16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan for Study CT-AMT-061-01

STATISTICAL ANALYSIS PLAN FOR STUDY CT-AMT-061-01

Protocol Number:	CT-AMT-061-01
Investigational Drug and Drug Number:	AMT-061 (AAV5-hFIXco-Padua); CCI
Indication:	Hemophilia B
Dosage Form/Dose:	2 x 10^{13} gc/kg AMT-061
Client:	uniQure biopharma B.V.

Protocol Title: Phase IIb, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B.

Date of Issue: 16 Jun 2021

Version: 2.0

Signed Agreement on Statistical Analysis Plan

FINAL SIGN-OFF SIGNATURES

Author: PPD
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Change Log			
Version No.	**Effective Date**	**Reason for the Change / Revision**	**Supersedes**
2.0	31 Mar 2021	Added alpha-fetoprotein and abdominal ultrasound as safety endpoints.	1.0
2.0	02 Apr 2021	Have mentioned that there will be a 2.5-year data cut to support a CSR.	1.0
2.0	02 Apr 2021	Have clarified that the main analysis of bleeding rates will count bleeds irrespective of whether the bleed was treated (with factor IX).	1.0
2.0	02 Apr 2021	Have provided some definitions related to target joints.	1.0
2.0	02 Apr 2021	Beginning with the 2.5-year (data cut) analysis, the contamination rule (for factor IX activity analysis) is hereby refined as follows. Factor IX activity assessments post-AMT-061 that are within 5 half-lives of exogenous factor IX use are considered contaminated and will be excluded from the analysis. Going forward, this 5-half-life contamination rule replaces the 10-day contamination rule. The rationale is to improve accuracy.	1.0
2.0	04 Apr 2021	A section on “Time Windows for Statistical Analysis” is provided to say how values from unplanned or unscheduled assessments can be used if there is a missing assessment at a planned scheduled visit. This was deemed necessary especially in light of delayed or missed visits due to COVID-19.	1.0
2.0	08 Apr 2021	The main ABR analysis is hereby to be excluding (from the person-time “at risk”) any time intervals (during the post-treatment period) for which there was "contamination" (by the 5 half-life rule) due to exogenous factor IX infusions/use. Bleeds during such time intervals are, however, still eligible to be counted.	1.0
2.0	21 Apr 2021	Have provided clearer wording for the definitions of “end of continuous prophylaxis” and the “post-continuous-prophylaxis period”	1.0

2.0	12 May 2021	For the CCI listings and CCI listings, it is now stated "Questionnaires completed during a bleeding episode or within 14 days of the start or resolution of a bleeding episode will be flagged. CCI assessments completed during a joint bleeding episode or within 14 days of the start or resolution of a joint bleeding episode will be flagged." The previous statement was "Questionnaires completed during a bleeding episode or within 7 days of the start or resolution of a bleeding episode will be flagged."	1.0
2.0	05 Jun 2021	Have changed the main ABR analysis to count all (unique) bleeds that occur (after the start point for counting bleeds toward ABR) in the total, irrespective of the investigator's designation of newness and trueness. This will be done for all ABR analyses except for a small number of sensitivity analyses. The reason is that the FDA (Food and Drug Administration) clinical team requested this.	2.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAV	adeno-associated virus
AAV5	adeno-associated viral vector serotype 5
AAV5-hFIXco	recombinant adeno-associated viral vector serotype 5 containing the wild type human FIX gene, codon-optimized for optimal expression in humans, under control of a liver-specific promoter (AMT-060)
AAV5-hFIXco-Padua	recombinant adeno-associated viral vector serotype 5 containing a codon-optimized Padua derivative of human coagulation FIX cDNA (AMT-061)
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
CCI	CCI
cDNA	complementary deoxyribonucleic acid
CRO	Contract Research Organization
CRP	c-reactive protein
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
CCI	CCI
FDA	Food and Drug Administration
FIX	coagulation factor IX
GGT	gamma-glutamyl transpeptidase
gc	gene copies
CCI	CCI
HBeAg	hepatitis B extracellular antigen

HBsAg	hepatitis B surface antigen
HBV DNA	hepatitis B virus deoxyribonucleic acid
HCV RNA	hepatitis C virus ribonucleic acid
CCI	CCI
hFIX	human coagulation factor IX
CCI	CCI
iCSR	interim Clinical Study Report
IFNγ	interferon gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-1β	interleukin-1beta
IL-2	interleukin-2
IL-6	interleukin-6
IMP	investigational medicinal product
INR	International Normalized Ratio
CCI	CCI
IU	international unit
IV	intravenous
LOD	limit of detection
MCP-1	monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NAB	neutralizing antibody
CCI	CCI
CCI	CCI
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class

TEAE	treatment emergent adverse event
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale

Trademark Information

SAS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data for the uniQure Study CT-AMT-061-01. The SAP should be read in conjunction with the study protocol. This version of the SAP has been developed using the CT-AMT-061-01 Protocol (Version 3.0 dated 10 Feb 2021) and the CT-AMT-061-01 CRF (Revision 13.0 dated 02 Apr 2020).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The overall objective of CT-AMT-061-01 is to assess the efficacy of a single dose of 2 x 10^{13} gene copies (gc)/kg AMT-061 on the Factor IX (FIX) activity levels at six weeks after dosing in subjects with severe or moderately severe hemophilia B.

2.2 Study Objectives for CT-AMT-061-01

2.2.1 Primary Objective

To confirm that a single dose of 2 x 10^{13} gc/kg AMT-061 will result in FIX activity levels of ≥ 5% at six weeks after dosing.

2.2.2 Secondary Objectives

- To assess effect of 2 x 10^{13} gc/kg AMT-061 on endogenous FIX activity at 52 weeks
- To assess effect of 2 x 10^{13} gc/kg AMT-061 on discontinuation of previous continuous prophylaxis
- To assess effect of 2 x 10^{13} gc/kg AMT-061 on total usage of FIX replacement therapy
- To assess effect of 2 x 10^{13} gc/kg AMT-061 on the annualized bleeding rate
- To assess effect of 2 x 10^{13} gc/kg AMT-061 on specific types of bleeding events (e.g. spontaneous bleeds, joint bleeds, and traumatic bleeds).

2.2.3 CCI

CCI

CCI [redacted]

2.2.4 Safety Objectives

The safety objectives include monitoring the following:

- Adverse Events (AE)
- Formation of anti-AAV5 antibodies (total immunoglobulin M and immunoglobulin G [IgM and IgG], neutralizing antibodies)
- AAV5 capsid-specific T cell response
- Formation of anti-FIX antibodies
- Formation of FIX inhibitors
- Hematology and serum chemistry results
- Shedding of vector DNA in blood and semen
- Inflammatory markers
- Aspartate aminotransferase (AST) / Alanine aminotransferase (ALT) elevations
- Use of corticosteroids required to preserve FIX activity in the context of AST/ALT elevations
- Abdominal ultrasound
- Alpha-fetoprotein (AFP)

2.3 Study Endpoints for CT-AMT-061-01

2.3.1 Efficacy Endpoints

2.3.1.1 Primary Efficacy Endpoint

- FIX activity level at Week 6 post AMT-061 dose.

2.3.1.2 Secondary Efficacy Endpoints

- Endogenous FIX activity level at Week 6 and Week 52 post AMT-061 dose
- Remaining free of previous continuous prophylaxis during 52 weeks following AMT-061 dosing
- Total usage of FIX replacement therapy until 52 weeks following AMT-061 dosing, excluding ad hoc prophylaxis for invasive procedures
- Annualized bleeding rate after 52 weeks of AMT-061 dosing (including a further break down of the frequency and percentage of spontaneous, traumatic, and joint bleeding events)

2.3.1.3 CCI [redacted]

CCI [redacted]

2.3.2 Safety Endpoints

Secondary safety endpoints include the following:

- AEs
- Hematology and serum chemistry parameters
- ALT/AST levels and corticosteroid use for ALT/AST elevations
- Parameters on antibody formation to AAV5 and hFIX
- AAV5 capsid-specific T cell response
- Inflammatory markers
- Vector DNA in semen and blood
- AFP

Safety endpoints are observed over the 52-week post-treatment follow-up phase and for an additional four years in the long-term follow-up phase. An additional endpoint in the long-term follow-up is abnormal findings on the abdominal ultrasound assessment. Please refer to protocol for more details.

3. STUDY DESIGN AND ANALYTICAL CONSIDERATIONS

3.1 Study Design

3.1.1 Overall Study Design and Plan

CT-AMT-061-01 study is a phase IIb, open-label, single-dose, single-arm, multi-center study to confirm the FIX activity in response to 2 x 10^{13} gc/kg AMT-061 administered to adult subjects with severe or moderately severe hemophilia B. There will be a screening phase, a treatment and post-treatment follow-up phase, and a long-term follow-up phase.

This study will be conducted at approximately 3 sites, for a minimum of 3 subjects. Subject eligibility according to the trial in- and exclusion criteria will be evaluated at Screening and during the period up to baseline (Day 0 pre-IMP) in the CT-AMT-061-01 study.

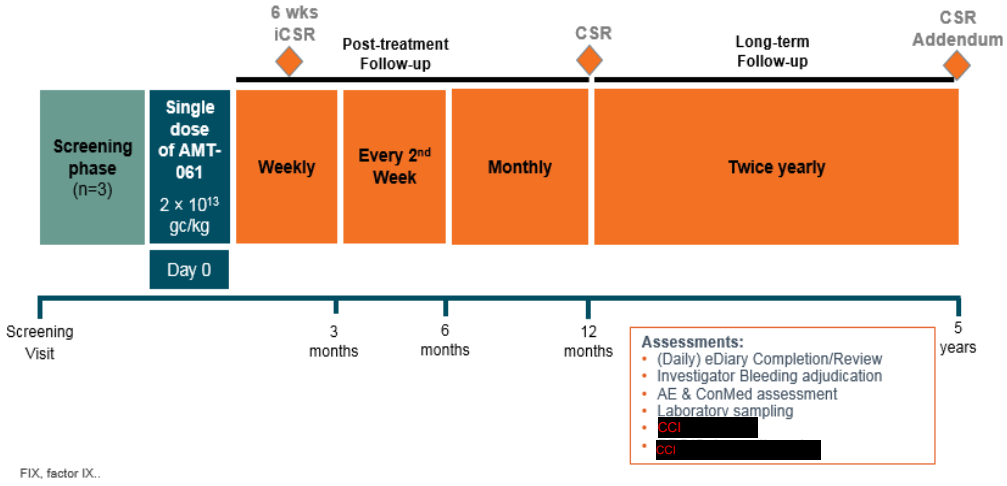
After a maximally six-week screening period, eligible subjects will receive a single intravenous dose of 2 x 10^{13} gc/kg AMT-061. After dosing, the subject will be followed for a total of five years (60 months). The post-dose follow-up visits are planned as follows:

- Weekly up to Week 12
- Every second week from Week 12 to Week 26
- Every month from Week 26 to Week 52
- Every half year from Week 52 to Month 60

All subjects will be monitored for 24 hours (overnight stay) after dosing. Dosing of subjects will be separated by a minimum of 14 calendar days to allow for subject safety monitoring of tolerance to the IMP, detection of AEs, and to ensure appropriate action can be taken in case any acute reactions arise.

The overall study design is summarized and illustrated in Figure 1.

Figure 1 Study Scheme



In CT-AMT-061-01, subjects who withdraw prior to IMP administration or within the first six weeks after IMP administration will be replaced. Subjects who discontinue after six weeks post IMP administration will not be replaced.

If a subject discontinues due to being lost to follow-up, then three documented attempts must be made to contact the subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact).

An interim analysis will be performed after Week 6 post-dose to determine the effect of AMT-061 on FIX activity.

After Week 52 post-dose, efficacy and safety data will be collected on all subjects. These subjects will be followed for another four years for evaluation of efficacy parameters and safety. Please refer to the protocol for more information.

3.1.2 Prior and Concomitant Medications

For the definition of prior medication/therapy, refer to Section 5.6.1 of the protocol. For the definition of concomitant medication/therapy, refer to Section 5.6.2 of the protocol. For operational definitions and detail, see Appendix 1, Data Handling Rules [under the category of "Prior and concomitant medication/treatment"].

3.2 Interim and Final Analyses

After six weeks post-dose, an interim analysis for efficacy will be done using the available data on FIX activity. Safety data will also be evaluated. The results will be reported in an interim Clinical Study Report (iCSR).

After 52-weeks post-dose, efficacy and safety data will be collected on all subjects. The data will be locked, analyzed, and reported in a Clinical Study Report (CSR).

After 2.5-years post-dose, efficacy and safety data will be collected on all subjects. The data will be locked, analyzed, and reported in a Clinical Study Report (CSR) addendum.

After 60-months post-dose, efficacy and safety data will be collected on all subjects. The data will be locked, analyzed, and reported in a CSR Addendum.

3.3 Sample Size

No formal sample size calculation is required for this trial. From a clinical perspective, a minimum of three subjects are considered sufficient to provide a reliable impression of the FIX activity levels and safety profile that will be demonstrated with a single dose of 2×10^{13} gc/kg AMT-061 at Week 6 post-dose. Additional subjects may be added based on the 6-week results and either DMC review or sponsor recommendation. Further information is available in the DMC Charter.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in Standard Operating Procedures (SOPs) of Everest Clinical Research. Detailed data management procedures are documented in the study Data Management Plan, Data Validation Check Specifications, and Integrated Safety Data Review Plan.

5. ANALYSIS POPULATIONS

5.1 Population Definitions

Study CT-AMT-061-01 subjects will consist of adult males with severe or moderately severe hemophilia B. Considering the small sample size (N=3), no analysis population will be defined. No formal statistical analyses will be performed – only descriptive statistics and plots. All available data on treated subjects will be included in all presentations.

6. STATISTICAL ANALYSIS

6.1 Statistical Analysis

No formal, inferential statistical analyses will be performed considering the small sample size used in Study CT-AMT-061-01.

All available data will be presented in plots, tabular displays, and listings to visualize individual effects for selected efficacy and safety measures. If applicable, continuous variables will be summarized with descriptive statistics including: the number of non-missing values, mean, standard deviation, median, minimum, and maximum. In some cases, the standard error of the mean and/or confidence intervals will be presented. Categorical variables will be summarized by number, percent of patients and, if applicable, the number of events.

The planned interim analysis at Week 6 is described in Section 6.2. The statistical analyses for the main CSR (at Month 12) and the 2.5-year CSR are described in Sections 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8. The analyses for the 12-month CSR followed the SAP text (version 1.0, 06 Aug 2018) as it existed at the time of the 12-month analysis. Any revisions to the SAP text that have been made since that time are to be applied to the 2.5-year CSR. The statistical analyses for the 60-month CSR Addendum are described in Section 6.9.

If for any reason additional dose groups (cohorts) of subjects are added to the study, then analyses will be performed separately by cohort.

6.2 Planned Interim Analysis

Six weeks after administration of AMT-061, a data-cleaning round will be performed to provide data for one interim analysis for efficacy using the available data on the primary efficacy parameter - FIX activity. The primary efficacy endpoint will be reported as detailed in Section 6.7.1. FIX activity will be summarized (and listed) by visit, overall and by patient, over the 6-week period since administration of AMT-061. By-subject plots of FIX activity over time will be overlaid with plots of exogenous FIX consumption (time of administration) and with the times of occurrence of bleeding events over the first 6 weeks subsequent to AMT-061 administration.

