase (EOP) 2 Sponsor questions.

FDA recommended to include a concurrent control arm. UNIQUE could consider a self-controlled study where subjects are on exogenous FIX for routine prophylaxis and subsequently receive AMT-060 since such a study design may decrease the risk of bias.

FDA requested to include additional analyses of bleeding rates that occur in the interval that follows discontinuation of routine prophylaxis with FIX until the end of study. In the event of excess breakthrough bleeding episodes in this interval, the Sponsor may need to reconsider the plan for early withdrawal of routine prophylaxis.

Overall development program: FDA found the overall development program to be inadequate. The development plan was not designed to provide robust data to determine the optimal timing to withdraw routine prophylaxis. The Sponsor had not yet identified a dose that appeared to be capable of achieving FIX levels that would obviate the need for on-demand treatment for control of bleeding. FDA recommended that Sponsor conduct additional dose-finding studies and evaluate for optimal timing to withdraw routine prophylaxis.

FDA recommended that the Phase 3 trial enroll subjects currently receiving or willing to be put on FIX prophylactic treatment. Also, FDA recommended the primary analysis be a self-controlled/paired NI comparison of bleeding rates between routine prophylaxis and AMT-060. The Agency said that the Sponsor can enroll on-demand subjects in the proposed study but consider the study outcome to be supportive data and to observe subjects for at least 52 weeks following administration of the investigational product in planning the trial. The Agency stated that FIX levels should be a key secondary endpoint.

Additionally, regarding the development and regulation of the anti-AAV NAb assay as a companion diagnostic, FDA encouraged UNIQUE to request a Pre-Submission Meeting with the Office of In Vitro Diagnostics and Radiological Health (OIR)/CDRH for advice. FDA encouraged the Sponsor to submit the same information (as that submitted with the Pre-Submission package to CDRH) as an amendment to the IND to document assay development.

- March 1, 2017: FDA provided meeting minutes for the EOP2 meeting

The Sponsor agreed to extend the observation period of the proposed Phase 3 study from 26 to 52 weeks. The Sponsor agreed to use bleeding rates as the primary endpoint. Traumatic and total bleeding rates would be secondary endpoints. FDA

recommended that the Sponsor collect detailed information on bleeding episodes with further analysis of bleeding types as secondary endpoints. The Sponsor proposed use of historical data as control and a 26-week lead-in period as self-control study. Due to excess bleeding risks resulting in unfavorable bleeding outcomes, the FDA recommended continuing exogenous prophylaxis for 1-2 weeks after administration as well as incorporate plans to counsel and caution subjects prior to treatment to limit high-risk behavior. The Sponsor clarified additional dose escalation would not be feasible since nonclinical studies suggest that an increase in dose does not lead to an increase in transduced cells or FIX cells. FDA expressed higher FIX levels were likely to demonstrate improvement in total bleeding rates. The Sponsor will consider NI margin and discuss in future other aspects of design.

- October 5, 2017: FDA BTB preliminary meeting responses

The Agency agreed that the design modification to use AMT-061 can be developed under the BTB granted for AMT-060. FDA tentatively agreed that data from the Phase 3 study along with supportive data from the Phase 1/2 study may support a Biologics License Application (BLA) submission for the proposed clinical indication.

FDA found the overall design of the proposed Phase 3 study acceptable. FDA requested the Sponsor to include details of the monitoring plan during the LTFU. FDA proposed that the Sponsor collect samples for AAV5 antibodies routinely during the study at different timepoints. FDA asked the Sponsor to consider communicating with OIR at CDRH regarding the planned companion diagnostic development. The interaction may provide useful information as to methods of collection, volume of samples necessary, and storage instructions prior to initiating a Phase 3 study.

FDA found the primary and secondary endpoints acceptable. FDA recommended that the Sponsor stagger enrollment to allow for subject safety monitoring and that the Sponsor submit the data from the dose confirmation study for FDA review and comment prior to start of the "Treatment Phase" of the Phase 3 study. FDA agreed that the dose confirmation study and the lead-in phase of the Phase 3 study can be conducted simultaneously.

- June 21, 2019: FDA's Type B BTB preliminary meeting response

FDA did not agree to the Sponsor's proposed target FIX activity level and threshold response rate based on a cited reference Soucie et al, 2018. FDA found the data from the reference not relevant to select a threshold in the intended population for the study. The Agency requested to obtain additional data from the ongoing study. The Agency suggested to use a validated central laboratory aPTT assay to select the target FIX activity level. However, the final decision can be made after the review of Phase 2b study results and data.

FDA indicated that the decision to conduct a field study with samples from Phase 3 subjects can be made after the review of the Phase 2b study results and the data on the effect of commonly used aPTT reagent on FIX activity measurements in patients post-dosing with AMT-061. The Agency suggested to ensure that subjects adhere to adequate prophylaxis regimen in the lead-in phase to allow a valid comparison of the ABR post AMT-601 administration to ABR under routine prophylaxis.

- August 2, 2019: FDA Type B BTD preliminary meeting responses concerning the inclusion of pediatric subjects in future clinical studies

The Agency did not agree to initiate a clinical trial using AMT-061 in adolescents based on the planned and ongoing preclinical and clinical studies (in adults). To justify enrolling adolescent subjects, the Sponsor should:

- Submit clinical data from studies with AMT-061 in adults to demonstrate sustained and robust steady state FIX levels and hemostatic outcomes.
- Submit long-term safety data from studies with AMT-060 in adults for FDA's review and evaluation of the safety profile of the product.
- Select an appropriate pediatric population that represents a population with an unmet medical need in the context of available therapies.
- Characterize the risks of the investigational product based on available preclinical and clinical data.
- The agency did not agree with the Sponsor's proposed development plan, choice of dose, and overall study design until additional efficacy and long-term safety data from the ongoing adult studies and planned clinical investigations were obtained.
- FDA requested additional data prior to initiation of the treatment of pediatric and/or adolescent subject

- November 19, 2019: FDA Type B CMC written response given to Sponsor

- July 24, 2020: FDA Type B written response

The agency did not agree with the Sponsor's proposed target FIX activity level of 20% and threshold response rate of 60% to support the use of FIX activity levels as a surrogate endpoint for accelerated approval. The Agency recommended to investigate the impact of assay variability on evaluation of FIX activity after administration of therapeutic FIX concentrates. If AMT-061 received accelerated approval based on the surrogate endpoint of FIX activity levels, provided an appropriate threshold can be established, the Agency recommended ABR as the primary endpoint in a post-approval verification study.

To achieve sustained stable transgene expression, the Agency suggested to evaluate factors that may potentially impact transgene expression of the investigational product. The agency recommended to use ABR as the primary efficacy endpoint with adequate follow-up duration to inform benefit-risk evaluation. Alternatively, the Sponsor was requested to justify the proposal for a surrogate endpoint as data for ABRs are collected contemporaneously. The Agency indicated that FIX activity level has its value independent of ABR and can be used as a key secondary or coprimary endpoint.

- June 2, 2021: FDA Type B pre-BLA preliminary meeting response

As the Phase 2b study consisted of only three subjects, the Agency stated they do not expect that pooling data from this study with that of the subjects from the Phase 3 study would provide a significant contribution. The FDA did not agree to the

proposed approach to further analyze the impact of pre-existing high titer NABs against AAV5 on FIX activity through ongoing registries.

The FDA did not agree that the AMT-060/061 development and AAV5 NAb prevalence data support the safe and effective use of AMT-061 in patients with hemophilia B without the requirement of a companion diagnostic. The FDA recommended that UNIQURE to continue discussing their AAV5 NAb titer assay with CDRH and submit a premarket approval or humanitarian device exemption to CDRH in parallel with the BLA submission to the Center for Biologics Evaluation and Research (CBER).

FDA did not agree with the proposed cut-off date of December 17, 2021, for a 120-day safety update report because no agreement was in place regarding a cut-off date for the primary BLA submission which will ensure all subjects have at least 52 weeks of follow-up from the time of reaching steady state endogenous FIX activity levels post-AMT-061 infusion. FDA requested that UNIQURE submit a summary of the proposed content of the 120-day safety update report, including but not limited to, safety data to be included and presentation format(s).

The FDA did not agree that the >60-month (5 year) FIX expression data provide support for the durability of FIX expression because the >60-month FIX expression data come from subjects treated with AMT-060, which is a different product than AMT-061.

FDA agreed that the product is eligible for consideration of a rolling review by virtue of its BTD. However, FDA requested additional information to determine whether we agree to proceed with a rolling review. The FDA requested to submit an amendment to the IND describing the proposed submission schedule, including dates each module would be submitted. The FDA indicated that the decision to grant Priority Review Designation will be made based on the review of the BLA application at the time of filing.

Additional Clinical Comments: The FDA did not prospectively agree to exclusion of subjects with a baseline AAV5 NAb titer of 3,123, or the subjects who received a partial dose of AMT-061, from several analyses. The FDA requested to include following in the BLA submission: 1) narratives for all SAEs, study discontinuations due to AEs, AEs of special interest, surgeries, exposure to systemic corticosteroids, FIX inhibitors, bleeding events, and exposure to exogenous FIX; 2) one dataset that includes AST and ALT levels, corticosteroid use, corticosteroid indication, and corresponding FIX levels including a summary of analysis to evaluate the impact of corticosteroid on FIX activity levels and ABR in the clinical study report (CSR); and 3) one dataset that includes bleeding events, ABR, and exogenous FIX use.

- January 20, 2022: Acceptance of IND ownership

CSLB notified the FDA that it accepts the role as the new Sponsor of the IND and that UNIQURE has transferred all sponsorship rights and responsibilities for IND 016248 to CSLB effective January 20, 2022.

- February 10, 2022: Sponsor's response to the FDA's pre-BLA information request (IR)

The Sponsor agreed with the FDA and is planning to include the efficacy data from the Phase 1b study, separate from the Phase 3 efficacy data, in the relevant portions of the BLA.

CSL Behring accepted FDA's pre-BLA meeting recommendation and used as primary analysis the ABR for 52 weeks following FIX stable expression in all enrolled subjects (Months 7-18). The data cut-off for the primary analysis of the Phase 3 study CT-AMT-061-02 was September 13, 2021. The complete CSR and data package with the FDA recommended endpoint will be submitted in the original BLA planned for March 21, 2022. CSLB noted that they are not requesting a rolling BLA review as the original BLA will contain the complete set of data for the primary analysis.

The projected data cut-off for the month 24 analysis of the Phase 3 study CT-AMT-061-02 is February 28, 2022 for all subjects that remain in the trial.

The 120-day safety update report will provide updated safety and additional efficacy data. CSLB confirmed that they are not planning to request a rolling BLA review.

- February 8, 2022: FDA pre-BLA meeting IR in response to the October 29, 2022 CSLB response to the pre-BLA Type B meeting

You propose omitting an integrated summary of effectiveness from your BLA, which is acceptable. However, to allow the most comprehensive assessment of the clinical experience with AMT-061, please include the efficacy data from your Phase 2b study separate from the efficacy data from your Phase 3 study, in the relevant portions of the BLA.

Your proposed plan for the 120-day safety update report may be acceptable; however, please clarify the data cut-off dates for your primary analysis and your month 24 analysis of the Phase 3 study CT-AMT-061-02.

In your pre-BLA meeting, you asked about eligibility for rolling BLA review (Sponsor Question 8). In these follow-up questions, you note your plan to submit your BLA on March 21, 2022; however, it is not clear whether you plan to submit a complete BLA or still wish to pursue a rolling submission. Please clarify this point. Note that the rolling review plan, including the schedule for submission of each portion of the BLA, should be agreed upon prior to submission of any portion of the BLA. If you are still interested in pursuing a rolling review, please refer to the guidance document "Expedited Programs for Serious Conditions – Drugs and Biologics" at <https://www.fda.gov/media/86377/download>. Appendix 2 details the process for rolling review.

## **2.6 Other Relevant Background Information**

Not applicable.



### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. The submission consisted of the five modules in the CTD structure. The modules were adequately organized and integrated to allow the conduct of a complete clinical review.

#### 3.2 Compliance With Good Clinical Practices And Submission Integrity

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

Bioresearch Monitoring (BIMO) inspections were issued for one foreign and four domestic clinical study sites that participated in the conduct of Study CT-AMT-061-02. The inspections did not reveal significant issues impacting the integrity of the data submitted in support of this application.

#### 3.3 Financial Disclosures

<b>Covered clinical study</b> (name and/or number):
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>34</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="margin-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p style="margin-left: 40px;">Significant payments of other sorts: _____</p> <p style="margin-left: 40px;">Proprietary interest in the product tested held by investigator: _____</p> <p style="margin-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: _____</p> <p style="margin-left: 40px;">Is an attachment provided with details of the disclosable financial interests/arrangements? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant)</p> <p style="margin-left: 40px;">Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)</p>

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0  
Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

There were no investigators with any significant financial disclosures to report.

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

##### **4.1 Chemistry, Manufacturing, and Controls**

Please refer to the CMC review memo for details. The CMC review team concluded that the AMT-061 manufacturing process and controls can yield a product with consistent quality attributes.

Throughout clinical trials, the manufacturing process was optimized (b) (4). The current manufacturing process produces the drug product with critical quality attributes that are comparable to those of clinical lots used in Phase 3 studies. The lot release protocol template for AMT-061 was submitted to CBER for review and found to be acceptable after revisions.

##### **4.2 Assay Validation**

Assay validation for the neutralizing antibodies to AAV was performed by CDRH. CDRH determined that the data provided to support the assay utilized in the clinical trials and for the modified assay submitted as a companion diagnostic in a Premarket Application (PMA) were not sufficient to support assay validation. The reported results from the assay utilized in the clinical trial should be interpreted with caution as they are not considered validated or reliable.

##### **4.3 Nonclinical Pharmacology/Toxicology**

Please refer to the Pharmacology/Toxicology Memo for details. IV administration of AMT-061 in male nonhuman primates at dose levels ranging from  $5 \times 10^{12}$  to  $9 \times 10^{13}$  gc/kg was well tolerated and resulted in dose-dependent transgene expression in the liver and increased mean plasma FIX enzymatic and clotting activity compared to concurrent controls.

##### **4.4 Clinical Pharmacology**

Clinical pharmacology review confirmed expression of FIX Activity and protein expression following a single infusion of AMT-061 in majority of the subjects. No concerns were noted in alpha-fetoprotein levels or abdominal ultrasound abnormalities after AMT-061 treatment. Levels of inflammatory markers IL-1 $\beta$ , IL-6, and MCP-1 were generally unaffected by AMT-061 treatment. Initial elevations were noted with IL-2 and IFN $\gamma$  following AMT-061 treatment as could be expected following exposure to a viral vector. However, values returned to predose levels for IL-2 and IFN $\gamma$  by Month 4.

The Clinical Pharmacology review concludes: *From a clinical pharmacology perspective the viral kinetics, FIX protein expression and FIX activity support the proposed single*

dose of  $2 \times 10^{13}$  gc/kg of HEMGENIX. Please refer to the Clinical Pharmacology Memo for further details.

#### **4.4.1 Mechanism of Action**

AMT-061 is an AAV5-based gene therapy designed to deliver a copy of gene encoding Padua variant of human coagulation FIX (hFIX-Padua). Single IV infusion of AMT-061 results in cell transduction and an increase in circulating FIX activity in patients with hemophilia B.

#### **4.4.2 Human Pharmacodynamics (PD)**

FIX activity was increased following administration of AMT-061 and was maintained through Month 12, with a mean FIX activity of  $41 \pm 22\%$  and at Month 18, the mean FIX activity was  $37 \pm 21\%$ .

#### **4.4.3 Human Pharmacokinetics (PK)**

FIX expression increased following administration of AMT-061. Vector biodistribution and viral shedding were evaluated with this product. The PI appropriately discusses vector shedding.

#### **4.5 Statistical**

Please refer to the Statical Review memo for further details. The primary objective of the Phase 3 study was to demonstrate NI of AMT-061 following treatment as compared to a 6-month lead-in period. The primary efficacy analysis was an NI comparison between the ABR during Months 7 to 18 post AMT-061 and that during the 6-month lead-in period, with an NI margin of 1.8 on the ABR rate ratio. 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 efficacy evaluation period (EEP). This approach excluded the period within the 5 half-life 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 routine prophylaxis(RP) during EEP, and the approach described above did not incorporate their data in the analysis model appropriately. Imputation of ABR for these subjects was provided by the statistical reviewer. The statistical reviewer confirmed the primary statistical analysis. See the statistical review memo for details.

#### **4.6 Pharmacovigilance**

Please refer to the Office of Biostatistics and Pharmacovigilance (OBPV) Review Memo for further details.

The sponsor will conduct routine and enhanced pharmacovigilance activities as outlined in the Pharmacovigilance Plan, version 2, and two safety-related PMRs under section 505(o) of the FDCA, to assess the unexpected serious risk of bleeding due to failure of expected pharmacological action of HEMGENIX in the presence of pre-existing anti-AAV5 neutralizing antibodies (PMRs listed below). The sponsor is also planning a voluntary, 15-year observational study and a long-term clinical extension study. The

review team determined that a Risk Evaluation and Mitigation Strategy (REMS) is not required for this product.