The ratio of FIX activity (%) to FIX protein (%) will be tabulated. A table will also be provided to summarize the FIX activity (%) by patients with or without pre-existing neutralizing antibodies to FIX. A scatter plot of FIX activity (%) by baseline titer of neutralizing antibodies to

AAV5 will also be presented to show the correlation of baseline titer of neutralizing antibodies to AAV5 and FIX activity at Week 6.

Treated bleeding episodes and annualized treated bleeding rates during the post prophylaxis period (as defined in Section 6.7.2) will be tabulated by the following bleed types: all bleeds, spontaneous, traumatic, medical/dental, and other.

The annualized dose of Factor IX replacement during the post IMP period and the actual exogenous Factor IX use overall and by patient will be tabulated.

The incidence of treatment-emergent adverse events, serious adverse events, TEAEs in descending frequency, related adverse events, and related serious adverse events will be tabulated.

Additional figures showing ALT/AST Levels (U/L) and corticosteroid use for ALT/AST elevations over time, T-cell (AAV5-capsid) ELISPOT ((SFC)/million PBMCs) over time, and inflammatory markers over time will be produced. Subject disposition and demographic data will be listed for all subjects screened and all subjects treated. Baseline characteristics will be listed and will include the following: hemophilia B history, joint status at screening, bleeding history in the year prior to screening, history of previous FIX replacement therapy use, prior medication/therapy, medical and surgical history, and FIX gene sequencing.

Additional efficacy endpoints will be listed and include the following: FIX protein concentration (%).

Safety listings will include the following: Treatment-emergent adverse events, serious adverse events, TEAEs of special notification, potentially clinically significant (PCS) laboratory values, PCS vital signs, other laboratory values, vector shedding, and inflammatory markers.

Table, listing, and figure shells for the 6-week interim analysis can be found in Appendix 4 of the DMC Charter.

The results will be reported in an interim Clinical Study Report (iCSR).

6.3 Data Handling Rules and Definitions, Including Handling of Missing Data

Missing data will be maintained as missing in the safety and efficacy datasets, unless specified otherwise.

Data for Adverse Events Summaries by Severity and Relationship to Study Drug

For the AE summaries by severity (mild, moderate, or severe), an AE with missing severity will be deemed as severe. For the AE summaries by relationship to study drug, an AE with a missing relationship to study drug will be deemed as definitely related. Seriousness cannot be imputed as 'Yes' by default, since this would affect the reconciliation between trial database and registry of SAEs.

Data for Laboratory and Vital Sign Summaries (Continuous Parameters)

Data from unscheduled visits will not be used for by-visit summaries (unless they were assigned to a scheduled visit based on the use of an analysis window as given in Section 6.3 under the subsection "Time Windows for Statistical Analysis"). Data from both scheduled and unscheduled visits will be used for determining incidence of clinically significant values.

Data for All Laboratory Summaries

For safety laboratory values, laboratory values of '>=x' or '<=x' will be taken as the value of x in the analyses. If a laboratory value is prefixed with '>': the available original value +0.001 will be used for table summaries; if a laboratory value is prefixed with '<', then the original value – 0.001 will be used in table summaries.

Study Day and Day of Assessment or Event

Study Day and Day of Assessment or Event definitions are provided in Appendix 1, Data Handling Rules.

Time Windows for Statistical Analysis (to be applied in case of missing scheduled-visit data):

Scheduling difficulties due to the coronavirus disease (COVID-19) pandemic may result in an increased number of missed, delayed, or unscheduled visits. Scheduling difficulties may also result in the performance of assessments at a scheduled visit where performance of the assessment was not originally planned. As an action to mitigate risk, analysis windows will utilize such unplanned assessments as follows. A schema for the assignment of such unplanned assessments to scheduled time points for visit-based endpoint analysis and summary (for visit-based efficacy and safety endpoints) will be defined as follows:

- An unplanned assessment will be assigned to a scheduled visit only if that visit has a missing value for the relevant endpoint and the visit was a scheduled time point for the performance of the assessment per the study protocol.

- Analysis windows for the assignment of unplanned assessments will range from the previous visit at which the endpoint is planned to be collected to the next visit at which the endpoint is planned to be collected.

- The unplanned assessment closest in time within the analysis window (either before or after) will be used to replace a missing assessment for a scheduled visit. If two unplanned

assessments are both the closest in time, with one being before and the other being after, the earlier assessment will be used.

- For visit-based efficacy endpoints, values obtained before the post prophylaxis period will not be candidates to be used for imputing missing values for post-treatment visits that are during the post prophylaxis period.
- For all visit-based endpoints, values obtained prior to treatment will not be used for imputing missing values for post-treatment-period planned assessments.
- Only values from unplanned assessments (not planned assessments) will be used to replace a missing scheduled assessment.
- An unplanned assessment may be used more than once provided it lie within the analysis window for two consecutive scheduled time points at which the assessment was not performed as planned.

For factor IX activity and factor IX protein, only central-laboratory unplanned-assessment values will be candidates for assignment to a scheduled visit that has no central-laboratory value.

An exception to the above windowing rules is that Vital Signs will have values assigned to analysis visits according to the visit windows given in Table 6 (Analysis Study Time Windows for Vital Signs Assessments).

Any other rules for missing data handling will be given in the endpoint-specific sections.

6.4 Subject Disposition and Analysis Populations

No formal analysis population is defined. All available data on treated subjects will be included in the efficacy and/or safety analysis of the data. A disposition table for CT-AMT-061-01 for all subjects will be provided. Summary tables with information regarding protocol deviations and withdrawal reasons (reasons for subject withdrawal from the study) will also be provided.

The data on subject disposition and informed consent will be listed.

6.5 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented. The following descriptive statistics will be included: number of observations, mean, standard deviation, median, minimum and maximum for quantitative data. For qualitative data, frequency counts and percentage will be determined.

Other baseline data including: Medical History and Concomitant Illnesses, Prior and Concomitant Medication/Therapy, Hemophilia B Status and History, History of Bleeding and FIX use, blood pressure, pulse, body temperature, physical examination results, height, and weight will be presented in listings. Gene sequencing results (FIX gene mutation) will be listed.

Medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and listed for each subject

6.6 Investigational Product Exposure

Listings for exposure to investigational product will be presented.

6.7 Efficacy Analyses

All efficacy analyses will be performed for all treated subjects. All presentations will be done on an individual level or by using descriptive statistics. Plots and tabular displays will be created, visualizing individual effects for the selected efficacy measures as specified in the following sections.

6.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the FIX activity level at Week 6 post dose. If FIX replacement therapy was used within 10 days of the Week 6 post-dose time point, the Week 8 post-dose FIX activity level will be used. If FIX activity is still contaminated, then the Week 10 post-dose FIX activity level will be used, etc. This would result in a corresponding postponement of the nominally Week-6 interim efficacy analysis.

FIX activity levels will be presented in % of normal units. Descriptive statistics (across visits) including the mean, standard deviation, median, minimum, and maximum will be presented at six weeks after dosing by subject. Such descriptive statistics will also be displayed by visit across subjects.

The Week 6 primary analysis of FIX Activity will proceed as follows. FIX activity will be summarized (and listed) by visit over the 6-week period since administration of AMT-061. By-subject plots of FIX activity over time will be overlaid with plots of exogenous FIX consumption (start and end times) and with the times of occurrence of bleeding events over the first 6 weeks subsequent to AMT-061 administration.

Plots of FIX activity levels over time per subject will be presented. Descriptive statistics and plots will display uncontaminated results only, i.e. FIX activity levels that are not affected by exogenous FIX use during the trial. Alternatively, the by-subject FIX activity plots may display the time of exogenous FIX use instead of altogether omitting the contaminated FIX results. The required wash out period (in order to consider a FIX activity level to be “unaffected” – i.e. “uncontaminated”) will be 10 days. FIX activity level over six weeks after dosing (by subject) will also be listed and will include a flag for contaminated results. These analyses will be presented in the Week 6 iCSR.

The above-mentioned set of analyses – being done for the Week 6 CSR will also be carried out for the Week 52 main CSR (and 2.5 Years CSR), but over the time period of 52 Weeks (and 2.5 Years) instead of over 6 weeks.

For the Week 6 and 52-Week data-cut analyses, the contamination rule, as stated above, was 10 (discrete) days. Specifically - Factor IX activity levels during the period of use or within 10 days after the end of use of exogenous factor IX replacement therapy were not included in these analyses; the last (calendar) day of use and the subsequent nine (calendar) days are considered to be contaminated. Beginning with the 2.5-year (data cut) analysis, the contamination rule is hereby refined as follows. Factor IX assessments post-AMT-061 that are within 5 half-lives of exogenous factor IX use are considered contaminated and will be excluded from the analysis. Going forward, this 5-half-life contamination rule replaces the 10-day contamination rule. Both the date and time of the exogenous factor IX infusion start and the blood sampling for factor IX activity assessment will be taken into account to determine whether there was contamination. If the factor IX activity assessment was performed prior to the infusion start time, then the assessment is not considered to be contaminated by that infusion. See further detail in the Data Handling Rules Appendix in this document [under the category of "Contamination due to exogenous factor IX (infusion) use"].

6.7.2 Secondary Efficacy Endpoints

FIX activity over 52 weeks (and 2.5 years) (post IMP administration), annualized FIX consumption, Prophylaxis FIX replacement therapy use over 52 weeks (and 2.5 years), and on-demand FIX replacement therapy use over 52 weeks (and 2.5 years) will be presented using descriptive statistics across subjects for each visit and across time for each subject.

Bleeding episodes and annualized bleeding rates in the post-prophylaxis period and type (spontaneous bleeds, joint bleeds, and traumatic bleeds) will also be presented using descriptive statistics. All events that are emergent during the period will be counted.

The end of continuous prophylaxis requires 3 events: (1) study drug was administered, (2) uncontaminated factor IX activity (post-study drug) has since been observed to be >= 5%, and (3) the subject has not used exogenous factor IX for some contiguous time period of at least 15 days after study drug administration. The tenth day of the first 15-day contiguous period where these criteria are met is then taken as the end of prophylaxis. The Post-Continuous-Prophylaxis period begins on the day after the end of continuous prophylaxis. If the field for whether the bleed was treated is missing, then (for conservativeness) it will be assumed that the bleed was treated with factor IX. If the assessment field for newness of the bleed is missing, then (for conservativeness) it will be assumed that the bleed is new. If the assessment field for trueness of the bleed is missing, then (for conservativeness) it will be assumed that the bleed is true. A supplemental analysis will count only bleeds that were treated with exogenous factor IX. A supplemental analysis will count only bleeds that are assessed by the investigator to be new and true bleeds (per entry on the CRF).

In the analysis (from the 2.5-year data cut henceforth), any person-time during the post-treatment period within 5 half-lives subsequent to exogenous factor IX use will not be counted in the time at risk of (having) a bleeding event. Both the date and time of the exogenous factor IX injection start will be taken into account to identify time periods to be excluded. Nevertheless, any bleeds occurring during the post-prophylaxis period should still be counted as events, even if they

occurred during a time interval of "contamination". See further detail in the Data Handling Rules Appendix in this document [under the category of "Contamination due to exogenous factor IX (infusion) use"].

Per subject plots of FIX activity levels over time, and per-subject plots of FIX replacement therapy use over time will be presented.

A plot of the cumulative number of bleeding episodes by type (spontaneous, traumatic, and joint bleeding events) over intervals of time will also be provided.

All data will also be listed.

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6.8 Safety Analyses

6.8.1 Adverse Events

The version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current at the time of database lock will be used to code verbatim terms for AEs for final analysis of the data. A glossary of MedDRA preferred terms used for adverse events reported in the study along with the associated Investigator's verbatim term will be provided.

An adverse event is considered on-treatment (i.e. treatment-emergent) if an event occurs after the dose of study drug, or if the AE worsened during the study after the dose of IMP (intensity and/or severity changed to a worsened grade). An adverse event that begins on the same date as the dose of study drug is treatment-emergent if the AE begins after the time of dose or if the time of AE onset is unknown. Adverse events are collected from the time informed consent is signed.

All treatment-emergent AEs are tabulated by SOC and preferred terms within each SOC according to the MedDRA terminology list. TEAEs will also be tabulated by severity (mild/moderate/severe using the Common Terminology Criterion for Adverse Events severity grades) and by relationship (related/not related) to trial medication, using frequency counts (number of subjects with event and number of events) and percentages. Similar tables will be created for TEAEs leading to premature treatment discontinuation (i.e. for which the infusion of study drug was stopped mid-infusion), deaths, and SAEs.

These summary tables will be presented by decreasing frequency of occurrence based on SOC and Preferred Term.

An AE overview table will be created displaying the number of subjects (and percentage) experiencing an event and the number of events for: Any TEAE, Mild/moderate/Severe TEAE, Related/Unrelated TEAE, Serious TEAE, and TEAEs leading to discontinuation (i.e. for which the infusion of study drug was stopped mid-infusion).

The summary tables will be accompanied by individual subject listings of all AEs, including information on AE number, actual AE description, date/time of start and end of AE, preferred term (MedDRA), SOC (MedDRA), severity, relationship/causality, type of AE, seriousness and outcome. Pre-existing AEs will be flagged. Pre-existing AEs are not considered to be treatment-emergent, except in case of worsening during/after trial treatment (to be collected as separate AE). Separate listings will be created for SAEs and deaths. AEs qualifying for special notification will also be tabulated for those types that can be identified programmatically. The categories of AEs qualifying for special notification are tabulated below.

6.8.1.1 Adverse Events of Special Notification

Table 1 Adverse Events of Special Notification

Adverse Events of Special Notification:
AEs related to the IMP administration procedure
Suspected or confirmed cases of opportunistic or serious infections that in the investigator's opinion might be related to the IMP
Unexpected reactions (e.g., hypersensitivity, immunological, toxic or other as consequence of a change in the construction or function of the viral vector [e.g., generation of replication competent virus])
AEs related to product failure (including lack of efficacy)
AEs related to mandatory concomitant medication (e.g., immunosuppression)
AEs related to medical devices which form part of the product or are used for application of the product
Development of any new/recurrent cancer.

The categories of adverse events qualifying for special notification are shown above. Please see Section 7.2 of the protocol for more detail.

6.8.1.2 Severity of Adverse Event

If an AE changes severity over time, the maximum severity (i.e. intensity) will be reported.

6.8.1.3 Relationship between IMP and Adverse Event

Please refer to section 7.3.2 of the protocol for the definition of Related and Not Related to IMP.

6.8.2 Changes in Abdominal Ultrasound

To monitor subjects for liver fibrosis and potential occurrences of liver malignancies, abdominal ultrasound assessments will be performed. These ultrasound assessments will occur every 6 months beginning with the Month 30 Post-Treatment Visit.

A table will be used to summarize normal and abnormal results at each visit. All abdominal ultrasound data will be listed.

6.8.3 Physical Examination (Including Height and Weight)

Any physical examination abnormality identified at the Screening will be documented in the subject's source documents and on the medical history eCRF. Any physical examination abnormality reported after the Screening Visit for a subject is to be reported as an adverse event. Thus, these will be included in listings of adverse events and summarized in adverse event summaries, if applicable. Abnormalities seen at the Screening examinations will be recorded as Medical History and listed.

6.8.4 Hematology and Serum Chemistry

The following serum chemistry safety laboratory parameters are taken at each visit: Serum electrolytes (sodium, potassium), creatinine, gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), C-reactive protein (CRP), albumin, total bilirubin, and glucose (non-fasting).

The following hematology safety laboratory parameters are taken at each visit: Hemoglobin, hematocrit, platelet count, red blood cells, and white blood cells with differential count (all expressed in % as well as in absolute numbers), activated partial thromboplastin time (aPTT) and prothrombin time (or INR [International Normalized Ratio])).

If there are multiple laboratory values for the same parameter at pre-dose of a visit or within the same post-dose study time window (if applicable) at a visit, the last value will be chosen for analysis.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment and for the pre-dose value and change from baseline at each post-baseline visit for scheduled lab assessments of continuous laboratory variables will be tabulated.

Table 2 Lab Parameters

Hematology	
Hemoglobin	White blood cells
Hematocrit	aPTT
Platelet count	Prothrombin time
Red blood cells	
Serum Chemistry	
Sodium serum electrolytes	ALP
Potassium serum electrolytes	C-Reactive Protein
Creatinine	Albumin
gamma-glutamyltransferase	Total Bilirubin
AST	Glucose (non-fasting)
ALT	
Coagulation	
aPTT	
PT	
Serology	
HIV 1/2 antibody differentiation	Antibodies detected/ not detected
HIV 1/2 screen	Reactive/Non-reactive
HBsAG	HBV DNA
	HCV RNA
Local Laboratory	
AST	
ALT	

A Clinically Significant Laboratory Abnormality as identified by the investigator after the study drug is administered will be recorded as an Adverse Event and tabulated as an AE in the AE analysis. Abnormalities occurring prior to the drug administration will be noted in medical history and presented in a data listing.

All laboratory data will be stored in the database with the units in which they were originally reported. Laboratory data not reported in International System of Units (SI units; Système International d'Unités) will be converted to SI units before data analysis.

The baseline measurement for a laboratory parameter will be the last available measurement prior to the study drug administration.

Table 3 Protocol-Recommended Study Time Window for Clinical Lab Assessments

Protocol-Recommended Study Time Window	Protocol-Recommended Time Interval for the Study Time Window
Post IMP 1 hour	±15 minutes
Post IMP 2 hours	±15 minutes
Post IMP 3 hours	±15 minutes
Day 1	±15 minutes
Day 3	±1 day
Week 1 to Week 12	±2 days
Week 14 to Week 26	±3 days
Week 31 to Week 48	±5 days
Week 52	±5 days
Month 18 to Month 90	±14 days

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment and change from baseline at each post-baseline visit for scheduled lab assessments of continuous laboratory variables will be tabulated. Data from unscheduled visits will not be used for the by-visit summaries (unless they were assigned to a scheduled visit based on the use of an analysis window as given in Section 6.3 under the subsection "Time Windows for Statistical Analysis"). Data from both scheduled and unscheduled visits will be listed. Both scheduled-visit data and unscheduled-visit data are candidates for clinically significant values. Percentages of subjects in each maximum post-baseline grade for a treatment will be calculated for each pre-dose grade for the treatment and also for all baseline grades combined. Laboratory abnormal values on-treatment will be flagged as High or Low values based on laboratory reference ranges provided by the laboratory that provides the respective laboratory data. The reference ranges for the central laboratory (Medpace) are provided in Appendix 4. These flags along with the reference ranges will be provided in the laboratory data listings.

Potentially Clinically Significant Laboratory Values Above/Below a Clinically Relevant Threshold on-treatment, based on CTCAE 4.03 and other criteria, will be identified based on the following thresholds:

Table 4 Potentially Clinically Significant (PCS) Laboratory Parameter Criteria

Central Laboratory	Post Baseline Criteria
Serum Chemistry	
Sodium serum electrolytes	NA
Potassium serum electrolytes	<3.0 mmol/L >6.0 mmol/L
Creatinine	>2 x ULN
Gamma-glutamyltransferase	NA
AST	>2 x Baseline
ALT	>2 x Baseline
ALP	>2 x ULN
CRP	NA
Albumin	NA
Total bilirubin	>2 x ULN
Glucose (non-fasting)	NA
Hematology	
Hemoglobin	<8.0 g/dL (<80 g/L) Increase of >40 g/L to a value above the ULN (upper limit of normal)
Hematocrit	NA
Platelet count	<50 x 10^9/L >999 x 10^9/L
Red blood cells	NA
White blood cells with differential count	<2 x 10^9/L >35 x 10^9/L
CD4+ count	≤200/µL
Coagulation	
aPTT	NA
PT (or INR (International Normalized Ratio)	NA
Serology	
HBsAg	NA
HBeAG	NA
HBV DNA	NA
HCV RNA	NA
Local Laboratory	
AST	>3 x ULN
ALT	>3 x ULN

NA: Not Applicable

Clinically significant laboratory values will be tabulated. All laboratory data for the parameter identified as potentially clinically significant for a subject will be listed. Low platelet counts are counted as being clinically significant only if they occur >= 4 weeks after IMP administration.

The data from the parameters AST and ALT concentrations (ratio to ULN) will also be presented in plots of individual profiles. Note that AST and ALT elevations will be examined in the framework of clinically significant laboratory values as described above.

On the listings, the reference range and flag indicating if the measurement in question is outside the reference range will be provided.

6.8.5 Vital Signs

Changes from Baseline in post-dose systolic blood pressure, diastolic blood pressure, pulse, and body temperature will be tabulated, where baseline is defined as the last assessment prior to IMP administration.

A **Clinically Significant Abnormality** in vital signs identified by the investigator will be recorded as an Adverse Event if it occurs after dose is administered. These adverse events will be included in the AE summaries; abnormalities prior to the start of treatment will be noted in medical history and listed.

Potentially clinically significant changes in systolic and diastolic blood pressure will be defined based on the following criteria:

Table 5 Potentially Clinically Significant Criteria for Systolic and Diastolic Blood Pressure Parameters

Parameter (mmHg)	Post-Baseline Criteria
Systolic Blood Pressure, increase	≥180 and increase from baseline ≥20
Systolic Blood Pressure, decrease	≤90 and decrease from baseline ≥20
Diastolic Blood Pressure, increase	≥105 and increase from baseline ≥15
Diastolic Blood Pressure, decrease	≤50 and decrease from baseline ≥15

mmHg = millimeter of mercury.

Vital sign measurements (Heart rate, systolic blood pressure, diastolic blood pressure, pulse, body temperature, weight, height) during the study will be displayed in a vital signs listing.

A summary of baseline weight, height, and BMI will be presented by treatment.

Summary statistics (n, mean, median, standard deviation and range) of the absolute value and change from baseline for systolic blood pressure, diastolic blood pressure, pulse, and body temperature will be tabulated by visit, and time point. Data from unscheduled visits will not be used for the by-visit summaries (unless they were assigned to a scheduled visit based on the use

of an analysis window as given in Table 6 below). Data from both scheduled and unscheduled visits will be listed. Time windows will be derived for each post-baseline visit using the time intervals for the study time windows detailed in Table 6.

Table 6 Analysis Study Time Windows for Vital Signs Assessments

Calculated Study Time Window (hours)	Time Interval for the Study Time Window
0.5	>0 to <45 min. post-dose
1	≥45 min. to <1.5 hr. post-dose
2	≥1.5 hr. to <2.5 hr. post-dose
3	≥2.5 hr. to <3.5 hr. post-dose
4	≥3.5 hr. to <5.0 hr. post-dose
6	≥5.0 hr. to <7.0 hr. post-dose
8	≥7.0 hr. to <10.0 hr. post-dose
12	≥10.0 hr. to <18 hr. post-dose
24	≥18 hr. to <30 hr. post-dose

6.8.6 Anti-FIX Antibodies

Blood sampling for measurement of anti-FIX antibodies will take place at the time points as specified in Table 2 and Table 4 of the Protocol. All data will be listed.

6.8.7 FIX Inhibitors

Blood sampling for measurement of FIX inhibitors will take place at the time points as specified in Table 2 and Table 4 of the Protocol.

The investigator may instigate that blood samples for FIX inhibitors are taken at additional visits in case (of suspicion) of detection of inhibitors as judged by the investigator.

All data will be listed.

6.8.8 FIX Recovery

Factor IX recovery will be assessed by measurement of Factor IX activity (%) 30 minutes after infusion of a challenge dose of FIX. This is referred to as Factor IX Recovery “maximum concentration [C_{max}] (%)”. Incremental recovery will be measured as the increase in activity (%) per unit infused (% per U/kg): C_{max} (%) minus Factor IX Activity (%) pre-Factor IX challenge, divided by the Factor IX Challenge dose (which is 40 U/kg). FIX recovery will be performed at baseline (Day 0 pre IMP). Additionally, measurement of FIX recovery and incremental recovery should be done at suspicion of FIX inhibitor as judged by the investigator.

All data will be listed.

6.8.9 Total (IgG and IgM) and Neutralizing Antibodies to AAV5

Blood sampling for measurement of Total (IgG and IgM) and Neutralizing Antibodies to AAV5 will take place at the time points as specified in Table 2 and Table 4 of the Protocol.

All data will be listed.

6.8.10 AAV5 capsid-specific T cells

Sampling for AAV5 capsid-specific T cells will take place at the time points as specified in Table 2 and Table 4 of the Protocol. In case of ALT elevation > 2x baseline, an additional sample should be taken.

All data will be listed and data will also be presented in plots of patient individual profiles.

6.8.11 Inflammatory Markers

Blood samples will be taken to assess IL-1β, IL-2, IL-6, IFNγ and MCP-1 (monocyte chemotactic protein-1) using enzyme-linked immunosorbent assay (ELISA). In case of ALT elevation > 2x baseline, an additional sample should be taken.

All data will be listed.

6.8.12 Vector DNA in Semen and Blood

Sampling of Vector DNA in Semen and Blood will take place at the time points specified in tables 2 and 4 of the Protocol.

Sampling should continue for the individual patient and for a specific matrix until 3 consecutive negative samples have been detected for the patient for that particular type of matrix.

All data will be listed. Furthermore, each individual patient profile will be presented graphically per matrix.

Time to first vector negative will be defined for each type of matrix and each patient as the post-treatment time point where a negative result is measured for the first time in a consecutive order of 3 or more time points with a negative result. Negative result is defined as a result of either '0' or '< LOD' (limit of detection). The time to first vector negative will be flagged on the above-mentioned listings and will also be summarized.

6.9 Statistical Analyses for the Month 60 CSR Addendum

The same analyses that are to be done for the Week 52 main CSR (and the 2.5 year CSR) – as described in Sections 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8 – will be repeated for the Month 60 CSR, but using the entire 60 months (instead of 52 Weeks [or 2.5 years]) of data.

7. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

Beginning with the 2.5-year (data cut) analysis, the contamination rule (for factor IX activity analysis) is hereby refined as follows. Factor IX activity assessments post-AMT-061 that are within 5 half-lives of exogenous factor IX use are considered contaminated and will be excluded from the analysis. Going forward, this 5-half-life contamination rule replaces the 10-day contamination rule. The rationale is to improve accuracy. By contrast, the protocol currently states the following: “The required wash out period (in order to consider a factor IX activity level to be “unaffected” – i.e., “uncontaminated”) will be 10 days.”.

8. STATISTICAL SOFTWARE

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using SAS (Version 9.4 or higher).

APPENDIX 1: DATA HANDLING RULES

Programming of the tables, listings and figures will be performed using SAS Version 9.4 or a more recent version. The following table presents the algorithms to be used in SAS to calculate the derived variables, including rules for handling other missing data or partial dates, or irregular/unexpected data issues.

Category	Description	Data Handling Rule
1. Age (years)	Age (years)	Age = integer part of ([Informed Consent date – Birth date + 1]/365.25)
2. Medical History	Medical History Begin Date of Condition	Begin date of condition will be imputed for all subjects as the 1st of the month for the purpose of computing the onset day.
3. Surgical History	Surgical History Date of Surgery	Date of surgery will be imputed for all subjects as the 1st of the month for the purpose of computing the onset day.
4. First Treatment Date	date/time of first study treatment	The date and time (24 hr. clock) of the first dose of IMP study treatment will be taken from the Dosing eCRF.
5. Last Visit Date	Date of Last Visit	Date of last visit according to the Visit eCRF.
6. Last Study Participation Date (STDM variable, typically named RFPENDTC)	Last Study Participation Date (STDM variable, RFPENDTC), where SDTM denotes Study Data Tabulation Model	Last study participation date is defined as last known date of contact, which is the later of the following dates: last visit date, date of the last dose, date of last contact if lost-to-follow-up, date of telephone follow-up, or death date.
7. Study Day Definitions	**Study Day** for assessment/event which occurs on or after the start of study treatment	Study Day = Date of assessment/event – date of the first dose of study treatment + 1.
	Study Day for assessments/events on days prior to the first dose of study treatment in the study	Study Day = date of assessment/event – first dose date of treatment in the study.
	Dose Day	**Dose Day** in the study is defined as the study day of the first dose of study treatment in the study (Study Day 1).
	Last Study Day	**For subjects who did not receive study treatment in the study**, Last Study Day is

Category	Description	Data Handling Rule
		defined as (the later of the last visit date and the date of last contact for subjects lost-to-follow-up from the Study Completion/Early Discontinuation CRF) – Date of Screening Visit + 1. **For subjects who received study treatment in the study,** Last Study Day is defined as (the later of the last visit date and the date of last contact for subjects lost-to-follow-up from the Study Completion/Early Discontinuation CRF) – first dose date in the study + 1.
8. Duration of event	The duration of any event	The duration of any event is defined as (stop date – start date + 1).
9. Multiple assessments for the same visit	Vital Sign and Laboratory assessments	• All data will be listed in data listings. • The last of multiple valid assessments within a post-baseline study time window will be used for summaries. • If there are multiple laboratory values for the same parameter at post-baseline pre-dose of a visit, the last value will be chosen for analysis. • The average of all available pre-dose vital sign measurements for a vital sign parameter taken prior to the start of dosing for the Treatment Period will be used for calculation of baseline for a parameter.
10. Special Lab Value Handling for Safety Lab values	Lab values with a prefix such as '>', '<', '+' and 'Less than' etc.…	• '>': use the available original value +0.001 in the analyses. • '<': use the available original value –0.001 in the analyses. • '+': use the available original value without the prefix in the analyses. • '>=': use the available original value in the analyses. • '<=': use the available original value in the analyses.
11. Prior and concomitant medication / treatment	Prior and concomitant medication/treatment	**1.** A medication/treatment (including herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) will be considered prior if the

Category	Description	Data Handling Rule
		start date of the medication/therapy is before the date of AMT-061 dosing. **2.** A medication/therapy will be identified as a concomitant (i.e. "post-treatment concomitant") medication/therapy if it is being continued by the subject at the date of AMT-061 dosing or is any new medication/therapy received during the post-treatment period. A medication with end date that is the same as the AMT-061 dosing date will not be considered to be concomitant (i.e. "post-treatment concomitant"). However, a medication with both start date and end date on the date of AMT-061 dosing is considered to be "post-treatment concomitant". **3.** Any medication/therapy that cannot be identified as Prior or Concomitant will be considered as being in each of the possible categories depending on available information.
12. Adverse event	Missing severity	For the AE summary by severity, an AE with missing severity will be deemed as Severe.
	Missing relationship to study drug	For AE summary by relationship, an AE with a missing relationship to study drug will be deemed as Definitely related.
	Treatment-emergent adverse event	An adverse event is considered treatment-emergent if an event occurs (or if there was a worsening [intensity and/or severity changed to worsened grades]) on or after the administration of the IMP. An adverse event that begins on the same date as the administration of the IMP is treatment-emergent if the AE begins after the time of administration or if the time of AE onset is unknown. A death is considered to be treatment-emergent if any of the adverse events that led to the death are treatment emergent.
		If the AE start date is partial/missing, then

Category	Description	Data Handling Rule
		• If AE start date is completely missing, then the AE is considered as treatment-emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment-emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
13. Hard coding	Hard coding for data analysis	Hard Coding is not allowed during data analysis unless agreed to in writing by uniQure.
14. CCI	CCI	CCI

APPENDIX 2: ANALYSIS DATASET SPECIFICATIONS

Analysis datasets will be built to gain efficiency and ensure consistency in data analyses and presentation for this trial. The specifications for each analysis data set will be prepared separately and will not be a part of this SAP.