Due to approval without a validated and reliable assay, a PMR will be issued at the time of approval to conduct a clinical study to observe safety events in those subjects with pre-existing positive NAb titers.

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

### **5.1 Review Strategy**

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

*Reviewer Comment: Dr. Kaushal, reviewed the clinical efficacy portion of this original application. There was no subject matter expert or Board Certified Hematology supervisor that provided input or advice on how to conduct or focus on the aspects of the review. Division supervision was provided on information/data presented to them for discussion.*

*Dr. Johnson, and Dr. Crisafi reviewed the clinical safety portion of this original application. Supervision was provided by Division managers.*

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

The following materials from the submission were reviewed:

<b>Module</b>	<b>Information</b>
1.6	Meetings
1.14	Labeling
1.18	Proprietary names
5.2	List of Clinical Studies
5.3.1	Reports of biopharmaceutic studies
5.3.5	Reports of efficacy and safety studies
5.3.5.2	Study Reports of Uncontrolled Clinical Studies
5.3.5.3	Reports of Analyses of Data from More than One Study
5.4	Literature References

### 5.3 Table of Studies/Clinical Trials

**Table 3. Clinical Studies Reviewed in this Application**

**Table 1: Listing of Clinical Studies**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status  Type of Report
Phase 1/2	CT-AMT-060-01	<a href="#">Module 5.3.5.2 CT-AMT-060-01 5-year CSR</a>	To investigate an AAV vector containing a codon-optimized human FIX gene (AAV5-hFIXco; AMT-060) administered to adult subjects with severe or moderately severe hemophilia B	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	Adult subjects with severe or moderately severe hemophilia B	Single dose with follow-up for 5 years postdose: 1 year Post-treatment Follow-up Period and 4 year Long-term Follow-up Period	Completed  Final CSR (5 years): 06 January 2022
Phase 2b	CT-AMT-061-01	<a href="#">Module 5.3.5.2 CT-AMT-061-01 2.5-year CSR</a>	To confirm the FIX activity level of etranacogene dezaparvovec (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B	Open-label, uncontrolled, single-dose, single-arm	Etranacogene dezaparvovec  3 subjects received $2 \times 10^{13}$ gc/kg  Single IV dose	3	Adult subjects with severe or moderately severe hemophilia B	Single dose with follow-up for 5 years postdose: 1 year Post-treatment Follow-up Period and 4 year Long-term Follow-up Period	Ongoing  Interim CSR (2.5 years): 07 December 2021 Final CSR expected: December 2023
Phase 3	CT-AMT-061-02	<a href="#">Module 5.3.5.2 CT-AMT-061-02 18-month CSR</a>	To demonstrate noninferiority of etranacogene dezaparvovec (AAV5-hFIXco-Padua, AMT-061) during the 52 weeks of stable FIX expression (Months 6 to 18) after administration to adult subjects with severe or moderately severe hemophilia B, compared with standard of care continuous routine FIX prophylaxis during the Lead-in Phase, as measured by ABR	Open-label, uncontrolled, single-dose	Etranacogene dezaparvovec  53 subjects received $2 \times 10^{13}$ gc/kg 1 subject received approximately 10% of the $2 \times 10^{13}$ gc/kg dose  Single IV dose	54	Adult subjects with severe or moderately severe hemophilia B	$\geq 6$ -month Lead-in Period with standard of care FIX prophylaxis Single dose of AMT-061 with follow-up for 5 years postdose: 1 year Post-treatment Follow-up Period and 4 year Long-term Follow-up Period	Ongoing  Interim CSR (18 months): 21 February 2022 Final CSR expected: July 2025

AAV = adeno-associated virus; AAV5 = adeno-associated virus serotype 5; AAV5-hFIXco = Recombinant adeno-associated viral vector containing a codon-optimized human coagulation factor IX cDNA; AAV5-hFIXco-Padua = recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA (etranacogene dezaparvovec); ABR = annualized bleeding rate; AMT-060 = AAV5-hFIXco (predecessor of etranacogene dezaparvovec); cDNA = complementary DNA; CSR = Clinical Study Report; FIX = factor IX; IV = intravenous; gc/kg = genome copies per kilogram; hFIX = human factor IX.

#### Efficacy Considerations for this BLA application review:

Efficacy review focused on the study results from the Phase 3 study, Study CT-CMT-061-02, in 54 adult subjects with severe or moderately severe hemophilia B.

Safety data considerations for this BLA application review:

The safety database was comprised of 3 subjects from Study CT-CMT-061-01 (n = 3) and 54 subjects from Study CT-CMT-061-02.

#### **5.4 Consultations**

No clinical consultations were requested or required during the review of this BLA.

##### **5.4.1 Advisory Committee Meeting (if applicable)**

An advisory committee was not convened for this product. The application did not raise significant safety or efficacy concerns that could not be addressed through information in label, consultative expertise was not required, and no public health concerns arose upon the review of this file.

##### **5.4.2 External Consults/Collaborations**

There were no external consults or collaborations sought for the review of this BLA.

#### **5.5 Literature Reviewed (if applicable)**

Nathwani AC, Reiss UM, Tuddenham EG, Rosales C, Chowdary P, McIntosh J, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med*. 2014; 371(21):1994-2004. e-pub ahead of print 20 Nov 2014. doi: 10.1056/NEJMoa1407309

Chandler RJ, LaFave MC, Varshney GK, Trivedi NS, Carrillo-Carrasco N, Senac JS, et al. Vector design influences hepatic genotoxicity after adeno-associated virus gene therapy. *J Clin Invest*. 2015;125(2): 870-880. e-pub ahead of print 22 Jan 2015. doi: 10.1172/jci79213

Nault JC, Datta S, Imbeaud S, Franconi A, Mallet M, Couchy G, et al. Recurrent AAV2-related insertional mutagenesis in human hepatocellular carcinomas. *Nat Genet* 2015;47(10):1187-1193. e-pub ahead of print 25 Aug 2015. doi: 10.1038/ng.3389

Mattar CNZ, Gil-Farina I, Rosales C, Johana N, Tan YYW, McIntosh J, et al. In Utero Transfer of Adeno-Associated Viral Vectors Produces Long-Term Factor IX Levels in a Cynomolgus Macaque Model. *Mol Ther*. 2017;25(8):1843-1853. e-pub ahead of print 4 May 2017. doi: 10.1016/j.ymthe.2017.04.003

Gjærde LI, Shepherd L, Jablonowska E, Lazzarin A, Rougemont M, Darling K, et al. Trends in Incidences and Risk Factors for Hepatocellular Carcinoma and Other Liver Events in HIV and Hepatitis C Virus-coinfected Individuals From 2001 to 2014: A Multicohort Study. *Clin Infect Dis*. 2016;63(6):821-829. e-pub ahead of print 17 Jun 2016. doi: 10.1093/cid/ciw38

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1

CT-AMT-061-02 is an ongoing open-label, single-dose, multicenter trial.

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

The primary objective was to demonstrate the NI of AMT-061 ( $2 \times 10^{13}$  gc/kg) during the 52 weeks following establishment of stable FIX expression (Months 7-18) post-treatment (AMT-061) compared to standard of care continuous routine FIX prophylaxis during the lead-in phase, as measured by the ABR.

Secondary efficacy objectives were focused on investigating the effect of  $2 \times 10^{13}$  gc/kg AMT-061 on the following:

- Endogenous FIX activity 6 months after a single AMT-061 treatment
- Endogenous FIX activity 12 months after a single AMT-061 treatment
- Endogenous FIX activity 18 months after a single AMT-061 treatment
- Annualized consumption of FIX replacement therapy
- Annualized infusion rate of FIX replacement therapy
- Discontinuation of previous continuous routine prophylaxis
- Trough FIX activity
- Prevention of bleedings (comparison for superiority)
- Prevention of spontaneous bleeding
- Prevention of joint bleeding
- Estimated ABR—during the 52 weeks following stable FIX expression (6-18 months)—as a function of pre-investigational medicinal product (IMP) anti-AAV5 antibody titers using the (b) (4) NAb assay (as a “correlation” analysis)
- Correlation of pre-IMP anti-AAV5 antibody titers using the (b) (4) NAb assay on FIX activity levels after AMT-061 dosing
- Occurrence and resolution of target joints
- Proportion of subjects with zero bleeding episodes during the 52 weeks following stable FIX expression (7-18 months) after AMT-061 dosing
- International Physical Activity Questionnaire (iPAQ)
- EuroQol-5 dimensions-5 levels (EQ-5D-5L) Visual Analog Scale (VAS)

#### 6.1.2 Design Overview

T-AMT-061-02 is an ongoing open-label, single-dose, multicenter, multinational trial, with a screening phase/period, a lead-in phase/period, a treatment plus a post-treatment follow-up phase/period, and a LTFU phase/period.

During the lead-in phase, which lasted for a minimum of 26 weeks (i.e.,  $\geq 6$  months), subjects recorded their use of FIX replacement therapy and bleeding episodes in their dedicated e-diary.

After the lead-in phase, subjects received a single-dose of AMT-061 at the dosing visit (Visit D) and were followed for 1 year (i.e., post-treatment follow-up phase; 52 weeks) to evaluate efficacy and safety. One of the secondary endpoints, endogenous FIX activity at 26 weeks after AMT-061 dosing, was assessed once the last subject had achieved 26 weeks after AMT-061 treatment. Following the post-treatment follow-up phase, subjects

continued into the LTFU phase for an additional 4 years, with visits planned every half year (6 months) for evaluation of safety and efficacy parameters. During the LTFU phase, subjects are instructed to document FIX usage and bleeding episode information in study-specific paper diaries. At the end of that 4-year LTFU phase, all safety and efficacy data will be reported in a CSR addendum covering the LTFU phase.

### 6.1.3 Population

Key Inclusion Criteria included:

- 1) Male subjects over 18 years of age with congenital hemophilia B with severe or moderately severe FIX deficiency
- 2) >150 previous exposure days of treatment with FIX
- 3) Stable prophylaxis for at least 2 months prior to screening

Key Exclusion Criteria included:

- 1) History of FIX inhibitors
- 2) Positive FIX inhibitor test at screening and Visit L-Final
- 3) Positive human immunodeficiency virus (HIV) serological test at screening and Visit L-Final, not controlled with antiviral therapy as shown by CD4+ counts  $\leq 200/\mu\text{L}$  (based on central laboratory results)
- 4) Hepatitis B (HBV) or hepatitis C (HCV) infection
- 5) Known significant medical condition that may have significantly impacted the intended transduction of the vector and/or expression and activity of the protein
- 6) Previous gene therapy treatment

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

Each subject was to receive a single IV infusion of the study drug. The volume of infusion depended on the subject's weight. The recommended dose of HEMGENIX is  $2 \times 10^{13}$  genome copies (gc) per kg of body weight.

### 6.1.5 Directions for Use

The study drug was given as a single dose by IV infusion.

### 6.1.6 Sites and Centers

The study was conducted at 33 sites, including 17 sites in the United States, 13 sites in the European Union, and 3 sites in the United Kingdom.

#### Reviewer comment:

*Site-related differences are expected to be minimal; therefore, it is reasonable to extrapolate data from sites outside the United States.*

### 6.1.7 Surveillance/Monitoring

A data monitoring committee (DMC) was involved in the monitoring of the overall AMT-061 program including this clinical trial. The purpose of the DMC was to monitor the safety of the subjects throughout the CT-AMT-061-01 trial and the current trial to evaluate response to the treatment in terms of FIX activity levels and to assess whether there is an impact of pre-existing anti-AAV5 NAb titers on clinical outcome following AMT-061.



### 6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was Annualized Bleeding Rates (ABR). Efficacy measurements included recording of bleeding episodes, FIX activity levels, and FIX protein concentration. FIX activity was measured by the one-stage assay.

Reviewer comment:

*The primary endpoint of ABR is disease specific, appropriate, and clinically relevant. This study was designed to compare each subject's ABR post treatment with his own baseline ABR while undergoing adequate routine prophylaxis. The endpoint of ABR requires demonstration of durability in the consideration of effectiveness. The intra-subject comparison as a control is appropriate.*

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the Statistical Review memo for further details.

Hypothesis testing for the primary endpoint was carried out as a one-sided NI test with an NI margin of 1.8. Formal statistical testing of the efficacy endpoints (where performed), using a hierarchical approach, tested for superiority at a one-sided alpha level of 0.025.

Except where specified, all continuous variables were summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, maximum, quartiles [Q1 and Q3]) and all categorical variables were summarized with frequency counts and percentages by treatment group. Data were presented by study phase as appropriate.

The ABR was determined for the lead-in period and the post-treatment period (for the 52 weeks following stable FIX expression [months 7-18 post-treatment]). The number of reported bleeding episodes was analyzed using repeated measures generalized estimating equations negative binomial regression model, which accounted for the paired design and the differential collection phases of the trial. Treatment (i.e., phase) was included as a categorical variable in the model. The estimated rate ratio, one-sided 97.5% Wald CI, and corresponding p value were determined. NI of AMT-061 was declared if the upper limit of the 97.5% Wald CI was less than the NI margin of 1.8. 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-life period 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 the EEP, and the approach described above did not incorporate their data in the analysis model appropriately. Imputation of ABR taking into account the data from these three subjects was provided by the statistical reviewer.

Reviewer Comments:

*The non inferiority margin was 1.8 on the ABR rate ratio. The Applicant picked this current routine prophylaxis regimens would results in mean ABRs of 2-3 bleeds/year. Applying an NI margin to these results with statistical power including a feasible sample size resulted in 1.8 on the ABR rate ratio. The statistical reviewer used a conservative approach for the imputation of a hypothetical ABR for subjects on routine prophylaxis*

during the EEP, Imputing an ABR of 20 was used for the EEP during this trial for all patients. This clinical reviewer agrees with this approach, although imputations of greater than 20 could have been used since those subjects had increased bleeding episodes in the lead in period. If ABRs imputed with a value of 53, the upper limit is greater than 1.8, meaning that AMT-061 is no longer “noninferior” to the lead-in treatment. On the other hand, the “superiority” claim no longer holds when ABR is at least 26, which might still be a reasonable imputation. Please refer to the Statistical Review memo for additional details on varying imputed ABRs and the NI margin of 1.8 on the ABR rate ratio.

#### **6.1.10 Study Population and Disposition**

Subjects were adult males with severe or moderately severe hemophilia B.

##### **6.1.10.1 Populations Enrolled/Analyzed**

All subjects who received the study drug infusion were analyzed (n=54).  
One subject did not receive the full dose (received only 10% of the dose).

###### **6.1.10.1.1 Demographics**

All subjects were male. The majority of subjects were White (74.6%). Please see Table 1 in Section 1.1.

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

There were 44 subjects (82%) with severe hemophilia B and 10 subjects with moderately severe hemophilia B. There were 215 bleeding events in the year prior to screening in 44 subjects. Out of the 215 bleeding events that occurred, 132 were joint bleeds. There were 31 subjects with prior (28 subjects) or ongoing HCV infection. Three subjects were HIV positive. At the time of screening, ten subjects had target joints identified.

###### **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. 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%).

##### **Reviewer Comments:**

One subject (Subject (b) (6) ) who received full treatment died at 464 days, which is approximately 15 months post treatment due to an event of cardiogenic shock and cardiorespiratory arrest which was fatal. This was assessed as not related to the study drug. Since this subject did not complete the 18 months of follow up, the treatment was incomplete.

This subject who only received 10% of the dose was due to an AE of a hypersensitivity reaction during drug administration. Post treatment, this subject reported two spontaneous bleeds and continued on routine prophylaxis until the end of the study, which is considered a study failure. This subject likely remained on prophylaxis since he did not receive the full dose of study drug.

### 6.1.11 Efficacy Analyses

The primary efficacy endpoint was the ABR from months 7 to 18 compared to the lead-in period.

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

The ABR for all bleeding episodes was reduced following AMT-061 treatment in comparison to the 6-month lead-in period. The lead-in period mean ABR was 4.19 [95% CI: 3.22, 5.45] and the mean ABR from Months 7-18 post treatment was 1.9 [95% CI: 1.04, 3.46]. The ABR rate ratio (EEP/lead-in period) of 0.46 [95% CI: 0.21, 0.81] meets the success criterion where the upper bound of the CI is less than 1.8.

*Reviewer Comment: The ABR was adjusted based on an imputed ABR of 20 for 3 subjects who never stopped routine prophylaxis (2 never stopped and 1 intermittently used prophylaxis). Using this imputed bleeding, the ABR post treatment is adjusted to 1.90 [95% CI: 1.04, 3.46 ] from 1.5 as originally reported by the Applicant.*

*This imputation of 20 bleeds was proposed by the statistical reviewer and reasonable, and this imputation was agreed upon by the Applicant. Considering that one of the subjects continued to have spontaneous bleeds despite continuous prophylaxis, this imputation may be favorable to AMT-061.*

ABR was evaluated by subtype of bleeds to include spontaneous bleeds and traumatic bleeds. The mean ABR by subtype of bleeds was reduced during Months 7 to 18 after treatment in comparison to the lead-in period. The mean spontaneous ABR was 1.52 following treatment and decreased to 0.44. The mean traumatic ABR decreased from 2.09 to 0.62 following treatment.