APPENDIX 3: CENTRAL LABORATORY REFERENCE RANGES FOR USE IN FLAGGING ABNORMAL VALUES

This appendix is provided as an attachment to this document.

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This appendix is provided as an attachment to this document.

APPENDIX 5: MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

This appendix is provided as an attachment to this document.

APPENDIX 3 CTCAE LABORATORY TEST CRITERIA AND CENTRAL LABORATORY REFERENCES RANGES FOR USE IN FLAGGING ABNORMAL VALUES

Phase IIb, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B

CT-AMT-061-01

Study Phase:	IIb
Investigational Medicinal Product (IMP):	AAV5-hFIXco-Padua (adeno-associated viral vector containing the naturally occurring Padua variant of human factor IX gene)
Indication:	Hemophilia B
Sponsor:	uniQure biopharma B.V. Paasheuvelweg 25a 1105 BP Amsterdam The Netherlands Phone: PPD
Author	PPD
Date of Issue	16 Jun 2021
Version	Version 3.0

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1. CTCAE V5.0 LABORATORY TEST CRITERIA

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Alanine aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	>ULN – 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Blood bilirubin increased	>ULN – 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 – 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 – 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Creatinine increased	>ULN -1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 -3.0 x ULN	>3.0 baseline; >3.0 – 6.0 xULN	>6.0 x ULN
GGT increased	>ULN – 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hemoglobin increased (a)	Increase in >0 – 2 gm/dL above ULN (a)	Increase in >2 – 4 gm/dL above ULN (a)	Increase in >4 gm/dL above ULN (a)	n/a
Anemia (hemoglobin decreased)	LLN- 10g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated

Investigations				
	Grade			
Laboratory Analyte	1	2	3	4
Leukocytosis (White blood cell increased)			>100,000/mm^3	Clinical manifestations of leucostasis (sic); urgent intervention indicated Note that the spelling is often “leukostasis” in the literature.
White blood cell decreased	<LLN – 3000/mm^3; <LLN – 3.0 x 10^9/L	<3000 – 2000/mm^3; <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3; <2.0 – 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L

2. PROTOCOL REFERENCE RANGE DEFINITIONS

Test Name	Subject Characteristics	Unit	Reference Range	Notable Values	Critical Values	Methodology
Chemistry						
Albumin	Adult	g/dL	3.5-5.5	-	-	Photometry
Alkaline Phosphatase	Adult	U/L	37-116	> 348	-	Photometry
ALT/SGPT	Adult	U/L	6-41	> 123	> 164	Photometry
AST/SGOT	Adult	U/L	9-34	> 102	> 164	Photometry
Bilirubin (Total)	Adult	mg/dL	0.10-1.10	> 2.00	-	Photometry
Creatinine	Adult	mg/dL	0.50-1.40	> 2.00	> 3.00	Photometry
Gamma Glutamyl Transferase (GGT)	Adult Male	U/L	11-52	> 156	-	Photometry
Glucose	Adult	mg/dL	60-115	< 50 or > 180	< 40 or > 450	Photometry
Potassium	Adult	Mmol/L	3.5-5.1	< 3.0 or > 6.0	< 2.8 or > 6.2	Ion Selective Electrode
Sodium	Adult	Mmol/L	134-144	-	< 120 or > 160	Ion Selective Electrode
Coagulation						
Activated Partial Thromboplastin Time (APTT)	All	Sec	23.9-40.0	-	> 70.0	Clotting
International Normalized Ratio (INR)	All	(None)	0.8-1.2	-	> 2.5	Calculation
EIA						
Interleukin-1 beta	Adult	pg/mL	< 0.61	-	-	ECLIA
Interleukin-6	Adult	pg/mL	< 8.60	-	-	ECLIA
MCP-1	All	pg/mL	200.0-722.0	-	-	ELISA

Test Name	Subject Characteristics	Unit	Reference Range	Notable Values	Critical Values	Methodology
Hematology						
Basophil %	All	%	0.0-4.0	-	> 7.0	Volume, Conductivity, Scatter
Basophil (Absolute)	All	10^3/µL	0.0-0.3	-	-	Volume, Conductivity, Scatter
Eosinophil %	All	%	0.0-10.0	-	> 20.0	Volume, Conductivity, Scatter
Eosinophil (Absolute)	All	10^3/µL	0.0-0.8	-	-	Volume, Conductivity, Scatter
Hematocrit	Adult Male	%	40-52	-	< 20 or > 60	Calculation
Hemoglobin	Adult Male	g/dL	13.6-18.0	-	< 7.0 or > 20.0	Photometry
Lymphocyte %	All	%	15.0-45.0	-	> 75.0	Volume, Conductivity, Scatter
Lymphocyte (Absolute)	All	10^3/µL	1.0-5.0	-	-	Volume, Conductivity, Scatter
Monocyte %	All	%	0.0-12.0	-	> 25.0	Volume, Conductivity, Scatter
Monocyte (Absolute)	All	10^3/µL	0.0-1.0	-	-	Volume, Conductivity, Scatter
Neutrophil %	All	%	40.0-80.0	-	-	Volume, Conductivity, Scatter
Neutrophil (Absolute)	All	10^3/µL	1.0-8.0	-	-	Volume, Conductivity, Scatter
Platelet	Adult	10^3/µL	140-400	-	< 40 or > 999	Impedence
Red Blood Cells	Adult Male	10^6/µL	4.30-6.00	-	-	Impedence
White Blood Cells	Adult	10^3/µL	3.5-11.0	-	< 2.0 or > 30.0	Impedence

Test Name	Subject Characteristics	Unit	Reference Range	Notable Values	Critical Values	Methodology
Immunology						
HBsAg	All	(None)	Non-reactive	-	-	Electrochemiluminescence Immunoassay
Hepatitis C Antibody	All	(None)	Non-reactive	-	-	Electrochemiluminescence Immunoassay
HIV 1 and 2 Screen	All	(None)	Non-reactive	-	-	
Molecular						
HCV RNA, Qualitative (by RT-PCR)	All	(None)	Not Detected	-	-	RT-PCR
Nephelometry						
hs-C-Reactive Protein	All	mg/L	0.0-3.0	-	-	Nephelometry
Special Chemistry (PPD)						
HIV-1 RNA	All	(None)	Not Detected	-	> Detected	Transcription Mediated Amplification

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APPENDIX 5 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGs) for CT-AMT-061-01

Phase IIb, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B

CT-AMT-061-01

Study Phase:	IIb
Investigational Medicinal Product (IMP):	AAV5-hFIXco-Padua (adeno-associated viral vector containing the naturally occurring Padua variant of human factor IX gene)
Indication:	Hemophilia B
Sponsor:	uniQure biopharma B.V. Paasheuvelweg 25a 1105 BP Amsterdam The Netherlands Phone: PPD
Authors	PPD / PPD / PPD / PPD
Date of Issue	16 Jun 2021
Version	Version 3.0

Change Log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
Version 2.0		Added table and listing for alpha-fetoprotein since this was added to the Protocol as a safety objective and endpoint. Provided some minor clarifications. Made some typographical corrections.	1.0
Version 3.0		Added table and listing for abdominal ultrasound since this was added to the Protocol as a safety objective and endpoint. Carried out any changes that were called for by the updated SAP text. Provided rules for precision of decimal display. Provided some minor clarifications.	2.0

General Instructions for TLGs

Following are the specifications for standard tables, listings, and graphs (TLGs).

Header

The following header should appear at the very top of each page of a table, a listing, or a graph (TLG) for CT-AMT-061-01 analyses:
Protocol: CT-AMT-061-01 AAV5-hFIXco-Padua

Footer

The following footer should appear at the bottom of each page of a TLG generated in SAS:

Report generated by program: protocol ID/sasdir/PGNAME.sas Version yyyy-mm-dd hh:mm (Page n of N)

where: protocol ID = CT-AMT-061-01 and PGNAME = SAS program name. Version will be replaced by "Draft" or "Final" where X corresponds to the DMC delivery number. Page number will be right justified.

Title

At least two (2) lines should be reserved for the whole title. The first line is for the TLF number (i.e., title index #) and the actual title (title); and the second line is reserved for the analysis population descriptor (Population). All titles should be centered, as shown in the following example:

Table 1.5.3 Demographics
Analysis Set: Safety Population

Footnotes

- In general, a footnote serves as a brief explanation/clarification/definition/concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or related directly to the displayed content of a TLF. Detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, should be addressed in the text of the statistical analysis plan (SAP).
- All footnotes should follow immediately after a horizontal solid line. There should be one and only one space between the last footnote and the footer.
- Each line of a complete footnote should end with a period. When a footnote needs more than 1 line, one (1) period is needed.
- Large data listings will have footnotes on the first page only.
- Please include a footnote as follows if any of the following values appears in a table, listing, or figure:
    - NA = Not Applicable
    - UN = Unknown
    - UNK = Unknown
    - ND = Not Done
    - NC = Not Calculated
    - If more than one of these values appears in a single table, listing, or figure, present a footnote explaining the abbreviation for all of the values that appear. These should appear on one line with abbreviation definitions separated by a semicolon. The footnote should end with a period.

- For any output for which the first page will have only footnotes, suppress the column headers on the first page.

Row Labels/Column Labels:

- The mockups will reflect the preferred style of capitalization.

Page Layout

- All output should be in landscape orientation. A margin of 1.5, 1, 1, and 1 inch should be on the top, right, left, and bottom, respectively.
- All efforts should be made to present all Treatment groups in one page.
- All efforts should be made to maximize readability of the text and data presented in the outputs. This includes adjusting column widths and spacing independently from the mocks column widths and spacing.

Page Format

- There should be a solid line at the top of the tables and listings just below the title.
- There should be a solid line just below the column headings that runs completely across the width of the tables and listings.
- There should be a solid line at the bottom of the tables and listings just above the footnote(s) on every page.

Font

- The default font to be used in the actual study tables/listings should be Courier New 8 point, which is approximately equivalent to the acceptable font size of Times New Roman 9-10 in accordance with the FDA's guidance on Electronic Common Technical Document Specification.
- The use of Courier New 7 point is optional for some tables/listings and will be determined at the study level by the Study Biostatistician and Study Programmer. However, it is recommended that this option be used primarily for data listings.

Descriptive Statistics

By default, descriptive statistics in this template covers: n, Mean, Median, Standard Deviation (SD), Minimum (Min), and Maximum (Max). Unless otherwise specified, the minimum and maximum values should be reported to the same number of decimal places as the original data. Unless otherwise specified in the actual table shells, the mean, estimated (LS) mean, standard deviation, and median should be displayed to one more decimal place than the minimum and maximum. Unless otherwise specified, the standard error of the mean will be displayed to two more decimal places than the minimum and maximum. When the same table shell is being used for more than one endpoint, the above decimal-precision rules should take precedence over the number of decimal places shown in the mock table.
For listings, when the Result (at a postbaseline visit or time point) is of the form "<x" or ">x", then do not display the change from baseline. For listings, when the Baseline Value is of the form "<x" or ">x", then do not display the change from baseline at any postbaseline time point.

Rounding for Percentage

- Unless specified in the actual table shells for a study, all percentages will be rounded to 1 decimal place in all TLFs.
- Unless specified in the actual table shells for a study, p-values will be presented with 4 decimal places.

Alignment of Decimals

- It is recommended that all the decimal places be aligned in summary tables, as shown in the following example:

```
                                Decimal Align

n                              xxx
Mean (SD)                       xx.xx (xx.xx)
Median                          xx.xx
Min; Max                        xx.x; xx.x
```

- When numbers with decimal points are included in brackets (e.g., percentages), have the brackets aligned to the right and then padded to allow for all possible percentages and then the left brackets will also be aligned. For example:

Brackets Align

(99.9%) (xx.x%)
(9.9%) (x.x%)

- It is recommended that all column entries in a summary tables and listings are aligned to the center.
- Columns for text fields are all left justified. Columns with whole numbers are all right justified.
- For graphs, the lines are distinguishable and that the symbols for each line are appropriate. Legend is consistent across output for Treatment names and abbreviations.

Use of N versus n

- N = total number of subjects in the defined analysis set.
- n = total number of subjects in the specific category.
- If N is specified in the column heading then any reference to the number of subjects in the body should be small n, as shown in the following example:

Demographic Parameter	Treatment Group A (N=xxx)	Treatment Group B (N=xxx)	Total (N=xxx)
Age (years)			
n	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
SD	x.x	x.x	x.x
Median	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx

A Note for Subject Data Listings

- Observed Dates/AE Severity/Relationship to investigational product is used in subject data listings.
- Observed values or raw assessment scores are used in data listings along with their derived values used in analyses, e.g., raw assessment scores and derived total scores.
- If a full date is not available, please use the available partial date.
- If there are no observations that qualify for a listing please output the following: “No observations qualify for this listing”
- Only central laboratory results will be presented except for aPTT FIX activity results and local ALT/AST values.

Data Handling Rules

Here are some additional data handling rules for FIX (factor nine) therapies to help calculate total annualized FIX therapy rates.

For start dates having a missing day (but with non-missing month), the start date will be imputed as the 15th of the month, unless this imputation would make the start date to be on or subsequent to the end date.
For start dates having a missing day (but with non-missing month), end date will be imputed as the 15th of the month, unless this imputation would make the start date to be on or prior to the start date.

Start or end dates having a missing month will result in a missing date.

Total dose for a FIX record will consist of the dose times the frequency divided by time:

Doses recorded as ‘ONCE’ will have total dose equal to reported dose.
Doses recorded as ‘ONCE WEEKLY’ will have total dose equal to reported dose * (end date – start date + 1)/7

Doses recorded as 'OTHER: EVERY X-Y D' or 'OTHER: EVERY X-Y DAYS' will have total dose equal to reported dose * (end date – start date + 1)/(Average of X and Y)

Total doses will be summed over a period and divided by the time of the period in years to obtain annualized rates.

Notes about time intervals for tabulation:

- The 0-6 mo. Post-dose time interval ends on post-dose Day 183.
    - The beginning of this time interval may be dependent on the endpoint or the analysis and is specified for the particular endpoint and/or analysis.
- The 7-12 mo. Post-dose time interval ends on post-dose Day 365.
- The Year 1 time interval ends on post-dose Day 365.
    - The beginning of this time interval may be dependent on the endpoint or the analysis and is specified for the particular endpoint and/or analysis.
- The Year 2 time interval is from post-dose Day 366 to post-dose Day 730.
- The Year 3 time interval is from post-dose Day 731 to post-dose Day 1096.
- The Year 4 time interval is from post-dose Day 1097 to post-dose Day 1461.
- The Year 5 time interval is from post-dose Day 1462 to post-dose Day 1826.