During the lead in period, the majority of subjects (40/54, 74.1%) experienced bleeding episodes. A total of 136 bleeding episodes were reported, including 118 treated bleeding episodes. During Months 7 to 18 of the post-treatment period, the majority of treated subjects (34/54, 63%) had zero bleeding episodes. During this post-treatment period, 54 bleeding episodes were reported, including 30 treated bleeding episodes.

There were 18 subjects who used FIX replacement products in the EEP. All doses were administered during a bleeding event, except for three subjects who continued to receive FIX replacements as discussed earlier.

Traumatic and spontaneous bleeding episodes were reported in 12 subjects and nine subjects, respectively. There were 50 spontaneous bleeds in the lead-in period compared to 14 post treatment. There were 77 joint bleeds in the lead-in period compared to 19 joint bleeds post treatment.

There were nine subjects that had higher ABRs in the treatment period compared to the lead-in period. One subject received a partial dose. One subject discontinued. Four of these subjects had positive NAb titers to AAV. Two of these nine subjects failed treatment (nonresponders) as they continued on routine prophylaxis.

#### Reviewer comments:

*This product shows decrease in ABR from the lead-in period to the post-treatment period. However, a positive effect will be seen in those subjects with high baseline*

ABRs, unless there is no transgene expression/nonresponder. High baseline ABRs are a result of either inadequate routine prophylaxis or noncompliance to RP. Per IR response received on July 29, 2022, the Applicant reports that at least 70% of subjects were compliant with their prescribed prophylactic dosing regimen. Prophylaxis regimen compliance was defined as: "Actual number of days subject received prophylactic Factor IX infusion excluding Factor IX use for other purposes/Total number of days subject should receive prophylaxis Factor IX as prescribed." During the prophylaxis lead-in period, 45/54 (83%) and 38/54 (70%) subjects were  $\geq 70\%$  and  $\geq 85\%$  compliant to the prophylaxis regimen, respectively.

There were 6 subjects whose hemophilia history and clinical course during the lead-in period suggested that their prophylaxis during the lead-in period may not have been optimal for their bleeding pattern. These subjects had ABRs of 5.12, 5.83, 6.96, 10.67, 11.36, and 12.66 during their lead-in period. Of the 6 subjects who may not have had an optimal prophylaxis regimen in the lead-in period, 5 were  $\geq 70\%$  compliant with their prescribed regimen.

If subjects are on "adequate" prophylaxis and still have high ABRs, these would be the most informative subjects for responding to gene therapy. The ABR for treated bleeds was 3.5 and decreased to 0.84 for the post-treatment period.

Overall, there was a reduction in ABR in Months 7-18 post administration of the product, including reduction in spontaneous and joint bleeds. This therapy did not completely resolve all bleeds for all subjects, but a majority of subjects had zero bleeding episodes during this follow-up time period. Measuring ABR over a longer follow-up time period will allow for more robust evaluation of the long-term efficacy.

#### **6.1.11.2 Analyses of Secondary Endpoints**

Stable FIX expression was noted following treatment with AMT-061.

##### FIX activity:

The one-stage aPTT-based assay was used as a primary assay for PK assessment of FIX protein concentration and FIX activity. FIX protein concentration or FIX activity values that were measured more than 5 half-lives after the most recent FIX-replacement administration was used to support efficacy evaluation and referred to as "uncontaminated FIX levels". The FIX activity measured by chromogenic assay was consistently ~2-fold lower than those measured by one-stage (aPTT-based) assay across all the clinical studies.

FIX activity increased post AMT-061 administration. At 6 months post-AMT-061 treatment, the mean FIX activity was  $38.95\% \pm 18.72\%$  (range: 8.2% to 97.1%). The FIX activity was maintained through Month 12, with a mean FIX activity of  $41.48\% \pm 21.71\%$  (range: 5.9% to 113.0%). At Month 18, the mean FIX activity was  $36.90\% \pm 21.40\%$  (range: 4.5% to 122.9%).

Nine subjects were treated with corticosteroids for ALT elevation of either  $> 2$  times upper limit of normal (ULN;  $n = 8$ ) or  $> 2 \times$  baseline value ( $n = 1$ ). Subjects with ALT elevation had approximately 44% lower mean FIX activity at Month 18 compared to those that did not have ALT elevation. The 9/53 subjects (17%) that were treated with corticosteroid for ALT elevations exhibited approximately 63% lower mean FIX activity at

Month 18 compared to those who did not receive corticosteroid coadministration. Subjects were treated for 51-130 days.

**Reviewer Comment:**

*Further discussion of ALT elevation is in the Safety Review below. ALT elevation is likely the result of T-cell response toward capsid proteins and may cause the lower FIX activity as noted. All subjects discontinued steroid use prior to Week 26 and no other form of immunosuppression was used in this study. The durability of FIX levels for those with steroid use will be informative to determine if the initial T-cell response will be blunted long term by this intervention.*

Patient-reported outcome assessments were made throughout the study. The Phase 3 study evaluated health-related quality of life using the Hemophilia Specific Quality of Life Index (Hem-A QoL). The Hem-A QoL assessment showed improvement in domains of feelings, work and school, and treatment burden compared to the lead-in period.

**Reviewer Comment:**

*Due to the single-arm trial, reliable assessments of patient-reported outcomes cannot be made. This information was not included in the label.*

### 6.1.11.3 Subpopulation Analyses

In AAV vector-based gene therapies, pre-existing anti-AAV NABs may impede transgene expression at desired therapeutic levels. In the clinical studies with AMT-061, an unvalidated clinical trial assay was utilized to assess pre-existing anti-AAV5 NABs. There were 21 subjects with a positive NAB to AAV5. These NAB titers were measured at baseline prior to infusion of the gene therapy product. These NAB titers were in the range of 1:8.5 - 3212.

Twenty of the subjects had titer values up to 1:700 (Range 1:8.5 - 678). One subject had a NAB titer of over 1:3000. The following table shows all subjects with a positive NAB.

**Table 4. Subjects with Positive Anti-AAV5 NABs**

Subject ID	Baseline AAV5 NAb Titer	FIX Levels Month 6	FIX Levels Month 12	FIX Levels Month 18	Baseline ABR	ABR Month 7-18
(b) (6)	8.5	52.6	56.5	39.8	2.0	0.0
	11.1	50.4	43.7		1.5	4.1
	13.7	90.4	73.6	57.9	0.0	0.0
	14.9	37.4	44.8	39.8	6.7	1.3
	21.0	27.1	28.3	26.0	6.3	0.0
	23.3	13.8	13.2	12.0	11.4	5.4
	23.3	37.9	38.8	37.7	5.8	1.0
	25.8	42.6	48.6	39.8	5.5	2.0
	37.1	42.6	41.1	35.6	1.9	0.0
	41.3	13.0	12.8	12.0	5.1	1.1
	56.9	30.6	32.9	28.7	1.8	0.0
	57.8	16.3	16.3	13.8	0.0	0.0
	98.5	8.2	11.5	10.3	7.0	0.0
	111.5	48.6	49.0	48.4	4.5	0.0

Subject ID	Baseline AAV5 NAb Titer	FIX Levels Month 6	FIX Levels Month 12	FIX Levels Month 18	Baseline ABR	ABR Month 7-18
(b) (6)	115.1	33.8	47.9	42.5	5.7	1.0
	198.9	10.5*	28.7*	11.6*	12.7	36.2
	449.9	10.3*	8.5	9.1*	6.3	8.1
	481.9	29.2		21.6	10.7	0.0
	558.3	28.4	30.2	32.0	1.3	0.0
	678.2	43.5	42.0	31.4	1.7	0.0
	3212.3	9.5*	40.8*	26.0*	0.0	1674.0

Source: FDA Analysis

Abbreviations: ABR, annualized bleeding rate; FIX, Factor IX; NAb, neutralizing antibody.

Four of these subjects had higher ABRs during the EEP compared to their baseline ABR. As the clinical trial assay was not validated and the data are limited, no conclusion regarding correlation with positive NAb titers and efficacy can be reached. However, as there was one subject with very high NAb titers who had significant bleeding post treatment, a safety PMR study will be required to assess the association between serious risk bleeding to lack of pharmacological effect and and pre-existing high anti-AAV5 NAb titers.

Reviewer Comment:

*Overall, there is limited data for subjects with positive NAb titers. One subject with the highest titer of 1:3212, failed this treatment, continued on routine prophylaxis with multiple bleeding episodes. However, there is no clear correlation of positive NAb titers and efficacy. There were nine subjects with higher ABRs post treatment compared to baseline. These included subjects with and without NABs. It is noted that the four subjects with positive NABs had much higher ABRs compared to those with negative NABs.*

*The Applicant has proposed (b) (4) to be included in the indication statement in the label. Throughout the development program, advice was given regarding a companion diagnostic to be approved contemporaneously with the product. CDRH's review concluded that the device (assay) did not generate reproducible results, provided erroneous results, and the analytical study data were deficient. Based on this, the assay was not valid or reliable for its intended use. CDRH's evaluation is concerning for the assay that was used in the clinical trial, and therefore the reliability of the NAB results of all subjects is questionable.*

*Due to the limited data and unreliable assay used, it is unknown if higher titer NABs will result in lack of efficacy. The FDA Guidance for In Vitro Companion Diagnostic Devices states that, "If FDA determines that an IVD [in vitro] companion diagnostic device is **essential to the safe and effective use** of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication if the IVD companion diagnostic device is not approved or cleared for that indication."*

*In this case, there is uncertainty that this device (assay) is essential for the effective use of this product. Due to this uncertainty, additional data would need to be collected with a reliable and valid assay. This assessment cannot be made until more subjects with a wide variability in NABs show some correlation with efficacy or safety.*

*It is concerning that one subject with high NABs had no efficacy with this product and approval of the product is without restriction to exclude high-titer or high-risk subjects. Approval of this product without the assay was decided by the Office Director, as there are limited data to support the assay is essential to the safe and effective use of the product. This may be problematic for the clinician when deciding whether to administer this product to a patient, as there will be no mechanism to assess for an NAB without an NAb assay to AAV. Although a clinician will be able to follow patients in regards to FIX activity levels and bleed rates, the primary decision to administer therapy when there may not be a prospect of benefit is concerning. If a subset of subjects receives this product with limited efficacy, this may preclude these subjects from receiving another gene therapy. Moreover, the key information of whether a NAB is present will not be known. However, as noted earlier, there is no clear association between pre-existing NABs and efficacy.*

*A safety PMR issued at time of Approval may provide more information on NAB titer level and safety signals, including bleeding events. Based on the results of the PMR study, if there is a clear association identified between a threshold level of pre-existing NABs and the safe and effective use of the product, then revision of the package insert will be considered at that time. However, this will take many years and the PMR data may not include many subjects with high titers which will be uninformative. There may be subjects not enrolled in the PMR study who will be dosed with the approved product without any data on NAB titer.*

#### **6.1.11.4 Dropouts and/or Discontinuations**

One subject died during the study. One subject discontinued during treatment (received 10% of dose). There were no other discontinuations. Please see Safety section below on details of death and discontinuation of treatment due to hypersensitivity reaction.

#### **6.1.11.5 Exploratory and Post Hoc Analyses**

Exploratory analyses of correlation of NAB titer to efficacy were performed. There was no correlation noted. However, FIX activity was lower in those with higher NAB titers. The mean FIX activity at Month 12 was 42%  $\pm$  22 % in subjects with NABs titer  $\leq$ 1:100 (n = 45) and FIX activity was 36%  $\pm$  17% in subjects with NABs titer >1:100 to <1:700 (n = 5). The mean FIX activity at Month 12 was 42%  $\pm$  22% in subjects with NABs titer  $\leq$ 1:350 (n = 47) and 27%  $\pm$  17% in subjects with NABs titer >1:350 to <1:700 (n = 3).

#### **Reviewer Comment:**

*Overall, there are limited data in subjects with NAB titers with only 5 subjects with titers above 100 and below 700. There are only 4 subjects with titers over 350 and below 700.*

*FIX activity is the only measure of transgene expression, and it is difficult to establish a level that correlates to a particular ABR. Durability data of FIX expression over time will show if those subjects with NAB titers continue to have decreasing levels. If this occurs, this would further highlight the risk associated in subjects with pre-existing positive NAB titers.*

## **6.1.12 Safety Analyses**

### **6.1.12.1 Methods**

For details of monitoring, please refer to Section 6.1.7

As Study CT-AMT-061-02 contributed the majority of the subjects for the safety analysis population (54 or 57), the safety review of Study CT-AMT-061-02 is described in the context of the Integrated Overview of Safety, Section 8. Where appropriate, study specific comments are provided in this section.

Adverse events were actively solicited by the investigator at screening, the lead-in phase, treatment, and during the post-treatment follow-up period. During the post-treatment period, subjects were seen weekly from Weeks 1-12, monthly from Months 4-11, and had their final visit at Month 12 (Week 52). Subjects were then actively followed to assess long-term safety/AEs every 6 months for an additional 4 years. Occurrence of AEs is continuously monitored, with at least quarterly check-ins between site staff and subjects.

### **6.1.12.2 Overview of Adverse Events**

For the ISS overview of adverse events, please see section 8.4.4 below. (Module 2.7.4, [Section 2.2.1.1](#)).

### **6.1.12.3 Deaths**

There were no deaths in Study CT-AMT-061-01.

One death was reported in Study CT-AMT-061-02 due to cardiogenic shock. Please see Section 8.4.1 for further details regarding Subject (b) (6) death.

### **6.1.12.4 Nonfatal Serious Adverse Events**

The applicant reported 17 SAEs in 14 subjects from Study CT-AMT-061-02. One of these fatal SAEs was fatal (see below description in Section 8.4.1).

### ***Please see Section 8.4.2 below for full details of SAEs 6.1.12.5 Adverse Events of Special Interest (AESI)***

The applicant refers to Adverse Events of Special Interest (AESIs) as Adverse Events of Special Notification (AESN). For further details on AESN, please see below Section 8.4.8.

### **6.1.12.6 Clinical Test Results**

Please see below Section 8.4.5.



#### **6.1.12.7 Dropouts and/or Discontinuations**

Please see below Section 8.4.3.

#### **6.1.13 Study Summary and Conclusions**

Overall, AMT-061 demonstrated efficacy with reduction in ABR during the EEP compared to baseline ABRs and increase in FIX expression. Efficacy was based on ABR during months 7-18 after treatment with AMT-061 compared with the ABR during the lead-in period. The mean ABR during months 7-18 was 1.9 bleeds/year [95% CI: 1.0, 3.4], compared with a mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio (Months 7 to 18 post-treatment/lead-in) was 0.46 [95% CI: 0.26, 0.81], demonstrating NI of ABR during months 7 to 18 compared to the lead-in period. The mean FIX activity levels over time, as measured by one-stage (aPTT-based) assay were 39% ( $\pm 18.7\%$ ), 41.5% ( $\pm 21.7\%$ ), 36.9% ( $\pm 21.4\%$ ) and 36.7 ( $\pm 19.0\%$ ) of normal, respectively, at 6, 12, 18, and 24 months.

The safety profile is acceptable. Please see Section 8, Integrated Overview of Safety, for specific safety findings and conclusions.

### **7.1 Indication #1**

#### **7.1.1 Methods of Integration**

Efficacy evaluation was primarily based on the Phase 3 study, CT-AMT-061-02. The data from Study CT-AMT-061-01 were considered supportive and only evaluated 3 subjects. The data from this earlier study support the efficacy of the Phase 3 study. As the studies were not identical and the Phase 1/2 study had limited number of subjects, the studies were not integrated. Therefore, an integrated summary of efficacy was not conducted.

#### **7.1.2 Demographics and Baseline Characteristics**

##### **As above. 7.1.3 Subject Disposition**

As above. 7.1.4 Analysis of Primary Endpoint(s)

##### **7.1.5 Analysis of Secondary Endpoint(s)**

As above.

##### **7.1.6 Other Endpoints**

As above.

##### **7.1.7 Subpopulations**

As above.

##### **7.1.8 Persistence of Efficacy**

As above in Section 6.

##### **7.1.9 Product-Product Interactions**

N/A

### 7.1.10 Additional Efficacy Issues/Analyses

As above

### 7.1.11 Efficacy Conclusions

As above.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

For analysis purposes, the safety population consists of all subjects who received AMT-061 to include 3 subjects from the Phase 2b trial CT-AMT-061-01 and 54 subjects from the Phase 3 trial CT-AMT-061-02. Adverse events were actively solicited by the investigator at screening, the lead-in phase, treatment, and during the post-treatment follow-up period. During the post-treatment period, subjects were evaluated weekly from Weeks 1-12, monthly from Months 4-11, and a final visit at Month 12 (Week 52). Subjects were then actively followed to assess long-term safety/AEs every 6 months for an additional 4 years. Occurrence of AEs was continuously monitored, with at least quarterly check-ins between site staff and subjects. See Section 6.1.7 for details on monitoring.