Notes about annualization of rates:

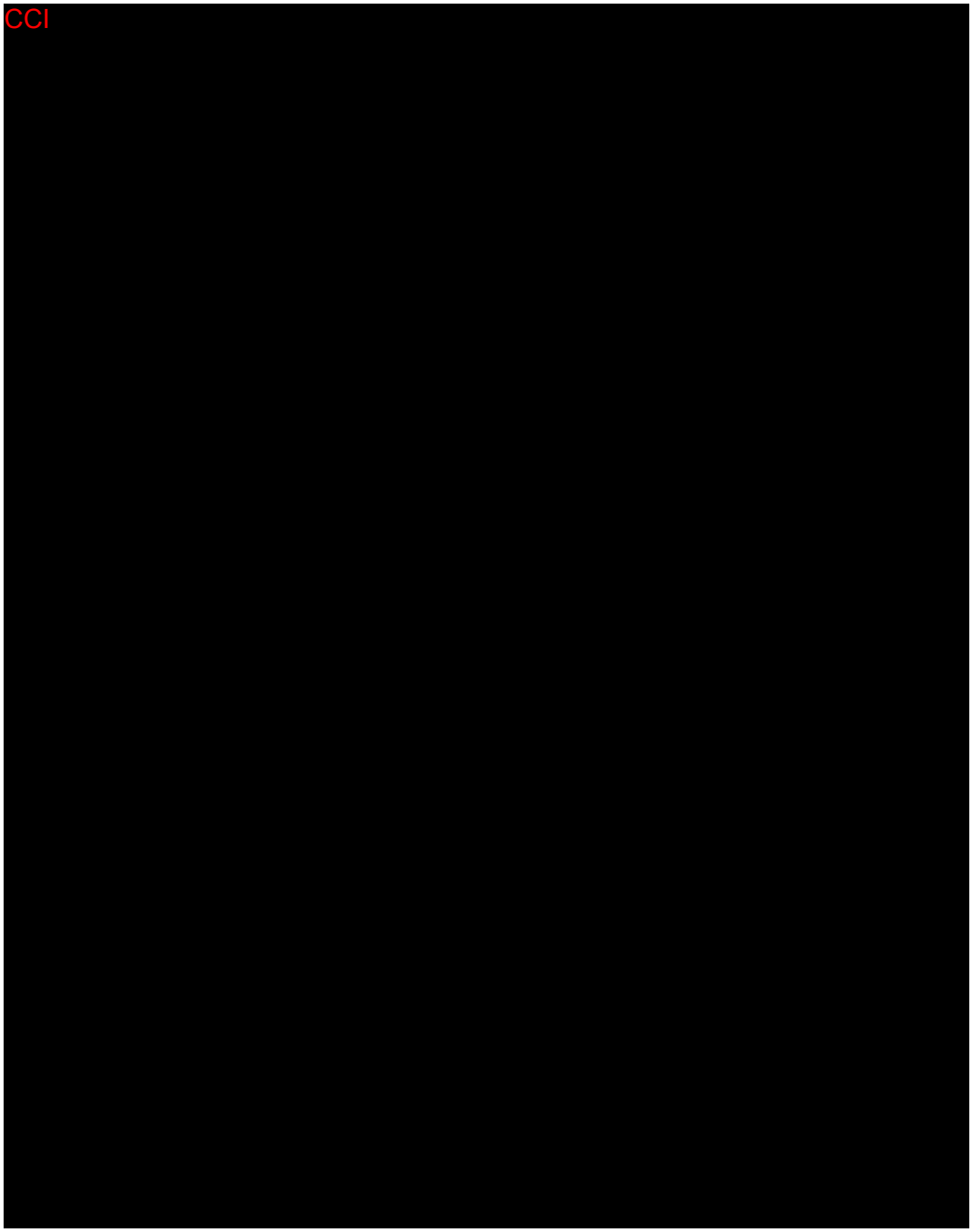
- An annualized rate is computed by dividing the total (quantity or count) by the number of person-years of observation ("at risk"), assuming that the duration of a year is 365.25 days. Equivalently, an annualized rate can be computed by dividing the total (quantity or count) by the number of person-days of observation ("at risk") and then multiplying the result by 365.25.

Notes about defining unique "joints" (for the purpose of the analysis of target joints):

- For the following joint locations, consider the joint to be identified uniquely by just the location: BACK, NECK.
- For the following joint locations, consider the joint to be identified uniquely by the combination of the location and the side/laterality (LEFT or RIGHT): ANKLE, ELBOW JOINT, FOOT, HAND, HAND DIGIT 1, HIP, KNEE JOINT, SHOULDER, TOE, WRIST JOINT. For identification purposes, consider a side/laterality of "BILATERAL" to pertain to two unique joints: LEFT and RIGHT (for the given location). For example, FOOT LEFT and FOOT RIGHT are two distinct joints; whereas FOOT BILATERAL is two joints: FOOT LEFT and FOOT RIGHT.
- For the following joint locations, consider the joint to be identified uniquely by the combination of the location, side/laterality (LEFT or RIGHT), and direction (LOWER or UPPER): ARM, LEG. For identification purposes, consider a side/laterality of "BILATERAL" to pertain to two unique joints: LEFT and RIGHT (for the given location and direction). For example, LEG LEFT LOWER and LEG LEFT UPPER are two distinct joints; whereas LEG LEFT BILATERAL is two joints: LEG LEFT LOWER and LEG LEFT UPPER.

TABLE OF CONTENTS FOR TLGs

CCI


CCI

SHELLS FOR TLGS

Subject Demographic, Disposition, and Baseline Summary Tables

Table 1.1 Subject Disposition
Analysis Set: All Subjects Screened

	Total (N = X) n (%)
Screened	x (xx.x)
Treated	x (xx.x)
Completed 52-Weeks post-IMP	x (xx.x)
Completed 2.5 Years post-IMP	x (xx.x)
Completed Follow-Up Study	x (xx.x)
Early Withdrawal from Study	x (xx.x)
Adverse Event	x (xx.x)
Subject Withdrew Consent	x (xx.x)
Subject Lost-to-Follow-up	x (xx.x)
Other	x (xx.x)

The denominator for percentages of an indented row is the row that it is indented under.

Source: Listing 4.1.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to programmer: Only include early withdrawal reason if count is greater than 1. Denominator is the N from the "Total" column header unless it is an indented row.

Table 1.2 Subject Demographics
Analysis Set: All Subjects Treated

Parameter	Total (N = X)
Age (Years) [a]	
n	xx
Mean (SD)	xx.x (x.x)
Median	xx.x,
Minimum, Maximum	xx, xx
Gender [b], n (%)	
Male	xx (xx.x)
Ethnicity, n (%)	
Hispanic or Latino	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)
Race, n (%)	
American Indian or Alaska Native	xx (xx.x)
Asian	xx (xx.x)
Black or African American	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)
White	xx (xx.x)
Other	xx (xx.x)
Missing	xx (xx.x)
Height (cm)	
n	xx
Mean (SD)	xxx.x (xx.x)
Median	xxx.x
Minimum, Maximum	xxx, xxx

[a] Baseline age is the age in years at the time of Informed Consent.
[b] All subjects are male according to inclusion criteria 1.
[c] BMI = Body Mass Index = weight (kg)/(height^2 (m^2)).

Source: Listing 4.1.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

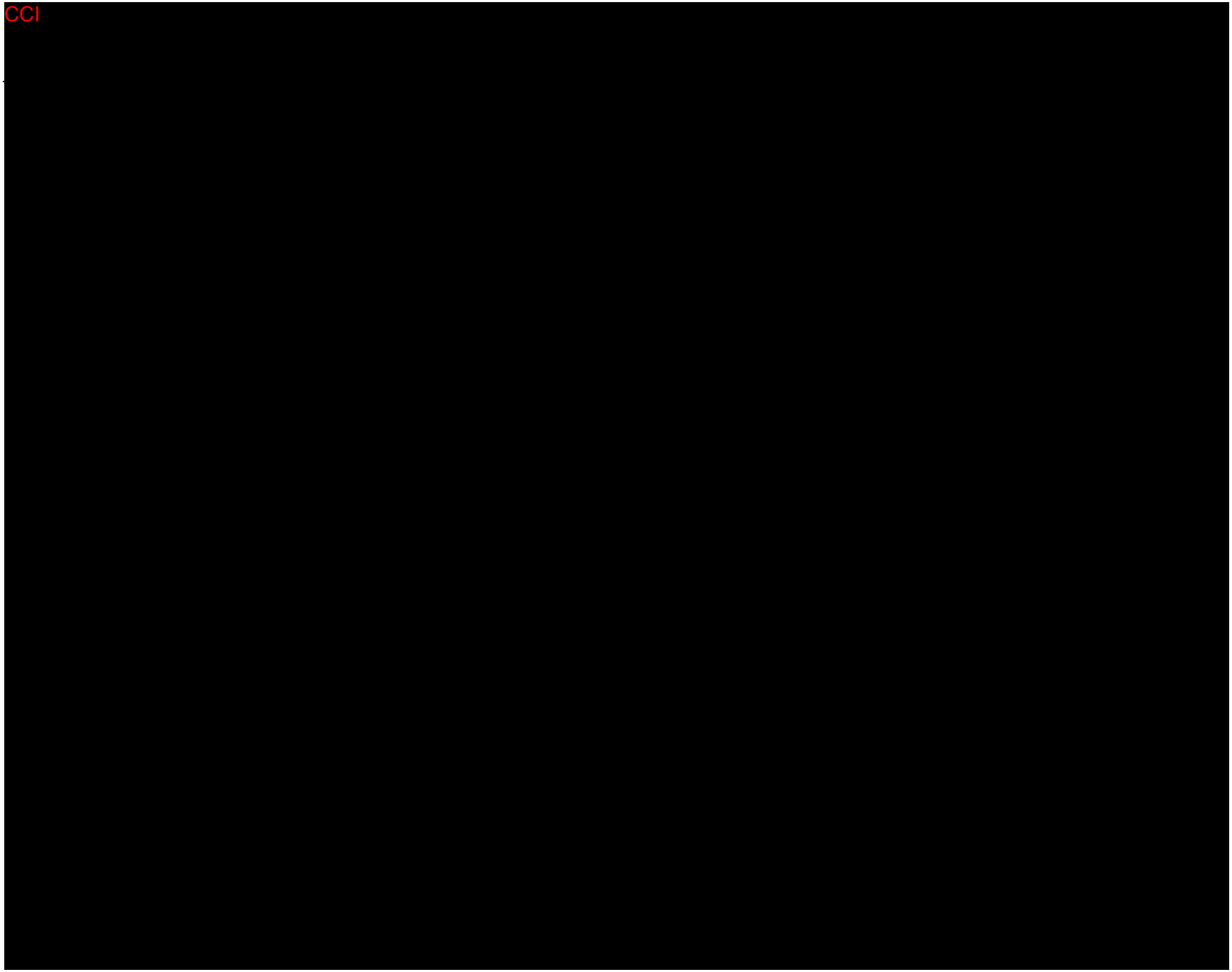
Table 1.2 Subject Demographics
Analysis Set: All Subjects Treated

Parameter	Total (N = X)
Weight (kg)	
n	xx
Mean (SD)	xxx.x (xx.x)
Median	xxx.x
Minimum, Maximum	xxx, xxx
BMI (kg/m^2)[c]	
n	xx
Mean (SD)	xx.x (x.x)
Median	xx.x
Minimum, Maximum	xx, xx

[a] Baseline age is the age in years at the time of Informed Consent.
[b] All subjects are male according to inclusion criteria 1.
[c] BMI = Body Mass Index = weight (kg)/(height^2 (m^2)).

Source: Listing 4.1.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to programmer: If any category has count of 0, do not display the row. Keep the summary for each parameter on the same page when breaking the table into multiple pages. Repeat titles, column headers, and footnotes on each page. Delete missing row if there are no missing values. Denominator is the N from the "Total" column header.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Safety

Adverse Events

Table 3.1.1 Overall Summary of Adverse Events
Analysis Set: All Subjects Treated

	All Subjects (N=x)
	n (%)[Events]
Subjects With at Least One TEAE[a]	xx (xx.x)[xxx]
Mild TEAE	xx (xx.x)[xxx]
Moderate TEAE	xx (xx.x)[xxx]
Severe TEAE	xx (xx.x)[xxx]
Subjects With TEAEs Related to Study Treatment [b]	xx (xx.x)[xxx]
Subjects With TEAEs Unrelated to Study Treatment [b]	xx (xx.x)[xxx]
Subjects With Serious TEAEs	xx (xx.x)[xxx]
Subjects With AEs of Special Notification	xx (xx.x)[xxx]
Subjects With TEAEs Leading to Premature Treatment Discontinuation	xx (xx.x)[xxx]
Deaths - All Causes	xx (xx.x)

[a] TEAE = Treatment-Emergent Adverse Event.
[b] Related = Possibly related or related.
MedDRA Version xx.x was used for coding.

Source: Listing 4.4.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Table 3.1.2 Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: All Subjects Treated

System Organ Class Preferred Term	All Subjects (N=x) n (%)[Events]
At Least One TEAE	xx (xx.x)[xx]
System Organ Class 1	xx (xx.x)[xx]
Preferred Term 1	xx (xx.x)[xx]
Preferred Term 2	xx (xx.x)[xx]
System Organ Class 2	xx (xx.x)[xx]
Preferred Term 1	xx (xx.x)[xx]
Preferred Term 2	xx (xx.x)[xx]
Etc.…	

TEAE = Treatment-Emergent Adverse Event.
MedDRA Version xx.x was used for coding.

Source: Listing 4.4.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Sort by decreasing frequency of occurrence based on system organ class. Within each system organ class, sort by decreasing frequency based on preferred term.

Table 3.1.3 Serious Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: All Subjects Treated

```
TEAE = Treatment-Emergent Adverse Event.
MedDRA Version xx.x was used for coding.

Source: Listing 4.4.2
```

Note to Programmer: Similar to Table 3.1.2. Replace "At Least One TEAE" with "At Least One Serious TEAE". Sort by decreasing frequency of occurrence based on system organ class. Within each system organ class, sort by decreasing frequency based on preferred term.

Table 3.1.4 Related Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: All Subjects Treated

```
TEAE = Treatment-Emergent Adverse Event.
MedDRA Version xx.x was used for coding.
[a] Related = Possibly related or related.

Source: Listing 4.4.1
```

Note to Programmer: Similar to Table 3.1.2. Replace "At Least One TEAE" with "At Least One Related TEAE [a]". Sort by decreasing frequency of occurrence based on system organ class. Within each system organ class, sort by decreasing frequency based on preferred term.

Table 3.1.5 Related Serious Treatment-Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: All Subjects Treated

```
TEAE = Treatment-Emergent Adverse Event.
MedDRA Version xx.x was used for coding.
[a] Related = Possibly related or related.

Source: Listing 4.4.2
```

Note to Programmer: Similar to Table 3.1.2. Replace "At Least One TEAE [a]" with "At Least One Related Serious TEAE [a]".