The Integrated Summary of Safety (ISS) Plan included subjects who received the full planned dose of AMT-061 or who received a partial dose of AMT-061 across studies CT-AMT-061-01 and CT-AMT-061-02.

### 8.2 Safety Database

**Table 5. Data Pools for Integrated Safety Analysis**

**Table 1 Data Pools for Integrated Safety Analysis**

Population	Study	Dose Regimen for Etranacogene Dezaparvovec	Pooled Groups for Integrated Analysis
Subjects with Hemophilia B	CT-AMT-061-01	Single $2 \times 10^{13}$ gc/kg dose	Total etranacogene dezaparvovec
	CT-AMT-061-02	Single $2 \times 10^{13}$ gc/kg dose	

gc/kg = genome copies per kilogram; ISS = integrated summary of safety; SAP = statistical analysis plan.

Source: Adapted from ISS SAP, Table 1.

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

Phase 2b trial: CT-AMT-061-01 (n = 3)

Phase 3 trial: CT-AMT-061-02 (n = 54)

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

The safety assessment detailed above in Section 6.1.12 pools data from both the Phase 2b, CT-AMT-061-01, and Phase 3, CT-AMT-061-02, studies.

All 57 subjects in the ISS Safety population were male. The mean age was 41.7 ( $\pm$  15.42) years and ages ranged from 19 to 75 years. Six subjects were aged >65 years. Of the 52 subjects who self-reported race, 41 (78.7%) subjects identified as White, 3

(5.8%) subjects identified as Black or African American, 2 (3.8%) subjects identified as Asian, and 6 (11.5%) subjects identified as other.

With respect to baseline characteristics, in Study CT-AMT-061-02, 28/54 subjects had hepatic steatosis with a controlled attenuation parameter (CAP) score <S2, 12 subjects had steatosis with a CAP score of ≥S2, and 14 subjects had missing information on CAP score. In Study CT-AMT-061-02, the majority (45/53) of subjects who received the full dose of AMT-061 had normal renal function, 7 subjects had mild renal impairment, and 1 subject had moderate renal impairment.

See Section 1.1 above for further demographic information

### **8.2.3 Categorization of Adverse Events**

Adverse Events were characterized as severe (including one death), adverse events of special interest (sponsor noted as adverse events of special notification), adverse events leading to treatment discontinuation, common adverse events, clinical test result adverse events and any adverse events in vital signs. All adverse events were characterized as severe, moderate or mild.

### **8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials**

As subjects received the same dose of AM-061 in both trials and had similar background characteristics, and so very few subjects contributed to analysis from the Phase 2 trial, no significant issues were raised with respect to pooling across trials.

### **8.4 Safety Results**

#### **8.4.1 Deaths**

There were no deaths reported in Study CT-AMT-061-01. One death was reported in Study CT-AMT-061-02. Subject (b) (6), a 75yo male with a medical history of atrial enlargement, benign prostatic hyperplasia, diverticulum intestinal, drug hypersensitivity, femoroacetabular impingement, hepatitis C, hiatus hernia, hypertension, nephrolithiasis, osteoarthritis, osteoporosis, prostatitis, renal cyst, atrial fibrillation, and atrial hypertension, experienced a fatal event of cardiogenic shock on Study Day 464 following a urinary tract infection.

On Study Day 463, the subject experienced an SAE of cardiogenic shock. The subject presented to the emergency department with "heart-pounding" palpitations since earlier the same morning and a 3-day history of fever with dysuria. The subject denied having chest pain or dyspnea. Vital signs revealed oxygen saturation of 98% on room air, heart rate of 110 beats per minute (bpm), blood pressure of 100/75 mm/Hg, and afebrile. Chest x-ray revealed congestion with some blurred consolidation. Electrocardiogram (ECG) revealed atrial fibrillation with a mean of 110 bpm.

The subject was diagnosed with urinary sepsis (reported as a non-serious adverse event). The subject had an episode of dyspnea while supine with complaints of bilateral rib pain which the subject reported was secondary to hiccups. Supplemental oxygen was administered. A repeat ECG revealed: atrial flutter that converted to sinus rhythm

without intervention, initial QRS widening, and a Grade 1 atrioventricular block; flecainide (150 mg IV SD) was given for treatment.

On Study Day 464, the subject experienced another episode of dyspnea with a productive cough and subsequently went into cardiorespiratory arrest. Cardiopulmonary resuscitation (CPR) was initiated. The subject was initially in ventricular tachycardia with immediate resumption of pulse and level of consciousness. The ventricular tachycardia resumed, and cordarone and CPR was restarted and the subject was intubated. Repeat blood gases revealed severe mixed acidosis. An examination revealed dilated pupils, which were non-reactive to light.

Computed tomography (CT) angiogram revealed no obvious opacification deficit affecting the bilateral pulmonary circulation and findings consistent with iatrogenic edema in the first instance. CT scan of the brain revealed no acute changes and signs of chronic ischemic leukoencephalopathy. CT scan of the abdomen revealed increase in the dependent bilateral pleural effusion with thickening in both lobes. During the scan, the subject experienced another episode of cardiorespiratory arrest and pulmonary edema due to cardiogenic shock preceded by bradycardia and hypotension. Resuscitation was resumed and continued for about 25 minutes without recovery of rhythm or pulse. Treatment of the event included epinephrine (3 mg IV SD), calcium gluconate (10 mL IV SD), norepinephrine (2 mcg/kg/min IV), cordarone (dose unknown), atropine (0.5 mg IV SD), sodium chloride 0.9% (500 mL IV QD), and sodium bicarbonate (100 mL IV SD). The event of cardiogenic shock was fatal. An autopsy was not performed.

The Applicant considered the event of paroxysmal atrial fibrillation as moderate in severity and not related to AMT-061. The Applicant considered the event of cardiogenic shock as severe in intensity and unrelated AMT-061.

After careful review of this subject's death, this reviewer considers that it is unlikely related to AMT-061 based on the multiple risk factors and the subject's multiple comorbidities and medical history of prior episodes of atrial fibrillation that likely contributed to the cardiogenic shock.

#### **8.4.2 Nonfatal Serious Adverse Events**

The applicant reported one SAE in one subject from Study CT-AMT-061-01. The applicant reported 17 SAEs in 14 subjects from Study CT-AMT-061-02. One of these SAEs was fatal (see above description in Section 8.4.1).

The below table shows the SAEs from both CT-AMT-061-01 and CT-AMT-061-02.

**Table 6. Summary of Serious Adverse Events by Subject (Study Safety Populations)**  
**Table 15 Summary of Serious Adverse Events by Subject (Study Safety Populations)**

Subject ID	Period	SAE Preferred Term	Severity	Relationship to Study Drug <sup>a</sup>	Action Taken with Study Drug	Outcome
<b>Study CT-AMT-061-01</b>						
(b) (6)	Post-treatment	Osteonecrosis	Moderate	Not Related	None	Ongoing (not recovered)
<b>Study CT-AMT-061-02</b>						
(b) (6)	Post-treatment	Haemarthrosis	Moderate	Not Related	None	Recovered/ Resolved
	Post-treatment	Blood Loss Anaemia	Severe	Not Related	None	Recovered/ Resolved
	Post-treatment	Jaw Fracture	Severe	Not Related	None	Recovered/ Resolved
	Post-treatment	Complication associated with Device	Moderate	Not Related	None	Recovered/ Resolved
	Post-treatment	Diverticulitis Intestinal Haemorrhagic	Moderate	Not Related	None	Recovered/ Resolved
	Post-treatment	Blood Loss Anaemia	Severe	Not Related	None	Recovered/ Resolved
	Post-treatment	Nephrolithiasis	Mild	Not Related	None	Recovered/ Resolved
	Post-treatment	Epilepsy	Moderate	Not Related	None	Recovered/ Resolved
	Post-treatment	Covid-19	Severe	Not Related	None	Recovered/ Resolved
	Post-treatment	Musculoskeletal Chest Pain	Mild	Not Related	None	Recovered/ Resolved
	Post-treatment	Hepatocellular Carcinoma	Severe	Not Related	None	Not recovered/ Not resolved
	Post-treatment	Transient Ischaemic Attack	Moderate	Not Related	None	Recovered/ Resolved
	Post-treatment	Peripheral Artery Aneurysm	Moderate	Not Related	None	Not recovered/ Not resolved
	Post-treatment	Cellulitis	Severe	Not Related	None	Recovered/ Resolved
	Post-treatment	Atrial Fibrillation	Moderate	Not Related	None	Recovered/ Resolved
	Post-treatment	Cardiogenic Shock	Severe	Not Related	None	Fatal

Subject ID	Period	SAE Preferred Term	Severity	Relationship to Study Drug <sup>a</sup>	Action Taken with Study Drug	Outcome
(b) (6)	Post-treatment	Upper Gastrointestinal Haemorrhage	Severe	Not Related	None	Recovered/ Resolved

COVID-19 = Coronavirus disease 2019; ID = identifier; NA = not applicable; SAE = serious adverse event.

<sup>a</sup> Related = related or possibly / probably related. Not related = unlikely related or unrelated. Assessments by the Investigator.

Per the Applicant, there were no treatment-related SAEs in Study CT-AMT-061-01 or CT-AMT-061-02. The majority of SAEs were mild to moderate in severity and the SAE profile was comparable between subjects with pre-existing seropositive or negative anti-AAV5 NABs.

#### Study CT-AMT-061-01

The Applicant noted one SAE in Sin Subject (b) (6); this subject had a history of avascular necrosis (osteonecrosis) affecting both hips, that was ongoing at the time of study enrollment. This subject developed moderate worsening of avascular necrosis (osteonecrosis) of the left hip on Study Day 197 post-AMT-061 administration. On the same day, the subject underwent femoral head decompression and on Study Day 720, an arthroplasty of the left hip was performed. The Applicant considered this SAE to be recovering/resolving and to be unrelated to AMT-061. The clinical reviewer agrees with that this osteonecrosis was unrelated to AMT-061.

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

Of the above listed SAEs that occurred in Study CT-AMT-061-02, the events of musculoskeletal chest pain, hepatocellular carcinoma, transient ischemic attack, peripheral artery aneurysm, cellulitis, atrial fibrillation and cardiogenic shock required further investigation by the clinical reviewer to assess concerns regarding attribution to AMT-061.

Subject CT-AMT-061-(b) (6) 1experienced mild musculoskeletal chest pain and was admitted to the hospital on Study Day 3. This subject reported a two day history of elevated blood pressure. An EKG, ECHO and chest XR were normal and there were no signs of heart disease or pulmonary embolism. The musculoskeletal chest pain resolved within 24 hours. The clinical reviewer believes that due to the temporal nature of this SAE to AMT-061 administration, it cannot be ruled out that it may be related to AMT-061, although this SAE may be related to exercise, as the Applicant presumes.

Subject CT-AMT-061-02-(b) (6) was diagnosed with hepatocellular carcinoma on Study Day 443. This SAE is considered an Adverse Event of Special Interest (AESI). For further details, please see Section 8.4.8 below.

Subject CT-AMT-061-02-(b) (6) experienced a moderate transient ischemic attack on Study Day 229 and a moderate peripheral artery aneurysm on Study Day 920. These SAEs are considered Adverse Events of Special Interest (AESI). For further details of these events, please see below Section 8.4.8.

Subject CT-AMT-061-02-(b) (6) expereinced severe cellulitis of the left lower leg requiring hospitalization on Study Day 540. On Study Day 550, a skin biopsy taken from the ventral side of the subject's right upper leg revealed basal cell carcinoma. These

events are considered AESIs and for further information, please see below Section 8.4.8.

Subject CT-AMT-02-(b) (6) experienced a severe epileptic seizure on Study Day 187 following a one-week history of slower cognition and impaired concentration. This subject is a 73yo male who experienced agitation, drowsiness and decreased capacity of the left arm while at home. This was followed by a sudden onset of acute shaking and left-sided motor hemiplegia within the ambulance while en route to the hospital. NIH stroke scale score was 11. A brain CT and angiography of neck vessels revealed an intrathoracic goiter and complete occlusion of the V4 segment of the right vertebral artery (presumably on a chronic basis). Cerebral MRA revealed marked arteriosclerosis at the left carotid siphon and proximally at the right posterior cerebral artery. On Study Day 192, on imaging, two small nodular injuries at the level of the right lung were noted (see below Section 8.4.8 AESI for further details). On Study Day 202, the SAE of epilepsy was considered recovered/resolved. The Applicant considered the SAE of epilepsy as moderate in severity and unrelated to AMT-061. This clinical reviewer concurs with the Applicant that this SAE was unrelated to AMT-061, especially as this subject has a history of a vertebral artery occlusion at baseline.

Subject CT-AMT-061-02-(b) (6) experienced moderate atrial fibrillation and severe cardiogenic shock and expired on Study Day 464. Please see above Section 8.4.1 for further details.

Per the clinical reviewer's assessment, the events of hemarthrosis, blood loss anemia, jaw fracture, complication associated with device (dysfunction with internal left knee prosthesis), nephrolithiasis, epilepsy, COVID-19 and upper gastrointestinal hemorrhage were likely unrelated to AMT-061 per subject narratives.

#### **8.4.3 Study Dropouts/Discontinuation**

There were no treatment discontinuations in Study CT-AMT-061-01. One subject in Study CT-AMT-061-02 had to discontinue treatment due to an adverse event. Subject CT-AMT-02-(b) (6) had a severe hypersensitivity reaction requiring intramuscular epinephrine and only received 10% of the AMT-061 dose. Please see Section 6.1.12.5 for details.

No subjects discontinued Study CT-AMT-061-01 and two subjects discontinued Study CT-AMT-061-02- Subjects (b) (6). Subject (b) (6) died due to cardiogenic shock (See Section 8.4.1 for details). Subject (b) (6) discontinued Study CT-AMT-061-02 on Study Day 735. This subject had a baseline anti-AAV5 NAb titer level of 3212 at baseline. This subject had no transgene expression and experienced increased bleeds post-treatment.

#### **8.4.4 Common Adverse Events**

##### Lead-In Period

According to the Applicant's assessment, there was no lead-in Period in Study CT-AMT-061-01, therefore, no AEs were attributed to a lead-in Period. In Study CT-AMT-061-02, 42/67 (62.7%) enrolled subjects (study safety population including discontinuers) experienced 103 AEs during the  $\geq 6$ -month lead-in Period. Common AEs ( $>5\%$  of subjects) by the preferred term during the lead-in period (excluding discontinuers; N = 54) were nasopharyngitis (14.8%; 8 events) and arthralgia (7.4%; 4 events). All other AEs occurred in 2 (3.7%) or fewer subjects.

All 57 subjects treated with AMT-061 experienced at least 1 TEAE during the post-treatment period.

Per the Applicant's assessment, the most common TEAEs were arthralgia (36.8%), headache (31.6%), nasopharyngitis (26.3%), fatigue (24.6%), and ALT increased (21.1%). The most frequent TEAEs considered by the Applicant as treatment-related were ALT increased (15.8%), headache (15.8%), influenza-like illness (12.3%), and AST increased (8.8%). There were no reported thrombotic events.

Six (10.5%) subjects experienced 11 TEAEs in the neoplasms benign, malignant and unspecified (including cysts and polyps) system organ class. These included adenoma benign, basal cell carcinoma (BCC), benign breast neoplasm, colon adenoma, gastrointestinal neoplasm, HCC, meningioma, pancreatic neuroendocrine tumor, prostate cancer, and skin papilloma; all were assessed as not treatment-related by both the investigator and the Applicant.

According to the applicant, the most common treatment related AEs include headaches, ALT increase, AST increase, blood CPK increase, fatigue, chest discomfort, nausea, dizziness, malaise, infusion-related reactions, and influenza-like illness. There were no thrombotic events.

According to the clinical reviewer's assessment, overall, in both Studies CT-AMT-061-01 and CT-AMT-061-02, the most common reported adverse events were headache (44%), ALT increase (42%), AST increase (42%), blood creatine phosphokinase (CPK) increase (42%), arthralgia (35%), fatigue (26%), nasopharyngitis (26%), back pain (21%), and influenza-like illness (16%).

#### **8.4.5 Clinical Test Results**

The below clinical test results are based on pooled data from subjects who were enrolled in Study CT-AMT-061-01 and Study CT-AMT-061-02. Most laboratory abnormalities were NCI CTCAE v.1 Grade 1 or 2. There were 7 instances of Grade 3/4 laboratory abnormalities.

Notably, AMT-061 is an AAV5-based gene therapy that transfects the liver cells which may lead to transaminitis. The transaminitis is thought to be related to a T-cell mediated response. Twenty-four subjects had elevated alanine transaminase (ALT) levels post-AMT-061 infusion and 24 subjects had elevated aspartate transaminase (AST) levels



post-AMT-061 infusion. Nine subjects with ALT elevations received a tapered course of corticosteroids.

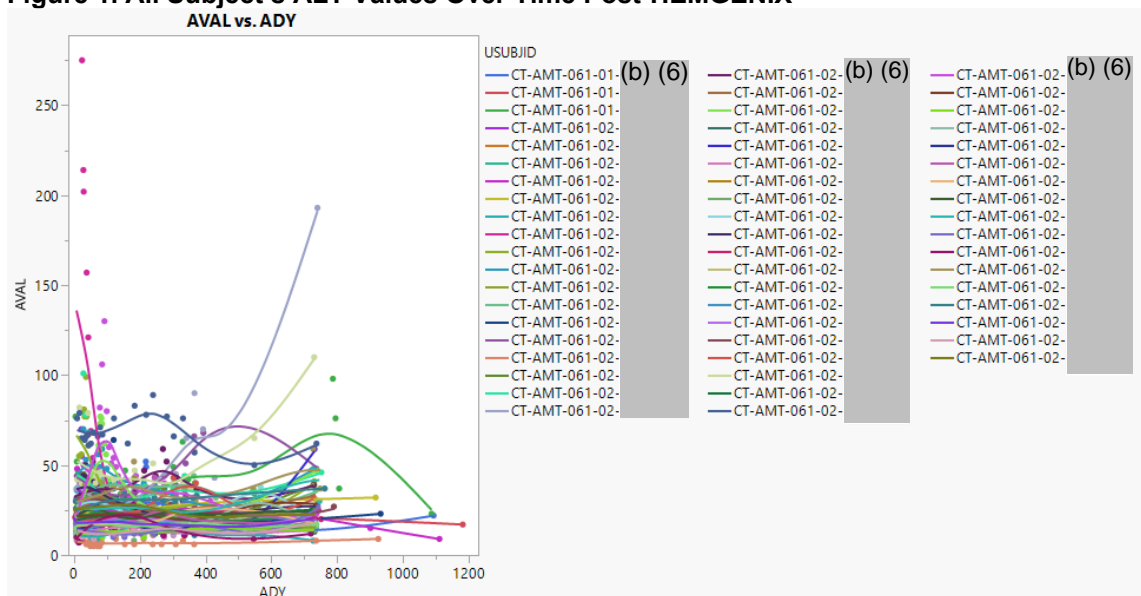
In the coagulation laboratory results, no subjects were found to have decreased prothrombin times (PT) post-AMT-061 infusions and only one subject was found to have a decreased partial thromboplastin time (PTT) (value = 20s) 18 months post-AMT-061 infusion. Eight subjects had mildly elevated platelet counts post-AMT-061 infusion.

See below for further details on laboratory results.

#### Abnormal Liver Function Tests

Figure 1 shows all subject's ALT values at different time points post AMT-061.

**Figure 1. All Subject's ALT Values Over Time Post-HEMGENIX**



\*\*The y-axis denotes ALT levels. The x-axis denotes the number of days post-AMT-061 administration.

There were 24 subjects who had elevated ALT values from Days 8 to 731 post-administration.

Five subjects had ALT elevations  $>2-3 \times \text{ULN}$  (range: 89 IU/L to 130 IU/L), one subject had an ALT elevation  $>3-5 \times \text{ULN}$  (193 IU/L), and one subject had an ALT elevation  $>5 \times \text{ULN}$  (275 IU/L). The event of ALT elevation  $>5 \times \text{ULN}$  occurred 3 weeks after AMT-061 administration.

Five subjects had AST elevations  $>2-3 \times \text{ULN}$  (range: 71 IU/L to 118 IU/L), three subjects had AST elevations  $>3-5 \times \text{ULN}$  (range: 127 IU/L to 163 IU/L), and one subject had an AST elevation  $>5 \times \text{ULN}$  (327 IU/L). The event of AST elevation  $>5 \times \text{ULN}$  occurred 11 months post-AMT-061 administration.

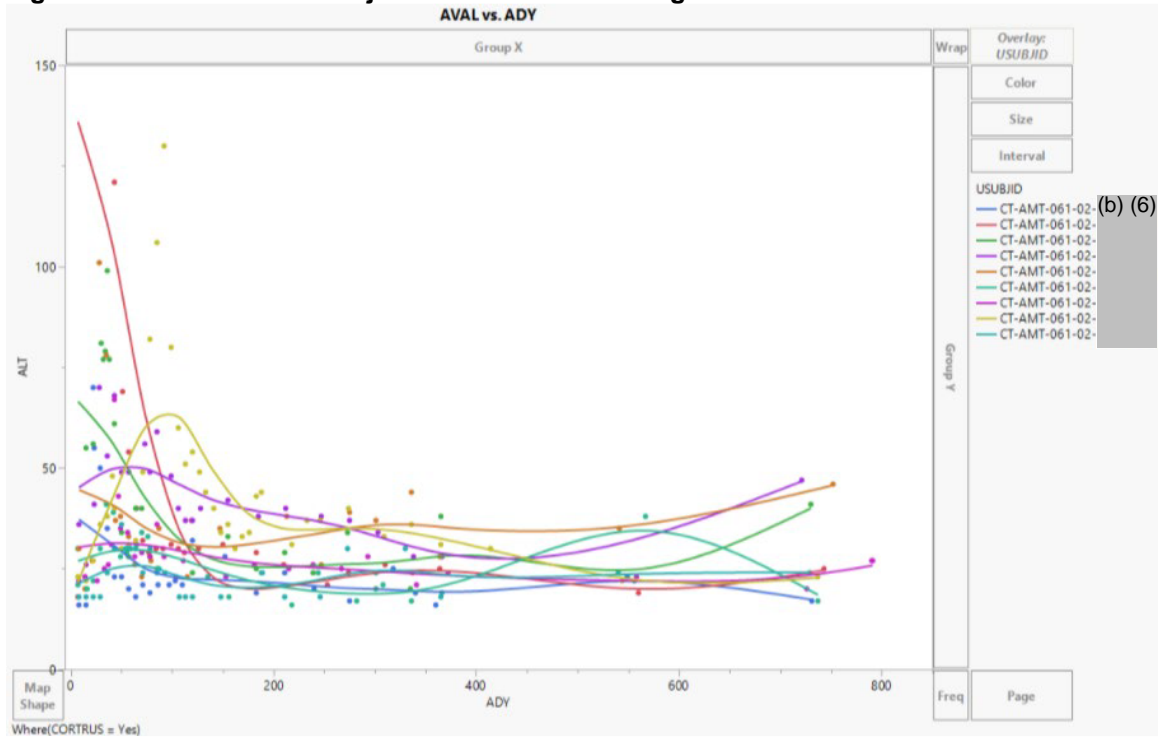
Seventeen subjects had elevations in ALT levels within the first 4 months after AMT-061 infusion (range: 41 IU/L to 275 IU/L), with eleven of these subjects' ALT levels resolving within 4 months post-infusion (range: 41 IU/L to 275 IU/L) and five of these subjects' ALT levels never normalizing as of last follow-up (range of values at 2-year follow-up: 48 IU/L to 110 IU/L). Seven additional subjects had ALT elevations with onset between Months 6 to 24 (range: 42 IU/L to 193 IU/L), of whom five of these subjects had additional risk factors for having elevated transaminase levels including HCV and HIV. ALT levels never normalized as of last follow-up (range of values at 2-year follow-up: 59 IU/L to 193 IU/L) in three of the subjects with ALT elevations with onset between months 6 to 24.

Nineteen subjects had elevations in AST levels within 3 months after AMT-061 infusion (range: 32 IU/L to 163 IU/L). Nine of these subjects' AST elevations resolved within 4 months post infusion (range: 35 IU/L to 163 IU/L), three resolved within 7 to 13 months post infusion (range: 35 IU/L to 62 IU/L), and seven of these subjects' AST levels never normalized as of last follow-up (range of values at 2-year follow-up: 36 IU/L to 327 IU/L). The remaining 5 subjects with AST elevation had onset of between 6 months and 2 years post-infusion (range: 36 IU/L to 127 IU/L) and AST levels had not normalized as of the last follow-up for one subject (AST at 2-year follow-up: 127 IU/L) who had additional risk factors for having elevated transaminase levels.

Nine subjects with ALT elevations received a tapered course of corticosteroids. The mean duration of corticosteroid treatment for the subjects with elevated ALT was 81.4 days. Nineteen of the 24 subjects with ALT elevations also had a related AST elevation. Twenty-one subjects had elevated transaminase levels and were not treated with corticosteroids

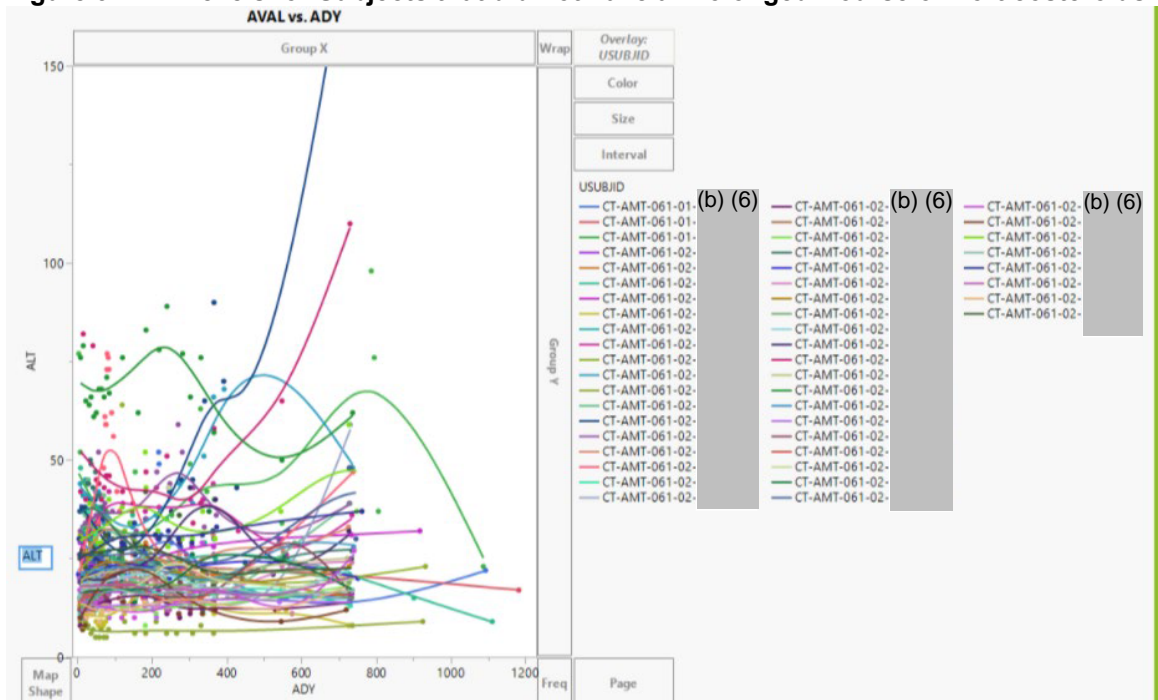
The below Figures 2 and 3 represent ALT levels for subjects with and without prolonged corticosteroid use, respectively.

Figure 2. ALT Levels for Subjects that Took a Prolonged Course of Corticosteroids



\*\*The y-axis denotes ALT levels. The x-axis denotes the number of days post-AMT-061 administration.

Figure 3. ALT Levels for Subjects that did not Take a Prolonged Course of Corticosteroids\*



\*\*The y-axis denotes ALT levels. The x-axis denotes the number of days post-AMT-061 administration.

Figure 2 illustrates that the subjects who received corticosteroids for ALT elevation were less likely to experience ALT elevations at later dates. The subjects who did not receive corticosteroids for elevated ALT levels were more likely to continue to experience elevated ALT levels, even after periods of normal ALT levels. Figure 3 illustrates that the subjects who did not receive corticosteroids for elevated ALT elevations post-AMT-061 administration experienced ALT elevations up to 2 years, unlike the subjects who received corticosteroids post-AMT-061 administration.

#### CMP, CBC, and Coagulation Results

Most laboratory abnormalities were grade 1/2 per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Subject CT-AMT-061-02-(b) (6) experienced grade 3 decreased lymphocyte count. Local laboratory results on Study Day 54 and 59 revealed ALT of 0.5 ukat/L (normal range: 0.15-1.1 ukat/L) on both dates to follow-up on central laboratory ALT levels that were almost twice baseline. On Study Day 61, the subject was placed on oral prednisolone at 60 mg daily which was gradually tapered down to the final dose of 2.5 mg daily. On Study Day 64, central laboratory results revealed an absolute lymphocyte count of  $0.84 \times 10^9/L$  and percentage lymphocyte of 10.3%. No treatment was provided. Decreased lymphocyte count was attributed to corticosteroid use. On Study Day 93, the decreased lymphocyte count was resolved ( $1.7 \times 10^9/L$  [normal range: 1.1 to  $4.8 \times 10^9/L$ ]).

Subject CT-AMT-061-02-(b) (6) experienced grade 4 decreased hemoglobin (4.7 g/dL) on Study Day 999 that was considered unrelated to AMT-061 and due to rectal bleeding from hemorrhoids and severe symptomatic anemia.

#### Elevated Liver Enzymes in Subjects With Positive/Negative Anti-AAV5 NAb at Baseline

There were a total of 24 subjects with positive anti-AAV5 NAb at baseline, 21 subjects from the Phase 3 efficacy trial (CT-AMT-061-02) and 3 subjects from the Phase 2b trial (CT-AMT-061-01). Thirteen of the 24 subjects with positive anti-AAV5 NAb at baseline did not experience any elevation in either AST or ALT.

Of the 19 subjects who experienced both ALT and AST elevations post-AMT-061 infusion, five of them had positive anti-AAV5 NAb at baseline. Two of the five subjects with positive anti-AAV5 NAb at baseline had ALT levels  $>2 \times ULN$  but less than  $3 \times ULN$  (range: 98 IU/L to 101 IU/L) and one of the five subjects with positive anti-AAV5 NAb at baseline (anti-AAV5 Nab titer level: 41.3) had an ALT level  $>5 \times ULN$  (value: 275 IU/L).

Two of the five subjects with positive anti-AAV5 NAb at baseline had AST levels  $>2 \times ULN$  but less than  $3 \times ULN$  (range: 95 IU/L to 118 IU/L) and one of five subjects with a positive anti-AAV5 Nab titer at baseline (anti-AAV5 Nab titer level: 221) had an AST level  $>5 ULN$  (value: 327 IU/L).

There were a total of four subjects with positive anti-AAV5 NAb at baseline who experienced elevated AST levels post-AMT-061 infusion. Only one of these subjects had an AST level  $>2 \times ULN$  (value: 108 IU/L; titer level: 14). All four of these subjects had normal ALT levels post-AMT-061 infusion.

Three subjects with negative anti-AAV5 NAb at baseline had ALT elevations  $>2 \times \text{ULN}$  (range: 89 IU/L to 130 IU/L) and one subject with negative anti-AAV5 NAb at baseline had an ALT elevation  $>3 \times \text{ULN}$  (value: 193 IU/L).

Six subjects with negative anti-AAV5 NAb at baseline had AST elevations  $>2 \times \text{ULN}$  (range: 71 IU/L to 108 IU/L) and three subject with negative anti-AAV5 NAb at baseline had AST elevation  $>3 \times \text{ULN}$  (value: 127 IU/L to 163 IU/L).

One subject with a positive anti-AAV5 Nab level at baseline (titer level 1:3212) experienced an elevated ALT level  $<2 \times \text{ULN}$ . This subject had no elevations in AST post-AMT-061 infusion.

See Table 7 for further laboratory details.