Table 3.1.6 Fatal Treatment Emergent Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: All Subjects Treated

```
TEAE = Treatment-Emergent Adverse Event.
MedDRA Version xx.x was used for coding.
```

Source: Listing 4.4.3

Note to Programmer: Similar to Table 3.1.2. Replace "At Least One TEAE" with "At Least One Fatal TEAE". Sort by decreasing frequency of occurrence based on system organ class. Within each system organ class, sort by decreasing frequency based on preferred term. ***Do not produce if there are no fatal TEAEs.***

Table 3.1.7 Incidence of Treatment Emergent Adverse Events of Special Notification
Analysis Set: All Subjects Treated

	All Subjects (N=x)
	n (%)[Events]
AEs related to the IMP administration procedure	xx (xx.x)[xx]
Suspected or confirmed cases of opportunistic or serious infections that in the investigator's opinion might be related to the IMP	xx (xx.x)[xx]
Unexpected reactions (e.g., hypersensitivity, immunological, toxic or other as consequence of a change in the construction or function of the viral vector [e.g., generation of replication competent virus])	xx (xx.x)[xx]
AEs related to product failure (including lack of efficacy)	xx (xx.x)[xx]
AEs related to mandatory concomitant medication (e.g., immunosuppression)	xx (xx.x)[xx]
AEs related to medical devices which form part of the product or are used for application of the product	xx (xx.x)[xx]
Development of any new/recurrent cancer	xx (xx.x)[xx]

MedDRA Version xx.x was used for coding.

Source: Listing 4.4.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Table 3.1.8 Treatment-Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Highest Severity
Analysis Set: All Subjects Treated

System Organ Class Preferred Term	All Subjects (N=xx) Mild n (%)	 Moderate n (%)	 Severe n (%)	 Any Severity n (%)
At Least One TEAE	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
System Organ Class 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
System Organ Class 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
….				

TEAE = Treatment-Emergent Adverse Event.
Only the highest severity was counted for multiple occurrences of the same adverse event in one individual.
MedDRA Version xx.x was used for coding.

Source: Listing 4.4.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to programmer: Sort by decreasing frequency of occurrence based on system organ class in the "Any Severity" column. Within each system organ class, sort by decreasing frequency based on preferred term in the "Any Severity" column.

Table 3.1.9 Treatment-Emergent Adverse Events by MedDRA Preferred Term in Descending Frequency
Analysis Set: All Subjects Treated

	All Subjects (N=x)
Preferred Term	n (%)[Events]
Preferred Term 1	xx (xx.x)[xx]
Preferred Term 2	xx (xx.x)[xx]
Preferred Term 1	xx (xx.x)[xx]
Preferred Term 2	xx (xx.x)[xx]
Etc.…	

MedDRA Version xx.x was used for coding.

Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Sort table by descending n (%) and then by events, if necessary.

Laboratory Parameters

Table 3.2.1 Central Laboratory Parameters by Visit and Time of Assessment – Hematology Panel
Analysis Set: All Subjects Treated

Parameter (unit)	Visit	Statistics	Actual Value	Change From Baseline [a]
Parameter 1 (unit)	Baseline	n	xxx	NA
		Mean (SD)	x.xxx (x.xxx)	
		Median	x.xxx	
		Minimum, Maximum	x.xx, x.xx	
	Post-IMP 1 hour	n	xxx	xxx
		Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)
		Median	x.xxx	
		Minimum, Maximum	x.xx, x.xx	x.xx, x.xx

[a] Baseline is the last available measurement prior to IMP administration.
NA: Not Applicable.
Unscheduled visits that could not be assigned to a scheduled visit are not included. If there were multiple values for a visit, the last value was chosen for the analysis.

Source: Listing 4.5.2
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Repeat for all remaining visits according to "Table 3 Analysis Study Time Window for Clinical Lab Assessments in the SAP." Repeat the parameter at the beginning of each page under column header. Repeat for all continuous laboratory variables. Sort by parameter and visit. The table is to be based on central laboratory values.
The decimal precision in the mock table above is shown only as a placeholder and is not necessarily the right precision for any specific parameter. The needed decimal precision can vary across safety lab parameters (even within a class such as hematology, serum chemistry, or coagulation). In general, give the Maximum and Minimum the maximum number of decimal places that any value for the parameter has. Once the decimal precision for display for the Maximum and Minimum of a given parameter is established, then simply follow the rules (given near the beginning of this document) for decimal display of various statistics relative to the established decimal precision for the Minimum and Maximum.

Table 3.2.2 Central Laboratory Parameters by Visit and Time of Assessment – Serum Chemistry
Analysis Set: All Subjects Treated

Source: Listing 4.5.3

Note to Programmer: Similar layout to table 3.2.1

Table 3.2.3 Central Laboratory Parameters by Visit and Time of Assessment – Coagulation
Analysis Set: All Subjects Treated

Source: Listing 4.5.4

Note to Programmer: Similar layout to table 3.2.1

Table 3.2.4 Central Laboratory Parameters by Visit and Time of Assessment – Serology
Analysis Set: All Subjects Treated

Parameter (unit)	Visit	Statistics	Actual Value
Continuous Parameter 1 (unit)	Baseline [a]	n	xxx
		Mean (SD)	x.xxx (x.xxx)
		Median	x.xxx
		Minimum, Maximum	x.xx, x.xx
	xxx	n	xxx
		Mean (SD)	x.xxx (x.xxx)
		Median	x.xxx
		Minimum, Maximum	x.xx, x.xx
	xxx	n	xxx
		Mean (SD)	x.xxx (x.xxx)
		Median	x.xxx
		Minimum, Maximum	x.xx, x.xx
	. . .		

Parameter (unit)	Visit	Statistics	Actual Value
Categorical Parameter	Baseline [a]	Category 1, n (%)	xx (xxx.x)
		Category 2, n (%)	xx (xxx.x)
		. . .	
	xxxxx	Category 1, n (%)	xx (xxx.x)
		Category 2, n (%)	xx (xxx.x)
		. . .	
	. . .	. . .	

NA = Not applicable.
Unscheduled visits that could not be assigned to a study visit are not included. If there were multiple values for a visit, the last value was chosen for the analysis.
[a] Baseline is the last available measurement prior to IMP administration.
Reference range of normal: Hep B DNA "<1.29 log10 IU/mL".

Source: Listing 4.5.5
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Repeat for all scheduled visits. Repeat the parameter at the beginning of each page under the column header. Repeat for all serology laboratory variables. Sort by parameter and visit. Please do not include local laboratory values or use local laboratory values when defining baseline values. Continuous parameters can be tabulated in the same manner by which they are being tabulated in Table 3.4.1. The shell above gives examples of how to tabulate a continuous parameter or a categorical parameter.
The decimal precision in the mock table above is shown only as a placeholder and is not necessarily the right precision for any specific parameter. The needed decimal precision can vary across lab parameters (even within a class such as serology). In general, give the Maximum and Minimum the maximum number of decimal places that any value for the parameter has. Once the decimal precision for display for the Maximum and Minimum of a given parameter is established, then simply follow the rules (given near the beginning of this document) for decimal display of various statistics relative to the established decimal precision for the Minimum and Maximum.

Handle/tabulate "Hepatitis B DNA (log10 IU/mL)" as a categorical parameter, with the following categories "Detected" and "Not Detected". Count the value as "Detected" if the value > 1.29 (log10 IU/mL). Count the value as "Not Detected" if the value is <= 1.29 (log10 IU/mL). This format can be used because no values have been above the limit of detection for the visits where this parameter is assessed.
Use the sum of the "n"s across categories (for a given time point) as the denominator for percentages. Missing values should not be counted in the denominator.

Table 3.2.5 Laboratory Parameters by Visit and Time of Assessment – Alpha-fetoprotein (AFP)
Analysis Set: All Subjects Treated

Parameter (unit)	Visit	Category Statistics	Value
Parameter 1 (unit) (LLOQ = x.xx, ULOQ=x.xx)	Month 12	Overall (< LLOQ or >= LLOQ), n	xxx
		Median	<LLOQ
		Minimum, Maximum	<LLOQ, x
		< LLOQ, n (%)	xxx (xxx.x)
		>= LLOQ, n (%)	xxx (xxx.x)
		Mean (SD)	x.x (x.x)
		Median	x.x
		Minimum, Maximum	x, x
	Month 18	Overall (< LLOQ or >= LLOQ), n	xxx
		Median	x.x
		Minimum, Maximum	<LLOQ, x
		< LLOQ, n (%)	xxx (xxx.x)
		>= LLOQ, n (%)	xxx (xxx.x)
		Mean (SD)	x.x(x.x)
		Median	x.x
		Minimum, Maximum	x, x
	. . .		

Parameter (unit)	Visit	Category Statistics	Value
	Month 24	Overall (< LLOQ or >= LLOQ), n (%)	xxx (xxx.x)
		Median	<LLOQ x.x
		Minimum, Maximum	
		< LLOQ, n (%)	xxx (xxx.x)
		>= LLOQ, n (%)	xxx (xxx.x)
		Mean (SD)	x.x (x.x) x.x
		Median	x.x
		Minimum, Maximum	
	Month 30	Overall (< LLOQ or >= LLOQ), n	xxx
		Median	x.x
		Minimum, Maximum	<LLOQ, x.x
		< LLOQ, n (%)	xxx (xxx.x)
		>= LLOQ, n (%)	xxx (xxx.x)
		Mean (SD)	x.x (x.x)
		Median	x.x
		Minimum, Maximum	x, x
	. . .		

Parameter (unit)	Visit	Category Statistics	Value

LLOQ: Lower limit of quantification: AFP xx.xx IU/mL. ULOQ: Upper limit of quantification: AFP xx.xx IU/mL.
Lower limit of normal: AFP: xx.xx IU/mL. Upper limit of normal: AFP: xx.xx IU/mL.
A value is counted as "<LLOQ" if the value is < LLOQ.
[a] Baseline is the last available measurement prior to IMP administration.
NA: Not Applicable.
Unscheduled visits that could not be assigned to a scheduled visit are not included. If there were multiple values for a visit, the last value was chosen for the analysis.

Source: Listing 4.5.6
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: There is to be no column for Change from Baseline. This is because a substantial number of values are of the form "< x", which essentially means "<LLOQ". Display the minimum and maximum with the same number of decimal places that the original data have. Then display the other statistics with decimal precision according to the general rules given in the introductory section of this SAP Mocks document.

The range of quantification is "1.09 – 1000.00" IU/mL. These are the values for LLOQ and ULOQ, respectively. Use these values in the footnote, as appropriate.

In the footnote, replace "xx.xx" with the appropriate lower limit of normal, as applicable. In the footnote, replace "xx.xx" with the appropriate upper limit of normal, as applicable.

Table 3.2.6 Laboratory Parameters by Visit and Time of Assessment – Local Laboratory AST and ALT Levels
Analysis Set: All Subjects Treated

Source: Listing 4.5.1

Note to Programmer: Similar layout to table 3.2.1. This table includes laboratory results.

Table 3.2.7 Post-Baseline Newly Occurring or Worsening Potentially Clinically Significant Laboratory Values Based on CTCAE and Other Criteria
Analysis Set: All Subjects Treated

Parameter	Criteria Threshold	All Subjects (N = xx) n/N1 (%)
Hematology		
Hemoglobin (g/L)	< 80	xx/xx (xx.x)
	Increase > 40 to a value > ULN	xx/xx (xx.x)
White Blood Cell Count (10^9/L)	< 2	xx/xx (xx.x)
	> 35	xx/xx (xx.x)
Platelet Count (10^9/L) [a]	< 50	xx/xx (xx.x)
	> 999	xx/xx (xx.x)
CD4+ Count (/uL)	<= 200	
Chemistry		
AST	> 2 x baseline	xx/xx (xx.x)
ALT	> 2 x baseline	xx/xx (xx.x)
Alkaline Phosphatase	> 2 x ULN	xx/xx (xx.x)
Total Bilirubin	> 2 x ULN	xx/xx (xx.x)
Potassium (mmol/L)	< 3.0	xx/xx (xx.x)
	> 6.0	xx/xx (xx.x)
Creatinine	> 2 x ULN	xx/xx (xx.x)

n = number of subjects in the category. N1 = number of subjects with data for the parameter. % = 100 x n/N1.
ULN: Upper Limit of Normal.
Baseline is the last available measurement prior to IMP administration.
[a] Low platelet counts are only counted as being clinically significant if they occur >= 4 weeks post-IMP administration.

Source: Listing 4.5.7Report generated by program: PPD Version yyyy-mm-dd xx:xx
(Page n of N)

Table 3.2.8 Shift Table for Laboratory Hematology Data: CTCAE Grading
Analysis Set: All Subjects Treated

Parameter and Direction of Shift	Baseline Grade	Post-Baseline Highest Grade					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
		n (%)	n (%)	n (%)	n (%)	n (%)	n
Hemoglobin Increased	Grade 0 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 1 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 2 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 3 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 4 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Any Grade (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Missing (N=xxx)	x	x	x	x	x	x

Baseline is the last available measurement prior to IMP administration. Grading criteria according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Grade 5 is not shown as there were no deaths on the study.
Grade 0 = No Grade, Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe or medically significant but not immediately life-threatening, Grade 4 = Life-threatening, Grade 5 = Death.
N = number of subjects who received the treatment and had data in the baseline category with non-missing data Post-Baseline. n = number of subjects in baseline and post-baseline category. % = 100 x n/N.

Source: Listing 4.5.7
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Notes to Programmer: Repeat for each laboratory test required within Hematology. Include (shifts for the) the following parameters in the table: Hemoglobin, Leukocytes, and Platelets. Use the following labels for the "Parameter and Direction of Shift" column: "Hemoglobin Increased", "Leukocytosis (White Blood Cell Increased)", "Anemia (Hemoglobin Decreased)", "White Blood Cell Decreased", and "Platelet Count Decreased". Add Grade 5 to post-baseline categories shown if there are any deaths for the parameter. For the "Missing" Row, N="Population N" minus the "Any Grade N". Please do not include local laboratory values or use local laboratory values when defining baseline.

Table 3.2.9 Shift Table for Laboratory Chemistry Data: CTCAE Grading
Analysis Set: All Subjects Treated

Note to Programmer: Similar layout to Table 3.2.8

Figures: Laboratory Parameters

Figure 3.3.1 Individual Profile Plot of Central Lab ALT and AST Levels (U/L) and Corticosteroid Use Over Time-Period: From Study Day 1 to Cut-Off
Analysis Set: All Subjects Treated

ULN: Upper limit of normal; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.

Source: Listing 4.5.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Notes to Programmer: Create three separate line plots on one graph for ALT levels, AST levels, and corticosteroid use for ALT and AST elevations. Use the actual study day to calculate the visit in weeks. Label the x-axis "Visit (Weeks)." Label the y-axis "ALT and AST Levels (U/L)". The Corticosteroid use will display the time interval(s) over which such corticosteroid use occurred with a horizontal line from the start date to the stop date, but will not connect disjoint time intervals. Add the indication for corticosteroid use as text label for the corresponding time interval. The vertical position of this horizontal line is arbitrary. Label Day 0 "Pre-dose" on the figure. Add ALT ULN and AST ULN to figure. Add the following footnote "ULN: Upper limit of normal."

Figure 3.3.2 Individual Profile Plot of Average T-cell (AAV5-capsid) ELISPOT (SFU/300000 PBMCs) Over Time - Period: From IMP to Cut-Off
Analysis Set: All Subjects Treated

P: Specific AAV-5 response, N: No specific AAV-5 response, E: Equivocal AAV-5 response, X: Result uninterpretable due to PHA result.