**Table 7. Laboratory Testing**

Lab	High - # of Subjects	Low - # of Subjects	Grade 3-4	Notes	"Critical"
Leukocytes	11	8			
Lymphocytes	0	24	1 Grade 3 low (S242)		
Monocytes	10	--			
Neutrophils	15	0			
Hgb	2	27	1 (S201)	High in S244 and 260	1 subject flagged "critical" for Hgb $<8$ (S201)
HCT	3	20		High in S244, 253, and 260	
Erythrocytes	2	15		High in S213 and 260	
Platelets	7	8		High in 232, 268, 214, 221, 208, 203, 267, 205	
Estimated platelets	Increase d in 2	Decrease d in 6		Increased in S267 and 205	
PT	--	--		Range 11.4 to 19.2 and one subject at 30.9 (S265)	
aPTT	46	1		25 of 46 who had high results were also high at baseline. The low PTT (= 20 sec) was in S259 at 18 months	
INR	16	0	1 (S265)		
Sodium	1	6	1 Grade 3 low (S254)		
Potassium	3	2			
Creatinine	3	2			
Glucose	40	5			
ALT	20	5	1 Grade 3 high (S238)	Doesn't include 4 subjects who had AE of ALT elevation	
AST	24	7	1 Grade 3 high		]]

Lab	High - # of Subjects	Low - # of Subjects	Grade 3-4	Notes	“Critical”
GGT	6	6		6 high GGT excludes 4 subjects who had high baseline	
Albumin	2	0			
Alk Phos	2	7			
Bilirubin	12	0		Grade 1-2	2 subjects flagged “critical” for >2x ULN
AFP	2	--			
CRP	50				
CK	26	2	5 Grade 3-4 (213, 207, 253, 234, 247)		5 subjects flagged “critical” (same as Grade 3-4 subjects)

In the clinical reviewer’s assessment, the clinical laboratory data are acceptable. Most clinical laboratory abnormalities were low grade. There was 1 subject who experienced a grade 3 ALT elevation (related to AMT-061), 1 subject who experienced a grade 3 AST elevation (related to AMT-061), 1 subject who experienced a grade 3 hyponatremia and 5 subjects who experienced grade 3/4 creatine kinase elevations. There was 1 subject who experienced a grade 3 decreased lymphocyte count and 1 subject who experienced a grade 4 decreased hemoglobin (see above for narratives). Both the grade 3 decreased lymphocyte and grade 4 decreased hemoglobin events are unlikely related to AMT-061. However, the grade 3 decreased lymphocyte count may be due to prolonged corticosteroid use—please see section 6.1.12.5 Adverse Events of Special Interest under Adverse Events due to Prolonged Corticosteroid Use for further details. Subject CT-AMT-061-02-(b) (6) experienced a grade 3 elevated international normalized ratio; however, he did not experience any SAEs or AEs qualifying for special notification.

#### Vital Signs

##### Pyrexia

Three subjects had a temperature  $\geq 38^{\circ}\text{C}$ . One subject had a fever on Study Day 1 (infusion-related reaction), one subject had a fever on Days 8-9 (unlikely related), and 1 subject had a fever to  $39.6^{\circ}\text{C}$  on Study Day 8 that normalized to  $37.1^{\circ}\text{C}$  on Study Day 14. An additional two subjects were reported as having three instances of mild, unrelated fever, all with an onset of study day +196 or later.

##### Tachycardia

Thirteen subject experienced tachycardia post-AMT-061 infusion. Tachycardia onset ranged from study day 1 to study day 112. All tachycardic events are considered not related to AMT-061 by the Sponsor. However, two subjects experienced tachycardia on the day of AMT-061 infusion. Per clinical reviewer assessment, both events are considered an infusion related reaction.

##### Blood Pressure

Fifty subjects in the safety population experienced at least one occurrence of hypertension meeting the CTCAE criteria: however, a single event of CTCAE hypertension is not considered to fulfil the criteria for diagnosis of CTCAE hypertension.

There were two subjects who experienced elevated blood pressure for more than 2 visits. Subject CMT-AMT-02-(b) (6) had a grade 2 hypertension for 2 consecutive visits (day 41 and day 50) and returned to grade 1 levels (same as the baseline values) on the third visit (day 55). Subject CMT-AMT-02-(b) (6) had a grade 2 hypertension for 2 consecutive visits (day 8 and day 15) and returned to grade 1 levels (same as the baseline values) on the third visit (day 22).

The clinical reviewer's assessment, there are no significant safety concerns based on the review of the vital signs. The 2 cases of grade 2 hypertension (NCI CTCAE v.5 classification) are not considered to meet the diagnostic criteria for diagnosis of hypertension due to their transient nature

#### **8.4.6 Systemic Adverse Events**

Please see Section 6.1.12.

#### **8.4.7 Local Reactogenicity**

Please see Section 6.1.12.5.

#### **8.4.8 Adverse Events of Special Interest**

The applicant refers to Adverse Events of Special Interest (AESIs) as Adverse Events of Special Notification in this submission. The applicant noted no adverse events of special notification in study CT-AMT-061-01. The clinical reviewer noted a total of 38 adverse events of special interest that occurred to subjects either during or after AMT-061 infusion- 2 subjects who experienced a hypersensitivity reaction, 19 subjects who experienced infusion-related reactions, 1 subject who was diagnosed with hepatocellular carcinoma (HCC), 8 subjects who developed benign or malignant lesions, 4 subjects who developed hepatic steatosis and 3 subjects who experienced mild AE which may have been attributed to prolonged corticosteroid use.

The applicant noted 19 adverse events of special notification in 12 subjects (see below table). Per the applicant, no risk was identified in relation to carcinogenicity, autoimmunity, or off-target expression.

**Table 8. Narratives for Adverse Events Leading to Discontinuation and/or Qualifying for Special Notifications**

Subject ID	AE Preferred Term(s)
(b) (6)	Headache Urticaria Eye pruritus Infusion site reaction Dizziness
	Chest discomfort Dizziness Flushing
	Hypersensitivity
	Pyrexia
	Hepatocellular carcinoma
	Insomnia
	Basal cell carcinoma
	Abdominal pain upper Drug ineffective
	Infusion-related reaction
	Lymphocyte count decreased
	Infusion-related reaction
	Prostate cancer

The clinical reviewer agrees with the applicant that the above noted adverse events should be classified as adverse events of special notification in addition other adverse events noted below. The clinical reviewer noted several other adverse events of special interest below including hypersensitivity reactions, infusion-related reactions, TIA, the development of benign lesions, the development of malignant lesions, adverse events related to prolonged steroids use and hepatic steatosis.

There were no clear differences in adverse events (AEs) between subjects who had positive anti-AAV5 Nab titers and negative anti-AAV5 Nab titers at baseline, with the exception of one subject with Baseline Nab titers of 1:3212 who had no transgene expression and experienced increased bleeds post-treatment. See below for the analysis of adverse events between subjects with positive/negative anti-AAV5 NAb at baseline.

#### Hypersensitivity, Anaphylactic, or Anaphylactoid Reaction

Two subjects (CT-AMT-(b) (6) and CT-AMT-061-02-(b) (6) developed systemic hypersensitivity reactions while receiving the initial infusion. One subject (CT-AMT-02-(b) (6) had an infusion-related reaction. The Applicant considers these events as mild in nature. However, the clinical reviewer's assessment is that subject CT-AMT-02-



(b) (6) experienced a severe hypersensitivity reaction and subject CT-AMT-061-02-  
(b) (6) experienced a moderate hypersensitivity reaction.

Subject CT-AMT-(b) (6) experienced a severe hypersensitivity reaction requiring epinephrine. This subject only received 10% of the AMT-061 dose. On Study Day 1, shortly after the study drug infusion and the infusion was discontinued. The subject experienced flushing, sensation of warmth, shortness of breath, coughing, dizziness, leg cramps and elevated heart rate. The subject was treated with IV diphenhydramine and intramuscular epinephrine, as well as IV methylprednisolone, IV famotidine, and IV sodium chloride. The subject was evaluated in the ER but not admitted and the event resolved the same day.

Subject CT-AMT-061-02-(b) (6) reported a tightness of throat, but no difficulty swallowing, no dyspnea, and no tachycardia during infusion administration on Study Day 1. The subject then experienced swelling of the right neck below the right ear and a mild general itching sensation on the entire body. No swelling or redness was observed and the symptoms of tightness of throat and itching resolved 10 minutes after the infusion ended. The right neck swelling continued and was still visible 8 hours later but to a lesser degree. No treatment was administered for this event. The Applicant considered this event an infusion-related reaction, with tightness of the throat and swelling of the right neck as mild intensity and related to study medication administration. This event was considered resolved, however, the exact time is unknown. Given the symptoms, the clinical reviewer concludes that this was not an infusion related reaction but rather a moderate hypersensitivity reaction definitely related to the investigational agent.

#### Infusion-Related Reactions

Infusion-related reactions were observed in 19 (33%) subjects. Infusions were temporarily interrupted in 3 subjects and resumed at a slower infusion rate after treatment with antihistamines and/or corticosteroids.

Infusion-related reaction: In 7 subjects symptoms occurred during infusion, in 12 subjects after infusion. Symptoms occurring in  $\geq 5\%$  of subjects were: Dizziness, Flu-like symptoms and Headache. Symptoms occurring in  $< 5\%$  of subjects were: Abdominal pain, Abdominal discomfort, Chest discomfort, Chills, Eye pruritus, Fever (Pyrexia), Flushing, Hives (Urticaria), Infusion site reaction, and Tachycardia. Eleven subjects recovered on the day or day one after infusion. Eight subjects recovered within 8 days after infusion.

Of note, Subject CT-AMT-(b) (6) experienced a moderate infusion-related reaction. Subject CT-AMT-061-02-(b) (6) began to experience facial flushing 10 minutes after the infusion began on Study Day 1 and increased monitoring was initiated. The flushing resolved after 3 minutes. Then the subject started to shiver, reported a cold sensation, and the blood pressure increased to 150/81 mmHg. The study medication administration was then interrupted. The subject did not have tachypnea and oxygen saturation was 100% on room air. The subject then received hydrocortisone, chlorphenamine, and 5L of oxygen as a precaution. The subject's symptoms fully resolved. The study medication infusion was restarted at a slower infusion rate and was completed with no additional symptoms or complaints. The Applicant recorded these events as a mild infusion-related reaction related to the investigational agent with facial flushing, feeling cold, shivers, and rise in blood pressure. This event was considered resolved on the same day. Per clinical

reviewer assessment, this is a moderate infusion-related reaction definitely related to the investigational agent.

#### Treatment-Emergent HCC

Subject CT-AMT-061-(b) (6) developed hepatocellular carcinoma in Study CT-AMT-061-02 in a 68-year old male subject with multiple risk factors, including a history of HBV (1983), HCV (2003; eradicated 2016), alcohol use, and fatty liver disease. The subject did not show evidence of significant fibrosis/cirrhosis or steatosis at screening or before treatment with AMT-061.

On Study Day 365, an ultrasound per study protocol revealed a subcapsular lesion, prompting further assessment leading to the diagnosis of HCC. On Study Day 443, surgical excision of the lesion, the surrounding tissue, and a second lesion identified on an intraoperative ultrasound, was performed. The event of HCC was considered severe and unresolved as the final event outcome.

Results of the integration site analysis (performed by (b) (4)) were received on Study Day 512 and revealed 56 unique integration sites in the HCC and 39 unique integration sites in the HCC-adjacent sample, respectively, which indicated that <0.03% of the cells in the HCC and HCC-adjacent tissues had AAV integration. A dominant integration site was not identified, as would be expected had the AAV vector integrated and led to clonal expansion of the tumor cells. Whole genome sequencing (WGS) identified five additional integration sites and confirmed the lack of a dominant integration site in the HCC sample. WGS also revealed genetic alterations on chromosomes 1, 8, and on the X-chromosome of the HCC sample, typical for HCCs. WGS and RNA sequencing indicated a pattern of gene expression in the HCC-adjacent sample more characteristic of a premalignant state than of healthy liver tissue. Finally, miRNA analysis identified genes known to be associated with the progression and development of HCC.

On February 25, 2022, the subject underwent a liver transplant and the investigator confirmed that this would be considered the final resolution/treatment of the event (CT-AMT-061-02, 2-year CSR, Section 14.3.3, [Subject \(b\) \(6\)](#)). The Applicant assessed that mutations in these genes are consistent with HCC risk typical for patients with chronic HCV, which had been present in this patient for years until HCV treatment. Based on these results, it is concluded that while vector integration did occur to a minimal degree, it is unlikely to have been causally related to the development of HCC in the study subject. Four independent external experts reviewed these data and reached the same conclusion.

This safety reviewer agrees that, based on the Applicant's integration site analysis, as well as the fact that this subject had other risk factors (HCV, HBV, fatty liver, alcohol use) which may lead to the development of HCC, the event of HCC is unlikely related to the investigational agent although we cannot completely rule out the possibility that AMT-061 caused HCC in this subject.

CMC reviewers investigated this subject's case thoroughly and concluded that the relationship to AAV integration is unlikely. There was a similar amount of AAV in the tumor and normal tissue; however, there was not enough material to do a thorough analysis of the integration sites therefore AAV cannot be completely ruled out. In

addition, the integration site analysis did not indicate a dominant integration site as would be expected if the AAV vector had integrated and led to clonal expansion of the tumor cells.

Of note, 37 of the 57 subjects in the safety population had a history of 1 or more risk factors for the development of HCC.

Notably, in 34 subjects, infection with HCV, one of the most important risk factors associated with development of HCC, was present either alone or in combination with other risk factors as follows:

- Infection with HCV: 20 subjects
- Concomitant infection with HCV and HBV: 5 subjects, of which 2 subjects had additional risk factors (1 each of advanced age and liver steatosis)
- Infection with HCV and advanced age: 6 subjects, of which 1 subject had a history of diabetes
- Infection with HCV, liver steatosis, and obesity: 2 subjects
- Infection with HCV and diabetes: 1 subject
- Liver steatosis: 2 subjects
- Obesity: 1 subject

Subjects with any preexisting risk factors for HCC will receive abdominal ultrasound screenings and will be monitoring regularly (e.g., annually) for alpha-fetoprotein elevations in the 5 years following administration.

In addition, two colonic adenomas were discovered in this subject on Study Day 561. The applicant described this AE as mild and unrelated to AMT-061. This was considered resolved on the same day (Study Day 561). Per clinical reviewer's assessment, the development of these colonic adenomas were unlikely related to AMT-061. Two other subjects (CT-AMT-061-02-(b) (6) and CT-AMT-061-02-(b) (6) developed colonic adenomas post-AMT-061 infusion. See below for further information on these subjects.

### Thrombosis

There was no reported event of thrombosis; however, one subject experienced a transient ischemic attack (Subject CT-AMT061-02-(b) (6)) on Study Day 229 post-AMT-061 infusion. Thrombolysis was considered for this episode and found not necessary. The subject also experienced premature atrial, and some ventricular, contractions, however no atrial fibrillation was detected on the ECG. Magnetic resonance angiography of carotids showed no stenosis. Computerized tomography (CT) scan revealed soft plaque in the right carotid bulb without significant stenosis in internal carotid artery, some atherosclerosis in the cavernous segments of the internal carotid artery, bumpy intracranial distal M2 branches (presumably atherosclerotic) and no proximal occlusions, intracranial hemorrhage and no signs of recent ischemia. The subject received oral clopidogrel and the event was considered recovered/resolved on the same day.

FIX levels ranged from 4%-37.3% from Study Day 1 to Month 6. The subject's FIX activity over 18 months of steady state expression from Month 7 to Month 24 ranged from 34.2% to 52.6% and FIX activity measured at Month 18 was 42.5% and at Month 24 was 34.2%. On Post-treatment Study Day 218 (09Sep2020), prior to the current TIA, the subject's FIX activity level was 40%. The subject was discharged from the hospital on Study Day 230 and on Study Day 247, the factor IX level was 45%. The applicant assessed the TIA as unlikely related to AMT-061, although the contributory role of AMT-061 cannot be excluded.

This subject had a history of TIAs, including a similar TIA 1 year prior to dosing in November 2018. This subject also had a complicated medical history which included cardiovascular disease, including hypertension, iliac artery aneurysm, coronary artery disease, carotid atherosclerotic plaques without stenosis, aortic valve stenosis, aortic valve replacement, arteriosclerosis coronary artery and a coronary artery bypass graft.

In the opinion of the clinical reviewer, this TIA was likely unrelated to AMT-061 and more likely attributed to this subject's complicated medical history- which includes past TIAs and cardiovascular disease. In addition, this subject's FIX activity was 40% on Study Day 218 (nine days prior to TIA) and increased FIX activity would be expected if AMT-061 caused the TIA. In addition, this subject developed mediastinal lymphadenopathy on Day 735

On Study Day 735, this subject then experienced an SAE of growing aneurysmal dilatation of the right internal iliac artery and mediastinal lymphadenopathy. This aneurysmatic dilatation of the internal was found prior to receiving AMT-061; however, CT angiography on Study Day 925 should show slow growth of the right sided dilatation, dissection of the internal iliac right sided and hematoma with loss of contrast in the abdominal aorta (possible ulcer or possible dissection). Embolization occurred with supplementation of FIX and under apixaban. The applicant considered the event of the growing aneurysmal dilatation of the right internal iliac artery to be moderate in severity and not related to AMT-061. The applicant considered the mediastinal lymphadenopathy to be moderate in severity and possibly related to AMT-061, although did not provide a rationale for this attribution.

#### Subjects who developed benign and/or malignant lesions post-AMT-061

##### Subject CT-AMT-061-02-(b) (6)

This subject experienced multiple AEs post AMT-061 including a hyperplastic polyp, a nodule at the ileocecal valve (gastrointestinal neoplasm), worsening of nodule at ileocecal valve (gastrointestinal lymphoma), intracranial meningioma, and a pancreatic lesion (possible neuroendocrine tumor).

This subject is a 70-year-old male with a history of arterial hypertension and hypercholesterolemia and did not have any recorded history of cancer. He received AMT-061 on (b) (6). On Study Day 203 post AMT-061 infusion, the subject underwent a routine colonoscopy which identified polyp and gastrointestinal neoplasm (nodule at the ileocecal valve). The applicant assessed both events as mild in severity and not related to AMT-061. Both events were considered not recovered/not resolved. On Study Day 420, this subject had a repeat colonoscopy and worsening of the nodule at the ileocecal valve was reported and incorrectly coded as gastrointestinal lymphoma.

Follow-up information from the investigator in June 2022 clarified that the subject had a diagnosis of colon adenoma since (b) (6) (prior to CT-AMT-02 enrollment) and that the event of the nodule at the ileocecal valve did not represent a gastrointestinal lymphoma.

A PET scan was performed on Day 427 to further assess the colon adenoma and a nonspecific nodular focus of uptake was noted at the pancreatic body/tail. On Day 437, a pancreas CT scan did not show mass or other abnormal enhancement within the pancreas corresponding to the DOTATE-avid lesion seen on the previous PET/CT scan. The tissue corresponding to the area of uptake identified during the scan on Day 427 enhanced in a similar fashion to the adjacent pancreatic parenchyma and was also similar in contour compared to previous CT scans. Two follow-up pancreatic CT scans found no significant change in morphology of the pancreas and no focal lesion. The gastroenterologist confirmed that there were no abnormalities. On Study Day 450, the applicant reported an event of meningioma of moderate severity and not related to AMT-061. On Study Day 547, the applicant reported an event of peripheral arterial occlusive disease, which was moderate in intensity and considered unrelated to AMT-061.

This clinical reviewer concurs with the Applicant's assessment that the identified lesions are benign and not likely related to AMT-061. The clinical reviewer concurs with the Applicant's assessment that the identified peripheral arterial occlusive disease is likely not related to AMT-061 and may be related to this subject's multiple pre-existing co-morbidities including hypertension and hypercholesteremia.

Subject CT-AMT-061-02-(b) (6)

This subject is a 49-year-old male with a medical history of arthropathy and HCV. He received AMT-061 on (b) (6). On Study Day 162 post-AMT-061, a palpable lump behind the left nipple was noted and subsequently proven noncancerous by ultrasound. This event was considered resolved by Study Day 561. The applicant considered this event as not serious as it was confirmed to be non-cancerous by ultrasound and reported as unrelated to AMT-061.

This clinical reviewer concurs with the Applicant's assessment that the benign breast mass is unlikely related to AMT-061.

Subject CT-AMT-061-02-1(b) (6)

This subject is a 61-year-old male with a complicated medical history, including arthralgia, arthrodesis (b) (6), basal cell carcinoma (b) (6), chest pain (b) (6), fasciotomy (1992), hemophilic arthropathy, HCV (b) (6), hiatus hernia, hypercholesterolemia, hypertension, knee arthroplasty (b) (6), onychomycosis, osteopenia, post-traumatic neck syndrome, proteinuria (b) (6), seborrheic dermatitis, skin neoplasm excision (b) (6), type 2 diabetes mellitus, vitamin D deficiency, and gastroesophageal reflux disease. He received AMT-061 on (b) (6).

. On Study Day 184 and Study Day 261 post AMT-061, PSA levels were in normal range. On Study Day 284, MRI revealed 2 suspicious nodules. On Study Day 342 post AMT-061, a transrectal ultrasound-guided biopsy was performed and revealed prostatic adenocarcinoma less than 5% in 1 core. Urology recommended active surveillance for the subject with every 6 months PSA laboratory testing and a repeat MRI in one year.

This event of prostate adenocarcinoma is unlikely related to AMT-061 as this subject had symptoms of increased urinary frequency with nocturia prior to AMT-061 infusion in September 2019

Subject CT-AMT-02-(b) (6)

This subject is a 53-year-old male with a more than 4-year history of skin abnormalities which had started to itch, develop crusts, and was unresponsive to triamcinolone. He received AMT-061 on (b) (6).

On Study Day 540, this subject presented to the hospital with severe left leg cellulitis and was hospitalized. The subject was treated with antibiotics and the surgical service consultation confirmed no evidence of compartment syndrome or necrotizing fasciitis. The cellulitis was considered resolved on Study Day 559. On Study Day 547, the subject underwent a skin biopsy on the ventral side of the right upper leg, which was described as a nummular, pink, shiny plaque with some crust centrally on the ventral side of the right upper leg. This lesion was found to be basal cell carcinoma. The applicant considered the event of cellulitis of the left leg as severe and unlikely to be related to AMT-061. The Applicant considered the event of basal cell carcinoma as moderate in severity and unlikely related to the study medication.

This clinical reviewer concurs with the Applicant's assessment that this subject's severe cellulitis and basal cell carcinoma is unlikely related to AMT-061 due to his underlying, long-standing history of skin abnormalities.

Subject CT-AMT-(b) (6)

This subject is a 69yo male with a history of hemophiliac arthropathy who experienced tubular adenomas, a gallbladder polyp and bilateral renal cysts. The tubular adenomas were identified on Study Day 85. The Applicant considered these adenomas mild, recovered/resolved on Study Day 85 and not related to AMT-061. The bilateral renal cysts were identified on Study Day 169 with non-obstructive renal pyramidal calcifications (nephrocalcinosis). The Applicant considered the bilateral renal cysts, mild, ongoing and unrelated to AMT-061. The gallbladder polyp was noted on Study Day 940 and the applicant considers this event mild, ongoing and unrelated to AMT-061.

This clinical reviewer agrees with the Applicant that the above noted tubular adenomas (benign), bilateral renal cysts and gallbladder polyp are likely unrelated to AMT-061. The bilateral renal cysts were identified in the setting of nephrocalcinosis which may be a risk factor for the presence of simple renal cysts. The tubular adenomas were identified on Study Day 85- along with internal hemorrhoids and sigmoid and ascending diverticulosis. Diverticulosis is associated with a higher risk of polyps and adenomas. This subject also has a history of cholelithiasis (event on Study Day 169) and hepatic steatosis (Study Day 940), both of which are associated with gall bladder polyps.

Subject CT-AMT-061-02-(b) (6)

This subject is a 73yo male with a history of hemophiliac arthropathy who was noted to have two small nodular injuries at the level of the right lung on Study Day 192. These lesions were identified on imaging during this subject's hospitalization for a SAE of epilepsy (please see above Section 8.4.2). The applicant considered this event to be mild and unrelated to AMT-061. No further information was provided. The clinical reviewer believes that due to the location of these small pulmonary injuries, they are

unlikely related to AMT-061; however, as this event is considered ongoing, will continue to monitor through long term follow-up.

Subject CT-AMT-061-(b) (6)

This subject is a 43 yo male with a medical history of arthropathy who experienced a likely unrelated mild gallbladder polyp on Study day 366. The Applicant described this event as mild, ongoing and unrelated to AMT-061. The clinical reviewer agrees with the assessment that this gallbladder polyp is likely unrelated to AMT-061 as it was identified in the setting of hepatic steatosis (Study Day 366), which is a risk factor for the development of gall bladder polyps.

Subject CT-AMT-02-(b) (6)

This subject is a 31yo male with a medical history of hemophilic arthropathy. A non-clinically significant liver cyst was identified in the anterior right lobe on Study Day 548. The Applicant considered this event mild, ongoing and unrelated to AMT-061. The clinical reviewer agrees with this assessment. Hepatic cysts are typically incidental finding on imaging and rarely become cancerous lesions.

Hepatic Steatosis

Subject CT-AMT-061-02-(b) (6) is a 69yo male with a history of hemophilic arthropathy and hepatitis C. Hepatic steatosis was identified in this subject on Study Day 940 with an associated gall bladder polyp. Prior to this, the subject experienced cholelithiasis on Study Day 169.

Subject CT-AMT-061-02-(b) (6) is a 43yo male with a medical history of arthropathy. Hepatic steatosis was identified in this subject on Study Day 366 with an associated gall bladder polyp.

Subject CT-AMT-061-02-(b) (6) is a 22yo male and hepatic steatosis was identified in this subject on Study Day 730.

Subject CT-AMT-061-02-(b) (6) is a 34yo male with a history of hepatitis C. Hepatic steatosis was identified in this subject on Study Day 722.

Two subjects (CT-AMT-061-02-(b) (6) and CT-AMT-061-02-(b) (6) were found to have cholelithiasis on Study Day 513 and Study Day 169 respectively.

The Applicant assessed all four hepatic steatosis events as mild, ongoing and unrelated to AMT-061. The clinical reviewer agrees with the applicant that the hepatic steatosis events are unlikely related to AMT-016. However, AAV5-based gene therapy transfects the liver cells, it cannot be 100% ruled out.

Adverse events due to prolonged steroid use

Nine subjects with ALT elevations received a tapered course of corticosteroids. The mean duration of corticosteroid treatment for elevated ALT levels was 81.4 days. Five of the nine subjects who took corticosteroids for elevated ALT levels also experienced elevated AST levels.

No subjects in the ISS safety population who used corticosteroids to treat elevated transaminase levels reported treatment-emergent SAEs. In this population, there were a

total of 38 AEs related to AMT-061: 24 mild events, 12 moderate events, and 2 severe events (1 ALT increased and 1 AST increased). The most common related AEs were headaches (n = 3), elevated CK (n = 4), and malaise (n = 2). All of these events were considered mild per the applicant.

There were 69 unrelated AEs in this population: 62 mild events, 6 moderate events, and 1 severe event (hypertension). The most common unrelated AEs were joint pain (n = 9; 8 mild, 1 moderate), headache (n = 7; 5 mild, 2 moderate), cold (n = 6; all events mild), and fatigue (n = 3; all events mild).

Only one subject (CT-AMT-061-02-(b) (6)) experienced a NCI CTCAE v.5 Grade 3 decreased lymphocyte count on Study Day 64 that was likely due to corticosteroid use. On Study Day 57, the subject's ALT was 22 U/L, which was 1.69 times the baseline value (13 U/L). On Study Day 59, the subject experienced an adverse event of mild alanine aminotransferase increased (ALT increase [ $> 2$  times baseline value]). On Study Day 61, corticosteroids were administered with a tapering course of oral prednisolone. The ALT increased following the initiation of corticosteroids results showing 23 U/L but remained normal for the duration of the study. On Study Day 71, the event of alanine aminotransferase increased was considered recovered / resolved. The subject completed the taper of prednisolone on Study Day 134. The Grade 3 AE of decreased lymphocyte count resolved on Study Day 93. There were no significant reports of clinical sequelae due to prolonged corticosteroid use.

Below is a breakdown of infusion-related reactions by positive/negative anti-AAV5 NAb status for the seven subjects who experienced individual infusion-related reactions. Five of these seven subjects had positive anti-AAV5 NAb at baseline.



**Table 9. Subjects with Infusion-Related Reactions by Positive/Negative Anti-AAV5 Nab Status (Safety Population)**

Subject ID	Anti-AAV5 Nab Titer at Baseline	AE Preferred Term(s)	Study Day	Medication / Therapy	Severity	Duration of AE (Days)	Outcome of AE
<b>Positive Anti-AAV5 Nab Status</b>							
(b) (6)	558.3	Infusion site reaction, Eye pruritus, Urticaria, Headache, Dizziness	1	Diphenhydramine PO, IV, Hydrocortisone PO	Mild	1	Recovered / Resolved
					Mild	1	
					Mild	1	
					Mild	2	
					Mild	1	
(b) (6)	198.9	Hypersensitivity	1	Diphenhydramine IV, Methyl-prednisolone IV, Famotidine IV, Pinephrine IM, Lactated ringer bolus IV, Demerol IV, NS bolus (0.9%) IV	Moderate	1	Recovered / Resolved
(b) (6)	481.9	Infusion related reaction	1	Chlorophenamine IV Hydrocortisone IV	Mild	1	Recovered / Resolved
	3212.3	Abdominal pain upper	1	None	Mild	1	Recovered / Resolved
	23.3	Infusion related reaction	1	None	Mild	2	Recovered / Resolved
<b>Negative Anti-AAV5 Nab Status</b>							
(b) (6)	< LOD	Dizziness, Chest discomfort, Flushing	1	Benadryl IV	Moderate	1	Recovered / Resolved
					Moderate	1	
(b) (6)	< LOD	Pyrexia	1	None	Mild	1	Recovered / Resolved

AE = adverse event; hr = hour; IM = intramuscular; IV = intravenous; LOD = limit of detection; Nab = neutralizing antibody; NS = normal saline; PO = per os (oral);

All AEs were reported on the day of infusion and resolved on same day, except for the events of infusion related reaction (Subject (b) (6)) and headache (Subject (b) (6)), each of which resolved the day after onset.

Source: Study CT-AMT-061-02 18-month Listing 1.12.1, Listing 3.1.1, Listing 3.4.1, ad-hoc Listing 63.3.

Sponsor's response to clinical IR from 10-24-22, p. 14/23

Mild infusion-related reactions were common and found in 19 subjects. There were two serious hypersensitivity events. Overall, the rate and severity of infusion-related reactions are considered acceptable but patients should be monitored.

Individual infusion reactions occurred in 7 subjects during the infusion and in 12-subjects after the infusion. Symptoms were comprised of dizziness, flu-like symptoms, abdominal pain, infusion-site reaction, chills, and headaches. All symptoms resolved without sequelae. Eleven subjects recovered on the day or day one after infusion. Eight subjects recovered within 8 days after infusion. Two subjects had hypersensitivity reactions (see above for extended narratives) shortly after AMT-061 infusion, and one of these subjects

received epinephrine. Infusion-related reactions occurred more often in subjects positive for anti-AAV5 NAb at baseline.

Other AEs of interest included elevations in transaminase levels (please see Section 6.1.12.6 below for further details on laboratory data).

#### Adverse Events Occurring in Subjects with Anti-AAV5 NAb at Baseline

Twenty-four subjects were positive for anti-AAV5 NAb at baseline. All 24 subjects experienced at least one AE. Twenty-one of these subjects were enrolled in the Phase 3 trial, CT-AMT-061-02 and 3 subjects of these subjects were enrolled on the Phase 2b trial, CT-AMT-061-01.

Overall, the most common non-laboratory AEs experienced by subjects with positive anti-AAV5 NAb were arthralgia (n = 9 subjects, 38%), nasopharyngitis (n = 7 subjects, 29%), headache (n = 6 subjects, 25%), back pain (n = 5 subjects, 21%), fatigue (n = 5 subjects, 21%), pain in extremity (n = 5 subjects, 21%), infusion-related reaction (n = 5 subjects, 21%), C-reactive protein increase (n = 4 subjects, 16%), diarrhea (n = 4 subjects, 16%), influenza-like illness (n = 4 subjects, 16%), nausea (n = 4 subjects, 16%), oropharyngeal pain (n = 4 subjects, 16%), upper abdominal pain (n = 3 subjects, 9%), anemia (n = 3 subjects, 9%), influenza (n = 3 subjects, 9%), and upper respiratory tract infection (n = 3 subjects, 9%).

Sixteen of 24 subjects who were seropositive for anti-AAV5 NAb at baseline experienced a total of 37 AEs that were considered related to AMT-061. The most common non-laboratory AEs in this sub-population were headaches (n = 3 subjects, 19%), hypersensitivity reactions (n = 2, 13%) and nausea (n = 2, 13%). All of these non-laboratory AEs were considered mild except for one hypersensitivity reaction.

#### Adverse Event Occurring in Subjects Without Anti-AAV5 NAb at Baseline

Thirty-three subjects were negative for anti-AAV5 NAb at baseline and experienced a total of 302 AEs post-AMT-061 treatment. Two-hundred and thirty-four AEs (78%) were mild, 59 (19%) AEs were moderate and 8 (3%) AEs were severe. Some of the most common non-laboratory AEs experienced by subjects without anti-AAV5 NAb at baseline were headache (n = 13 subjects, 39%), arthralgia (n = 11 subjects, 33%), fatigue (8 subjects, 24%), flu-like symptoms (n = 4 subjects, 12%), back pain (n = 4 subjects, 12%) and diarrhea (n = 2 subjects, 6%).

Twenty-two of the 33 subjects who were negative for anti-AAV5 NAb at baseline experienced a total 57 AEs that were considered related to AMT-061. The most common non-laboratory AEs in this sub-population were headache (n = 6 subjects, 27%), flu-like symptoms (3 subjects, 14%), fatigue (n = 3 subjects, 14%), malaise (n = 2 subjects, 9%), joint pain (n = 2 subjects, 9%), achiness (n = 2 subjects, 9%), chills (n = 2 subjects, 9%), dizziness (n = 2 subjects, 9%) and nausea (n = 2 subjects, 9%).

In this population, the most common non-laboratory AEs that were considered related to AMT-061 infusion were mild in nature with the exception of 5 subjects who experienced 8 moderate events, including headache (2 events), joint pain (2 events), chest tightness

(12%, 1 event), flushing (12%, 1 event), dizziness (12.5%, 1 event) and decreased Factor IX activity (12.5%, 1 event).