Source: Listing 4.8.4
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Notes to Programmer: Please make the needle plot data label letter correspond to the interpretation comment code in the footnote and color-code them. Please include corresponding legend with the following values: E: Equivocal AAV-5 response; F: Result flagged 5 SFU < PHA result < 100 SFU; N: No specific AAV-5 response; P: Specific AAV-5 response; X: Result uninterpretable due to PHA result. Plot the average t-cell result for each visit. Label the x-axis "Visit (Weeks)." Label the y-axis "Average T-cell (AAV5-capsid) ELISPOT (SFU/300000 PBMCs)". Apparently the "averaging" was already carried out by the laboratory. Use the actual study day to calculate the visit in weeks. Label Day 0 "Pre-dose" on the figure. Please make sure the y-axis includes the clinically relevant cut-off of 5 SFU/300000 PBMCs. Add a reference line at y = 5 and label it "Results >= 5 SFU/300000 PBMCs are regarded as positive".

AAV Vector DNA in Semen and Blood

Table 3.4.1 Adeno-Associated Virus (AAV) Vector DNA Shedding - Number of Weeks to Negative
Analysis Set: All Subjects Treated

Excreta	Statistics	First Week Negative (N = X)
Semen	n	x
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Minimum, Maximum	xx.x, xx.x
Blood	n	x
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Minimum, Maximum	xx.x, xx.x

Time in weeks until first "0" or "<LOD" (limit of detection) in consecutive order of 3 or more timepoints with a negative result.

Source: Listings 4.8.6 and 4.8.7
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Figures: AAV Vector DNA in Semen and Blood

Figure 3.5.1 Individual Plot of AAV Vector DNA in Semen (copies/mL) Over Time - Period: From IMP to Cut-Off
Analysis Set: All Subjects Treated

Source: Listing 4.8.7
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Plot the result for each visit. Each subject will contribute a line on the figure. Label the x-axis "Visit (Weeks)." Label the y-axis "Vector DNA in Semen (copies/mL)". Use logarithmic spacing in the y-axis but label the ticks with the actual value on the original scale. Put major tick mark labels at 0 and at powers of 10 (i.e. at 10, 100, 1000, 10000, etc.). Put minor tick marks but no tick labels at 5, 50, 500, 5000, etc. Please avoid the Exx notation for y-axis numbers; show all digits of the number. Put any value of zero or (< LOD) in the position of "1" on the y-axis but label it as "<LOD" (not as "0"). Use the nominal study visit. Label Day 0 "Pre-dose" on the figure. Please add a horizontal line at LLOQ, and label it.

Figure 3.5.2 Individual Plot of AAV Vector DNA in Blood (copies/mL) Over Time - Period: From IMP to Cut-Off
Analysis Set: All Subjects Treated

Source: Listing 4.8.6
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Plot the result for each visit. Each subject will contribute a line on the figure. Use logarithmic spacing in the y-axis but label the ticks with the actual value on the original scale. Put major tick mark labels at 0 and at powers of 10 (i.e. at 10, 100, 1000, 10000, etc.). Put minor tick marks but no tick labels at 5, 50, 500, 5000, etc. Please avoid the Exx notation for y-axis numbers; show all digits of the number. Put any value of zero or (< LOD) in the position of "1" on the y-axis but label it as "<LOD" (not as "0"). Label the x-axis "Visit (Weeks)." Label the y-axis "Vector DNA in Blood (copies/mL)". Use the nominal study visit. Label Day 0 "Pre-dose" on the figure. Please add a horizontal line at LLOQ, and label it.

Please look into this comment from uniQure: "SS: Subject PPD *and* PPD *values at week 120 were inadvertently switched by CRL. Updated figure expected from file transfer received on 14-APR-2021." This is in reference to Month 30.*

Vital Signs

Table 3.6.1 Vital Sign Parameters
Analysis Set: All Subjects Treated

Parameter (unit)	Visit	Study Time Window of Assessment	Statistic	Actual Value	Change From Baseline [a]
Parameter 1 (unit)	Baseline [a]		n	xxx	NA
			Mean (SD)	x.xxx (x.xxx)	
			Median	x.xxx	
			Minimum, Maximum	x.xx, x.xx	
	Day 0	Post-Dose 0.5 hr	n	xxx	xxx
			Mean (SD)Median	x.xxx (x.xxx)	x.xxx (x.xxx)
			Minimum, Maximum	x.xxx	x.xxx
				x.xx, x.xx	x.xx, x.xx

NA: Not Applicable.
Data from unscheduled visits are not included.
[a] Baseline is the last available measurement prior to IMP administration.

Source: Listing 4.6.1
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

Note to Programmer: Repeat the parameter at the beginning of each page under column header. Repeat for the following parameters: systolic blood pressure, diastolic blood pressure, pulse, and body temperature, BMI, height, weight. Repeat for all post-dose timepoints. Sort by parameter, visit, and timepoint within Day 0 visit. The decimal precision in the mock table above is shown only as a placeholder and is not necessarily the right precision for any specific parameter. The needed decimal precision can vary across safety lab parameters (even within a class such as hematology, serum chemistry, or coagulation). In general, give the Maximum and Minimum the maximum number of decimal places that any value for the parameter has. Once the decimal precision for display for the Maximum and Minimum of a given parameter is established, then simply follow the rules (given near the beginning of this document) for decimal display of various statistics relative to the established decimal precision for the Minimum and Maximum. Please keep parameter on one line so that there is not blank line between "n" and "Mean". Please ensure an empty row before each new visit.

Table 3.6.2 Post-Baseline Newly Occurring or Worsening Potentially Clinically Significant Vital Signs
Analysis Set: All Subjects Treated

Parameter	Criteria Threshold	All Subjects (N = XX) n/N1 (%)
Systolic Blood Pressure (mmHg), increase	>= 180 and increase from baseline >= 20	xx/xx (xx.x)
Systolic Blood Pressure (mmHg), decrease	<= 90 and decrease from baseline >= 20	xx/xx (xx.x)
Diastolic Blood Pressure (mmHg), increase	>= 105 and increase from baseline >= 15	xx/xx (xx.x)
Diastolic Blood Pressure (mmHg), decrease	<= 50 and decrease from baseline >= 15	xx/xx (xx.x)
Tachycardia Event	>= 110 bpm and increase >= 15% from baseline	xx/xx (xx.x)
Bradycardia Event	<= 50 bpm and decrease >= 15% from baseline	xx/xx (xx.x)

n = number of subjects in the category. N1 = number of subjects with data for the parameter. % = 100 x n/N1. mmHg = millimeter of mercury. bpm = beats per minute.
Baseline is the last available measurement prior to IMP administration.

Source: Listing 4.6.2Report generated by program: PPD Version yyyy-mm-dd xx:xx
(Page n of N)

Note to Programmer: Remember to leave a space e.g. between ">=" and "180" and to leave a space e.g. between ">=" and "20". Please remember to use periods "." (instead of ";") in the footnote where the mocks show ".".

Table 3.7.1 Post-Treatment Abdominal Ultrasound Qualitative Results
Analysis Set: All Subjects Treated

	Abdominal Ultrasound Result		
	Normal	Abnormal	Missing
Visit	n/N1 (%)	n/N1 (%)	n
Month 30 (N = xxx)	xx/xx (xx.x)	xx/xx (xx.x)	x
Month 36 (N = xxx)	xx/xx (xx.x)	xx/xx (xx.x)	x
Month 42 (N = xxx)	xx/xx (xx.x)	xx/xx (xx.x)	x
. . .			

N1 = number of subjects with a non-missing qualitative result. n = number of subjects in the category. % = 100 x n/N1.

Source: Listing x.x
Report generated by program: PPD Version yyyy-mm-dd xx:xx (Page n of N)

“The following sections (pg#112-122) have been removed:

- Listing 4.1.1 Subject Disposition and Demographic Data ...Analysis Set: All Subjects Screened (Pg#112)
- Listing 4.1.2 Subject Disposition and Demographic Data ...Analysis Set: All Subjects Treated (Pg#113)
- Listing 4.1.3 Missed Visits...Analysis Set: All Subjects Screened (Pg#113)
- Listing 4.1.4 CSR Reportable Protocol Deviations Analysis Set: All Subjects Screened (Pg#114)
- Listing 4.2.1 Hemophilia B History...Analysis Set: All Subjects Treated (Pg#115)
- Listing 4.2.2 Joint Status at Screening...Analysis Set: All Subjects Treated (Pg#116)
- Listing 4.2.3 Bleeding History in Year Prior to Screening Analysis Set: All Subjects Treated (Pg#117)
- Listing 4.2.4 History of Previous Factor IX Replacement Therapy Use 30 days Prior to Visit 1 (Screening)...Analysis Set: All Subjects Treated (Pg#118)
- Listing 4.2.5 Factor IX Replacement Therapy Use (1 Year Prior to Visit 1 (Screening)...Analysis Set: All Subjects Treated (Pg#119)
- Listing 4.2.6 Prior or Concomitant Medication/Therapy Analysis Set: All Subjects Treated (Pg#120)
- Listing 4.2.7 Medical and Surgical History ...Analysis Set: All Subjects Treated (Pg#121)
- Listing 4.2.8 Factor IX Gene Sequencing ...Analysis Set: All Subjects Treated (Pg#122)”

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“The following sections (pg#173-205) have been removed:

- Listing 4.4.1 Adverse Events by Subject ID, Onset Day, Primary System Organ Class and Preferred Term...Analysis Set: All Subjects Treated (Pg#173)
- Listing 4.4.2 Serious Adverse Events (SAEs)...Analysis Set: All Subjects Treated (Pg#174)
- Listing 4.4.3 Listing of Deaths...Analysis Set: All Subjects Treated (Pg#175)
- Listing 4.4.4 On-Study Invasive Procedures...Analysis Set: All Subjects Treated (Pg#176)
- Listing 4.5.1 ALT and AST Values ...Analysis Set: All Subjects Treated (Pg#177-178)
- Listing 4.5.2 Laboratory Test Results (Hematology Panel) from Medpace Analysis Set: All Subjects Treated (Pg#179)
- Listing 4.5.3 Laboratory Test Results (Chemistry Panel) from Medpace Analysis Set: All Subjects Treated (Pg#180)
- Listing 4.5.4 Laboratory Test Results (Coagulation Panel) from Medpace Analysis Set: All Subjects Treated (Pg#180)
- Listing 4.5.5 Laboratory Test Results (Serology Panel) from Medpace Analysis Set: All Subjects Treated (Pg#181)
- Listing 4.5.6 Laboratory Test Results (Alpha-fetoprotein) from Medpace Analysis Set: All Subjects Treated (Pg#182)
- Listing 4.5.7 Potentially Clinically Significant Laboratory Values Analysis Set: All Subjects Treated (Pg#183-184)
- Listing 4.5.8 Laboratory Test Comments...Analysis Set: All Subjects Treated (Pg#185)
- Listing 4.6.1 Vital Signs, Weight, and Height...Analysis Set: All Subjects Treated ((Pg#186)
- Listing 4.6.2 Potentially Clinically Significant Vital Signs Analysis Set: All Subjects Treated (Pg#187-188)
- Listing 4.7.1 Investigational Product Exposure...Analysis Set: All Subjects Treated (Pg#189)
- Listing 4.8.1 Anti-Factor IX Antibodies and Factor IX Inhibitors Analysis Set: All Subjects Treated (Pg#190-191)
- Listing 4.8.2 Neutralizing Antibodies to AAV5 (titer) Data from Precision for Medicine Analysis Set: All Subjects Treated (Pg#192)
- Listing 4.8.3 Anti-AAV5 Antibodies (titer) from Unilabs Analysis Set: All Subjects Treated (Pg#193-194)
- Listing 4.8.4 Average T-cell (AAV5-capsid) ELISPOT ((SFU)/300000 PBMCs) Analysis Set: All Subjects Treated (Pg#195-197)
- Listing 4.8.5 Inflammatory Markers from Medpace Analysis Set: All Subjects Treated (Pg#198-199)
- Listing 4.8.6 Vector DNA -Blood (copies/mL) from Charles River Analysis Set: All Subjects Treated (Pg#200)
- Listing 4.8.7 Vector DNA -Semen (copies/mL) from Charles River Analysis Set: All Subjects Treated (Pg#201)
- Listing 4.8.8 End of Continuous Prophylaxis...Analysis Set: All Subjects Treated (Pg#202)
- Listing 4.8.9 Factor IX Recovery (%) Analysis Set: All Subjects Treated (Pg#203)
- Listing 4.8.10 Comments Not Listed Elsewhere...Analysis Set: All Subjects Treated (Pg#204)
- Listing 4.8.11 Abdominal Ultrasound...Analysis Set: Safety Population (Pg#205)

16.1.9.2 Data Monitoring Committee (DMC)

Data Monitoring Committee Charter

Trial IDs:	CT-AMT-061-01 and CT-AMT-061-02
Trial Titles:	CT-AMT-061-01: Phase IIb, open-label, single-dose, single-arm, multi-center trial to confirm the Factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B CT-AMT-061-02: Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B
Trial Indication:	Haemophilia B
Investigational Medicinal Product (IMP):	AAV5-hFIXco-Padua (adeno-associated viral vector containing the naturally occurring Padua variant of human factor IX gene)
Date:	21 January 2021
Version:	3.0
Sponsor:	uniQure biopharma B.V. Paasheuvelweg 25a 1105 BP Amsterdam The Netherlands Phone: PPD

CT-AMT-061-01 AND CT-AMT-061-02 DATA MONITORING COMMITTEE CHARTER REVISION LOG

Version #	Revision Date	Section(s) Modified	Brief Description of Revision(s) or Reason(s) for Revision
Version 1.0	06 April 2018	N/A	Original issue.
Version 2.0	27 April 2020	Section 1 and 2 Section 5, 10, and 11 Section 5.1 Section 8.3 and 8.4 Section 8.7	Changes to required document signatory. Clarification regarding NAB review timeline requirements. Update to DMC Membership requirements from 5 to 4 members. Update to DMC member meeting quorum number and voting number requirements from 4 to 3 members. Clarification regarding timeline for DMC member meeting minutes comments.
Version 3.0	21 January 2021	Section 2 and Appendix 2	Sponsor contact updated.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAV5	Adeno-associated viral vector serotype 5
AAV5-hFIXco-Padua	AMT-061; Adeno-associated viral vector containing the naturally occurring Padua variant of human coagulation Factor IX gene
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DMC	Data Monitoring Committee
FIX	Factor IX
gc	Gene copy
IMP	Investigational Medical Product
IRB	Institutional Review Board
NAB	Neutralizing antibody
PCS	Potentially clinically significant
rAAV5	Recombinant adeno-associated viral vector serotype 5
SAE	Serious adverse event
SC	Steering Committee
TFLs	Tables, figures, and listings

1. DMC MEMBERS' APPROVAL OF DATA MONITORING COMMITTEE CHARTER

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1. DMC MEMBERS' APPROVAL OF DATA MONITORING COMMITTEE CHARTER

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2. SPONSOR'S APPROVAL OF DATA MONITORING COMMITTEE CHARTER

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Clinical Development

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Date

3. INTRODUCTION

The Data Monitoring Committee (DMC) is a committee established by uniQure, composed of individuals with appropriate and relevant experience, to review data from the Phase IIb study CT-AMT-061-01 and the pivotal Phase III study CT-AMT-061-02 in their AMT-061 clinical development program.