Please see below for further information on elevated ALT levels in subjects with positive anti-AAV5 NABs at baseline.

Reviewer's comments:

*There was no clear difference in AEs between subjects who had positive anti-AAV5 NAB titers and negative anti-AAV5 NAB titers at baseline, with the exception of one subject with baseline NAB titers of 1:3212 who had no transgene expression and experienced increased bleeds post treatment.*

*Of the seven subjects who experienced infusion reactions (including one hypersensitivity reaction), five occurred in subjects who were seropositive for anti-AAV5 NABs at baseline. Titer levels in these subjects ranged from 1:23 - 3212. The subject with the anti-AAV5 NAB titer level of 1:3212 at baseline experienced a severe hypersensitivity reaction requiring epinephrine.*

The safety of AMT-061 in subjects who are seropositive for anti-AAV5 NABs versus subjects who are seronegative for anti-AAV5 NABs will be further evaluated in the safety postmarketing study (See below section 11.6).

## **8.5 Additional Safety Evaluations**

### **8.5.1 Dose Dependency for Adverse Events**

Not applicable; each subject received the same dose of AMT-061 at  $2 \times 10^{13}$  gc/kg.

### **8.5.2 Time Dependency for Adverse Events**

Corticosteroids were given to 9 subjects for liver enzyme elevation. Please see Section 6.1.12.6.

### **8.5.3 Product-Demographic Interactions**

Not applicable

### **8.5.4 Product-Disease Interactions**

Not applicable

### **8.5.5 Product-Product Interactions**

Not applicable

### **8.5.6 Human Carcinogenicity**

Please see Section 6.1.12.4.

### **8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Not applicable.

### 8.5.8 Immunogenicity (Safety)

No inhibitors to FIX were noted.

### 8.5.9 Person-to-Person Transmission, Shedding

#### AAV Vector Shedding in Semen

A subject was considered to be no longer shedding vector DNA if they had a negative laboratory result for 3 or more consecutive assessment timepoints postdose.

In Study CT-AMT-061-01, clearance of vector DNA from semen, indicating the absence of shedding, was determined for 2 subjects. The earliest that subjects were considered to be no longer shedding vector DNA from semen was 26.1 weeks (individual values of: 26.1 and 26.3 weeks) after etranacogene dezaparvovec treatment (CT-AMT-061-01 3-year CSR).

In Study CT-AMT-061-02, clearance of vector DNA from semen, indicating the absence of shedding, was confirmed in 32/54 (59.3%) subjects during the Post-treatment Period. The earliest that subjects were considered to be no longer shedding vector DNA from semen was 6 weeks postdose (1.9% of subjects [95% CI: 0.3, 12.4]). Median time to absence of shedding was 47.3 weeks (95% CI: 36.0, NE). The proportion of subjects testing negative increased at a continuous rate until Week 80, at which time 59.4% of subjects (95% CI: 46.7, 72.5) reached absence of shedding from semen; the proportion was the same at Week 96 (Month 24) (CT-AMT-061-02 2-year CSR, Table 3.7). Additionally, the majority (51/54) of subjects had a negative test result (ie., result < LOD) at their most recent testing.

#### AAV Vector Shedding DNA in Blood

In Study CT-AMT-061-01, clearance of vector DNA from blood, indicating the absence of shedding, was determined for 2 subjects during the Post-treatment Period. The earliest that subjects were considered to be no longer shedding vector DNA from blood was 31.1 weeks (individual values of: 31.1 and 78.3 weeks) after treatment with etranacogene dezaparvovec. Mean time to absence of shedding was 54.71 weeks.

In Study CT-AMT-061-02, clearance of vector DNA from blood was confirmed in 30/54 (55.6%) subjects following etranacogene dezaparvovec treatment. The earliest that subjects were considered to be no longer shedding vector DNA from blood was 17 weeks postdose (1.9% of subjects [95% CI: 0.3, 12.4]). Median time to absence of shedding was 52.3 weeks (95% CI: 48.3, NE). The proportion of subjects testing negative increased at a continuous rate until Week 78, at which time 55.8% of subjects (95% CI: 43.1, 69.3) reached absence of shedding from blood; the proportion was the same at Week 96 (Month 24). Additionally, the majority (53/54) of subjects had a negative test result (ie., result < LOD) at their most recent testing.

The clinical reviewer believes the AAV vector DNA shedding data from both trials CT-AMT-061-01 and CT-AMT-061-02 is acceptable. The majority of subjects had a negative test result for shedding of the AAV vector in blood and in semen (ie.- result <LOD) at their most recent testing. In AMT-061's prescribing information, patients are

told not to donate blood, organs, tissues or cells for transplantation. Please see the Clinical Pharmacology review memo for further review of the AAV vector DNA shedding.

## **8.6 Safety Conclusions**

### Safety

Overall, the safety profile of AMT-061 is acceptable. There were a total of 575 adverse events (AEs) based on the clinical reviewer's assessment. Most subjects experienced mild or moderate AEs. Sixty-five of the 575 adverse events were reported as at least possibly related to AMT-061. The applicant reported 18 SAEs in 15 subjects from both the Phase 2b trial-CT-AMT-061-01 and the Phase 3 trial-CT-AMT-061-02. One of these fatal SAEs was fatal (see above description in Section 8.4.1). In the clinical reviewer's assessment, none of the SAEs are attributed to AMT-061.

One death due to cardiogenic shock was reported in a subject with a history of atrial enlargement, atrial fibrillation, and atrial hypertension. This death was unlikely due to AMT-061 and more likely due to this subject's multiple underlying comorbidities.

The most common adverse reactions (incidence  $\geq 5\%$ ) were elevated ALT/AST, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, malaise, and fatigue. Individual infusion reactions occurred in 7 subjects during the infusion and in 12 subjects after the infusion. Nineteen of the 24 subjects with ALT elevations also had related AST elevations.

There was one subject who developed HCC and underwent tumor resection on Study Day 443. The HCC was investigated thoroughly and the relationship to AAV was not proven, particularly as the integration site analysis did not indicate a dominant integration site. However, as AMT-061 targets transgene expression in the liver, there may be a potential risk of HCC. The package insert notes potential risks of hepatotoxicity and HCC.

Although no significant association between anti-AAV 5 NAb and safety was observed, one subject with high titers experienced significant bleeding following treatment.

In conclusion, AMT-061 was well tolerated with an acceptable safety profile. However, given that one subject with high anti-AAV 5 NAb titers experienced significant bleeds following treatment with AMT-061, the Applicant will be required to conduct a safety PMR study to evaluate whether there is an association between pre-existing anti-AAV 5 and serious risk of bleeding due to lack of pharmacologic effect.

## **9. ADDITIONAL CLINICAL ISSUES**

### **9.1 Special Populations**

Not Applicable.

#### **9.1.1 Human Reproduction and Pregnancy Data**

Clinical studies evaluating AMT-061 required the use of contraception for the duration of the study. All subjects in Studies CT-AMT-060-01 and CT-AMT-060-02 were male, therefore no data exist on the effects of AMT-061 on pregnancy in a controlled setting.

### **9.1.2 Use During Lactation**

No data exist on the effects of AMT-061 on lactation in a controlled setting.

### **9.1.3 Pediatric Use and PREA Considerations**

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

### **9.1.4 Immunocompromised Patients**

Not applicable.

### **9.1.5 Geriatric Use**

The clinical studies included a total of 6 geriatric subjects with hemophilia B, aged 68 to 75 years at time of enrollment. No meaningful differences in the safety and efficacy profile were observed in these subjects compared to subjects aged 18 to 65 years, and no dose adjustment was made.

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

Not applicable.

## **10. CONCLUSIONS**

HEMGENIX has demonstrated efficacy with reduction in ABRs. The mean ABR during Months 7-18 was 1.9 bleeds/year with a 95% confidence interval (95% CI) of (1.0, 3.4), compared with a mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period.

The most common adverse events included elevations in ALT/AST, infusion reactions, malaise and fatigue. There is a concern related to increased risk of bleeding in patients with pre-existing anti-AAV 5 NAbs based on data from a single subject with very high NAb titers. This risk will be evaluated in a safety PMR study using a validated assay (see Section 11c). There is a potential for hepatocellular carcinoma, which is adequately described in the label, and will be evaluated in the 15-year long-term extension study. The safety profile is acceptable.

Thus, considering the magnitude of the effect on bleeding events, and the fact that the risks are generally mild, infrequent, and/or easily mitigated, the overall benefit-risk profile favors approval of HEMGENIX in patients with Hemophilia B who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

## **11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS**

### **11.1 Risk-Benefit Considerations**

See Table 10.

Table 10. Risk-Benefit Considerations and Recommendations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Hemophilia B is a hereditary bleeding disorder characterized by recurrent bleeding, which if left untreated leads to chronic arthropathy, muscular atrophy, and deformities.</li> <li>Treatment of bleeds may delay these complications but does not prevent them.</li> <li>Primary prophylaxis with regular FIX injections initiated at an early age is the standard of care.</li> <li>The short half-life of FIX replacement products requires frequent lifelong infusions. The psychosocial impact of this commitment can also be debilitating.</li> </ul>	<ul style="list-style-type: none"> <li>Hemophilia B is a hereditary, life-threatening disease.</li> <li>Hemophilia B can have a debilitating impact on physical and psychosocial well-being.</li> </ul>
<b>Unmet Medical Need</b>	<ul style="list-style-type: none"> <li>Available treatment options requiring lifelong infusions include:</li> <li>Plasma derived and recombinant FIX products are approved for treatment and prophylaxis of hemophilia B</li> </ul>	<ul style="list-style-type: none"> <li>There is an unmet need for the lifelong requirement for FIX replacement infusions in patients with hemophilia B.</li> </ul>
<b>Clinical Benefit</b>	<ul style="list-style-type: none"> <li>Two trials were submitted to evaluate the safety and effectiveness of AMT-061.</li> <li>The main efficacy outcome was a noninferiority test of ABR during Months 7-18 after AMT-061 treatment compared with ABR during the pretreatment lead-in period.</li> <li>The mean ABR during months 7-18 with AMT-061 treatment was 1.9 bleeds/year [95% CI: 1, 3.4] compared to an mean of 4.1 [95%CI: 3.2, 5.4] during the lead-in period.</li> </ul>	<ul style="list-style-type: none"> <li>The evidence of clinical benefit of ABR was demonstrated by reduction of bleeds in the efficacy evaluable period post treatment.</li> <li>ABR represents an appropriate clinical benefit endpoint for subjects with hemophilia B.</li> </ul>
<b>Risk</b>	<ul style="list-style-type: none"> <li>The most common adverse reactions with AMT-061 (incidence ≥5%) were elevated ALT/AST, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, malaise, and fatigue. Individual infusion reactions occurred in 7 subjects during the infusion and in 12 subjects after the infusion.</li> <li>9 subjects with elevated liver enzymes used corticosteroids for a mean of 81.4 days (range: 51 to 130)</li> </ul>	<ul style="list-style-type: none"> <li>AMT-061 has an acceptable safety profile, and the risks are addressed in the package insert</li> </ul>
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>The most substantial risks of treatment are hepatotoxicity, potential for HCC, serious risk of bleeding due to lack of pharmacological effect in subjects with pre-existing NABs, and infusion reactions. Risk management plans include the warnings and precautions and common adverse events listed in the prescribing information. There are two safety PMRs and a 15-year observational study.</li> </ul>	<ul style="list-style-type: none"> <li>The risks can be mitigated through routine medical management, adequate PI and the postmarketing plan proposed by the applicant as well as safety PMRs to assess the risk of bleeding due to lack of pharmacologic effect and pre-existing NABs</li> <li>The data do not support the need for a risk evaluation and mitigation strategy (REMS).</li> </ul>

## 11.2 Risk-Benefit Summary and Assessment

AMT-061 has demonstrated efficacy with reduction in ABRs during the efficacy evaluable period (EEP) compared to baseline ABRs and increased FIX expression. The mean ABR during Months 7-18 was 1.9 bleeds/year [95% CI: 1.0, 3.4] compared to a mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The mean FIX activity levels over time were 39% ( $\pm$  18.7%), 41.5% ( $\pm$  21.7%), 36.9% ( $\pm$  21.4%) and 36.7% ( $\pm$  19.0%) of normal, respectively, at 6, 12, 18, and 24 months.

The most commonly reported AEs included elevations in ALT/AST, infusion reactions, malaise, and fatigue. There is a concern related to increased risk of bleeding in patients with pre-existing anti-AAV5 NABs based on data from a single subject with very high NAB titers. This risk will be evaluated in a safety PMR study utilizing a validated assay (see Section 11c). There is a potential for HCC, which is adequately described in the United States Prescribing Information, and will be evaluated in the 15-year long-term extension study. The safety profile is acceptable.

The benefit risk profile of AMT-061 is favorable.

## 11.3 Discussion of Regulatory Options

The available data support regular approval for the indication of AMT-061 in patients with hemophilia B who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

In AAV vector-based gene therapies, pre-existing neutralizing anti-AAV antibodies may impede transgene expression at desired therapeutic levels. In the clinical studies with AMT-061, an unvalidated clinical trial assay was utilized to assess pre-existing neutralizing anti-AAV5 antibodies. There was no clear association between efficacy and safety and pre-existing NABs. As the clinical trial assay was not validated and the data are limited, no conclusion regarding association of positive NAB titers and efficacy or safety can be reached.

Due to the lack of a valid or reliable anti-AAV assay, and that the available data do not support a requirement of the assay for the safe and effective use of AMT-061, a companion diagnostic was not contemporaneously approved or required for this BLA approval.

## 11.4 Recommendations on Regulatory Actions

In consideration of granting priority review and regular approval to AMT-061 in adults with moderately severe and severe hemophilia B, the clinical team considered the following aspect the magnitude of benefit observed in the ABR.

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well-controlled clinical trial with supportive evidence from the initial clinical investigation and preclinical studies. The compelling evidence of treatment effect in the



single adequate and well-controlled trial is based on a highly persuasive, clinically meaningful, and statistically significant benefit in ABRs in a sufficient number of subjects utilizing the subjects' own ABRs 6 months prior to AMT-061 administration as the control, which is appropriate.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends regular approval of AMT-061, an AAV vector-based gene therapy indicated for the treatment of adults with hemophilia B (congenital FIX deficiency) who:

- Currently use FIX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

Based on the available data, the clinical efficacy and safety reviewers recommend regular approval of AMT-061.

### **11.5 Labeling Review and Recommendations**

The draft label has been modified to reflect the efficacy and safety data presented in this memo. The key change made was to not include the NAb titer assay as part of the indication statement and removal of all titer references throughout the label. Titer data and reference to the NAb titer assay was limited to Section 5.3 and Section 12.6.

The major changes to the draft label pertaining to safety include the following:

- 1) Addition of Anti-AAV5 study added to Section 5.3 for patients to contact CSLB

The major changes to the draft label pertaining to efficacy include the following:

- 1) Removal of all data regarding NAb data
- 2) Removal of p values for ABR, as the FDA does not agree with the superiority claim by the Applicant
- 3) Removal of phase 2 data in the Section 14. Clinical Studies
- 4) Revision of the ABR table to include imputation for those subjects who continued on RP and additional footnotes
- 5) FIX data moved to Section 13. Clinical Pharmacology

### **11.6 Recommendations on Postmarketing Actions**

Anti-AAV5 NAb may decrease or prevent expression of the FIX transduced gene product. There were 21 subjects with a positive NAb to AAV5. One of the subjects had a titer over 1:700 and that subject did not express FIX following AMT-061 treatment. Exogenous FIX prophylaxis was restarted for bleeding episodes in that high titer subject. There was no consistent, clear association between anti-AAV5 NAb and ABR or safety; however, there is uncertainty regarding potential risk of increased bleeding due to high anti-AAV5 NAb titers based on observations from a single subject.

A bleeding episode in hemophilia patients is primarily a lack of effect of treatment, but increased bleeding/lack of effect may also be considered a safety outcome under the definition of an AE in 21CFR600.80 which includes "any failure of expected pharmacological actions." The Food and Drug Administration Amendments Act (FDAAA)

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for one of three purposes. The important potential serious risk of increased bleeding with anti-AAV5 NAb qualifies for a PMR for the purpose of addressing an unexpected serious risk when available data indicates the potential for a serious risk.

The Applicant agreed to the following safety PMRs:

- 1) To validate a sensitive and accurate assay for the detection of anti AAV5 NAb, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher.
- 2) A postmarketing study to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of AMT-061 and pre-existing anti-AAV5 NAb to the AAV5 capsid of AMT-061 with a validated assay (required in PMR 1). The study will evaluate at least 35 patients with hemophilia B treated with AMT-061, to include at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 NAb titers. The assessment will compare pre- and post-treatment ABRs, with a lead-in period to establish the patients' baseline ABR on routine treatment and 18-month follow-up following AMT-061 administration.

**\*\*\*Do Not Change Anything Below This Line\*\*\***