The DMC will monitor the safety of the subjects during both trials. The DMC will evaluate 6 week interim efficacy data from CT-AMT-061-01 and confirm if the dose of 2 x 10^{13} gene copies (gc)/kg AMT-061 should be used in CT-AMT-061-02. In addition, the DMC will assess whether there is an impact of pre-existing neutralizing antibodies (NABs) titers on clinical outcomes following single treatment with AMT-061.

This Charter defines the roles and responsibilities of the DMC members, Sponsor, and other DMC administrative personnel, and will detail the frequency and timing of meetings, communication methods between the DMC and Sponsor, Principal Investigator, and study representatives, the maintenance of confidentiality, and details on data to be provided to the DMC and statistical considerations. This Charter will serve as the standard operating procedure for the DMC. The operating procedures of the DMC are based on and are in compliance with the Food and Drug Administration's "Guidance for Clinical Trial Sponsors [on the] Establishment and Operation of Clinical Trial Data Monitoring Committees" (March 2006),[1] World Health Organization's "Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards" (2005),[2] and the European Medicines Agency's "Guideline on Data Monitoring Committees" (2006).[3]

4. TRIAL DESIGNS

4.1 Study Treatment

uniQure is developing AMT-061 as a somatic gene therapy for hemophilia B.

AMT-061 (AAV5-hFIXco-Padua) is a recombinant adeno-associated viral vector serotype 5 (rAAV5) encoding the naturally occurring Padua variant of human coagulation Factor IX (FIX), under control of a liver-specific promoter. The FIX-Padua protein differs from the 'wild type' human FIX protein by a single amino acid and possesses an activity approximately 6-fold higher than wildtype FIX.

4.2 CT-AMT-061-01

CT-AMT-061-01 is a Phase IIb, open-label, single-dose, single-arm, multi-center trial to confirm the FIX activity level of the AAV5 vector containing the Padua variant of a codon-optimized human FIX gene (AAV5 hFIXco-Padua, AMT-061) administered to adult subjects with severe (FIX <1%) or moderately severe (FIX ≤2%) hemophilia B. In addition, the safety profile of AMT-061 will be assessed.

The trial will be conducted at multiple centers in the United States in 3 male (possibility of 6) subjects aged ≥18 years with congenital hemophilia B with either a known severe FIX deficiency, for which the subject is on continuous routine FIX prophylaxis or on-demand FIX

replacement therapy, or a known moderately severe FIX deficiency and a severe bleeding phenotype.

Subjects will receive a single infusion of 2 x 10^{13} gc/kg AMT-061 and will be followed for 1 year in a post-treatment follow-up phase, and then for an additional 4 years during a long-term follow-up phase. During the post-treatment follow-up phase, subjects will return to the clinic for scheduled safety and efficacy assessments. During the long-term follow-up, subjects will return to the clinic every half year for evaluation of efficacy parameters and safety. Occurrence of adverse events (AEs) will be continuously monitored, with at least quarterly contact moments between site staff and subject to discuss.

4.3 CT-AMT-061-02

CT-AMT-061-02 is a Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human FIX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B. The purpose of this Phase III trial is to demonstrate the efficacy of AMT-061 in terms of endogenous FIX activity and annualized bleeding rate, and to further describe its safety profile.

The trial will be conducted at multiple centers in multiple countries in approximately 56 male subjects aged ≥18 years with congenital hemophilia B with a known severe or moderately severe FIX deficiency for which the subject is on continuous routine FIX prophylaxis.

Subjects will participate in a lead-in phase (minimum of 6 months) were they will record their use of prophylactic FIX replacement therapy and bleeding episodes in their e-diary.

Criteria for Investigational Medicinal Product (IMP) dose administration in this trial include the following: availability of the interim results of the CT-AMT-061-01 dose confirmation trial that confirm the dose for AMT-061 for this trial (as confirmed by this DMC; see **Section 9**); the subject has adequate record keeping and adequate compliance with study activities during the lead-in phase as determined by the investigator, and subjects must still meet all inclusion and exclusion criteria.

Subjects will receive a single infusion of AMT-061 and will be followed for 1 year in a post-treatment follow-up phase, and then for an additional 4 years during a long-term follow-up phase. During the post-treatment follow-up phase, subjects will continue to record their use of FIX replacement therapy and bleeding episodes in the e-diary, and will return to the site for scheduled safety and efficacy assessments. During the long-term follow-up, subjects will return to the clinic every half year for evaluation of efficacy parameters and safety. Occurrence of AEs will be continuously monitored, with at least quarterly contacts between site staff and subject.

5. RESPONSIBILITIES AND TASKS OF THE DMC

The DMC is created for these 2 studies to review accumulating safety data, to confirm if the dose in the Phase IIb study should be used in the Phase III study, and to assess the impact of pre-existing NABs. The DMC's activities will protect the rights, safety, and well-being of the

subjects in the studies, will assist with monitoring the overall conduct of the studies, and will protect the validity and credibility of the studies.

The primary responsibilities of the DMC are the following:

1. Complete a confidentiality document and a Disclosures of Conflict of Interest.
2. Review the draft DMC Charter, comment and recommend modifications, and, after it is finalized, follow the directives of the Charter for the duration of the study.
3. Review the protocol and other provided study material as necessary to perform their DMC activities.
4. Review monthly serious adverse event (SAE) reports.
5. Review data provided after every set of approximately 10 subjects enrolled (depending on enrollment) to assess the impact of NABs, as described in **Section 10** and **Section 11**.
6. Review the DMC Data Report provided prior to each DMC safety data review meeting (safety tables and listings as described in **Section 11**).
7. Attend the DMC scheduled meetings and if necessary, any ad hoc DMC meetings.
8. Following review of the DMC Data Report and discussion of data during closed sessions of each DMC safety data review meeting, prepare recommendations to the Sponsor as described in **Section 8.5**, indicating if the studies should continue, be temporarily stopped to investigate a safety issue, be modified, or stopped due to an urgent safety issue.
9. Following review of 6 week interim efficacy data from CT-AMT-061-01 at the first DMC safety data review meeting, prepare a recommendation to the Sponsor confirming if the dose of 2 x 10^{13} gc/kg AMT-061 used in the Phase IIb study CT-AMT-061-01 is suitable or not for administration in the Phase III study CT-AMT-061-02, as described in **Section 9**. The DMC may, in discussion with the Sponsor, Principal Investigator, or the Steering Committee (SC), decide if 1, 2, or 3 additional patients are required for further confirmation of efficacy and safety with the dose under investigation, or they may recommend that a second dose be evaluated.
10. Review and approve the DMC meeting minutes as prepared by the DMC Secretary, following each meeting (see **Section 8.7**).
11. The DMC Chair will be responsible for the following additional functions:
    - Act as the primary contact for the DMC.
    - Lead the data review discussions during the closed sessions of the DMC safety data review meetings (see **Section 8.2.2**).
    - Review, approve, and sign the DMC recommendation letter drafted by the DMC Secretary, who will then provide the final letter to the Sponsor Contact, Principal Investigator, and DMC Administrator (see **Section 8.6**).

5.1 DMC Membership

The DMC will consist of 4 non-sponsor, independent voting members who have been approved by the Sponsor and the SC. They will be physicians and clinicians with expertise in the area of hemophilia. Each DMC member will be considered and recognized as an expert in his/her fields of practice and will be experienced and knowledgeable with the conduct of clinical trials. DMC members may not participate in the study as Investigators and are not

allowed to knowingly administer medical or any other type of care to any subject in the study during the study conduct.

One member (1) will be designated as the Chair of the DMC. The Chair will be the primary contact for the DMC with the Sponsor, SC, and Principal Investigator, communicating through the DMC Administrator, and will also lead the discussions during the closed sessions of the DMC safety data review meetings (see **Section 8.2.2**).

It is understood that the DMC members will be available to fulfill the DMC obligations for the entire planned 5 year period of the two studies specified in this Charter, until the studies are completed or terminated, and the final required DMC meeting has occurred and safety data have been reviewed by the DMC. In the event that a DMC member has to stop his/her participation in the DMC, it will be determined by the Sponsor in consultation with the DMC Chair if a replacement will be required. If a replacement is deemed required, they will be selected by the Sponsor and the SC. No replacement can be made without the approval of the Sponsor.

The members of the DMC are identified in **Appendix 1**.

5.2 Conflict of Interest

Members of the DMC should remain independent of the study. Prior to their participation on the DMC, the members will be asked to sign a form disclosing any conflicts of interest, whether scientific, financial, or other, and will be required to notify the Sponsor or designee of any changes that occur during their participation on the DMC.

Members of the DMC, and their immediate families, will not buy, sell, or hold stock, options, derivatives or any other financial instrument related to the Sponsor's company for the following periods: from the date applicable to the member's first DMC meeting until the first to occur of the following: (a) the last meeting of the DMC; (b) the study results are made public; or (c) until a year after the member's active personal involvement in the DMC ends.

Certain other activities are not viewed as constituting conflicts of interest but must be reported annually to the Sponsor: the participation of a member in educational activities supported by the Sponsor and occasional scientific consulting to the Sponsor on issues not related to the product in the study.

5.3 Confidentiality

All members of the DMC will treat all reports, meeting discussions, minutes, and recommendations of the DMC as confidential.

5.4 Reimbursement

DMC members will receive an honorarium for their time and effort on the committee. DMC members will be reimbursed for reasonable expenses related to attending DMC meetings, such as transportation, lodging, and meals. No other payment or future consideration will be provided.

5.5 Indemnity

DMC members will be indemnified by the Sponsor from third party claims relating to harm arising to study participants or other parties as a result of such DMC members' actions and decisions taken in good faith in accordance with the terms of this Charter. The foregoing shall not apply in the case of harm caused by the negligence or wrongful conduct of a DMC member.

6. RESPONSIBILITIES OF THE SPONSOR

The Sponsor is responsible for supplying safety and efficacy information to the DMC, Regulatory Authorities, and the Investigators. The Sponsor's responsibilities include the following:

1. Assure the availability of resources to the DMC so that the DMC may fulfill its responsibilities as described in this Charter.
2. Review the DMC recommendations. The Sponsor has the ultimate responsibility for all final decisions concerning whether or not the DMC recommendations will be implemented.
3. The Sponsor will be the responsible party for the design and conduct of the study, and regulatory reporting of SAEs in accordance with the applicable regulations.

The Sponsor Contact, identified in **Appendix 2**, or their designee, will be responsible for the following:

1. Review DMC recommendations and arrange for Sponsor review and decision.
2. Serve as a resource to the DMC for requests of additional data or other information.
3. Be available to address safety issues that occurred in the study.
4. Attend the open sessions of all DMC meetings.
5. On a monthly basis, ensure that the DMC Secretary is provided with a monthly cumulative SAE listing with event narratives from the study for distribution to the DMC.
6. Ensure that the DMC Secretary is provided with a cumulative SAE listing with event narratives for inclusion with the DMC Data Report prior to any DMC safety data review meeting.

7. RESPONSIBILITES OF THE DMC ADMINISTRATOR AND DMC SECRETARY

The Sponsor will engage a DMC Administrator and DMC Secretary to aid in planning, organizing, and coordinating DMC activities, disseminating meeting reports, and communicating between the DMC and the Sponsor. The DMC Administrator and DMC Secretary will sign a confidentiality agreement for their participation in the DMC activities. The DMC Administrator and DMC Secretary for the study listed in **Appendix 2**.

The DMC Administrator is responsible for the following:

1. Develop and facilitate the review and signing of the DMC Charter.
2. Plan, organize, and coordinate DMC activities in accordance with the established DMC Charter, including timely delivery of study data (e.g., DMC Data Reports).

3. Provide administrative and logistic services to the DMC, serving as the primary contact point for day-to-day operations and between the DMC and the Sponsor.
4. Plan, organize, and host each of the DMC meeting open sessions.
5. Provide periodic progress status reports of the DMC activities to the Sponsor as needed.

The DMC Secretary will assist the DMC Administrator and is responsible for the following:

1. Forward the DMC Data Reports, monthly cumulative SAE listings and narratives, and any safety-related information to the DMC members. Materials will be forwarded at least 5 business days before any scheduled DMC meeting or teleconference, and as soon as possible before any ad hoc teleconference, when applicable.
2. Attend both the open and closed sessions of the DMC meetings. Produce, distribute for review, and finalize DMC meeting minutes for each meeting, separately for the open and closed sessions (see **Section 8.7**).
3. Facilitate drafting of the Recommendations Letter based on the meeting minutes (see **Section 8.6**).
4. Maintain a secure central file of all data reports, all minutes, and all DMC Recommendation Letters submitted to the Sponsor.
5. Provide an archived copy of all maintained files to the Sponsor after the study database is locked and the DMC activities have concluded.

8. DMC MEETINGS

The DMC meetings are planned to either be face-to-face or via teleconference (see **Appendix 3** for schedule). The DMC will participate in an initial (kick-off) meeting (**Section 8.1**) and at least 9 safety data review meetings (**Section 8.2**). At the first data review meeting, the DMC will review subject safety and will also review efficacy data from study CT-AMT-061-01 and confirm the dose of AMT-061 to be used in study CT-AMT-061-02 (**Section 9**). Subsequent data review meetings will focus on subject safety and assessment of the impact of NABs and will occur approximately every 6 months during subject enrollment and then every 12 months until both studies have completed or have been terminated. Meetings focused on the impact of NABs will be organized as needed depending on the rate of subject enrollment.

Ad hoc meetings may take place if requested by the DMC or Sponsor (**Section 8.8**).

8.1 Kick-off Meeting

The initial (kick-off) meeting of the DMC will be held prior to enrolment of the first subject in the trials and will be an open meeting to provide the DMC with an understanding of the study expectations and to establish the DMC procedures. At the meeting, the DMC members will meet with Sponsor representatives to discuss both of the studies, review and finalize the DMC Charter, and discuss the proposed content of the DMC Data Report (see **Section 11**). Additional topics which may be discussed include: the frequency of meetings, the format of future meetings, specific analyses approaches, key safety variables to be reviewed for decision making, and the potential need for additional meetings. The DMC Charter will be finalized and signed off shortly after the meeting.

The DMC Chair approves the DMC Charter on behalf of the DMC. The DMC Charter must be approved prior to start of screening of subjects. Once the approved DMC Charter is accepted by all DMC members by signature, the DMC will be considered activated.

8.2 DMC Safety Data Review Meetings

The DMC will participate in at least 9 safety data review meetings. DMC data review meetings will consist of two open and one closed session. The DMC Secretary will record both open and closed sessions, and prepare minutes of the meeting (see **Section 8.7**).

8.2.1 Open Session I

The first open session will be hosted by the DMC Administrator and will include the DMC members, DMC Secretary, Sponsor representatives (may include the Principal Investigator), and the Study Biostatistician. At the open session, the Sponsor's representative(s) and study personnel involved in trial management will present an overview of the study's current progress status to the DMC. The open session should focus on the conduct and progress of the trial with special attention to safety and efficacy data. Data presented in the open session may include data on enrolment data, individual adverse events, baseline characteristics, and subjects lost to follow-up.

8.2.2 Closed Session

The closed session will be led by the DMC Chair and will only include the members of the DMC and the DMC Secretary.

The Sponsor's representative(s) as well as study personnel involved in trial management will leave the meeting/teleconference prior to the start of the closed session. The DMC closed session will begin once the DMC Secretary confirms only the attendees for the closed session are on the teleconference web-link and telephone call-in line; connections to the session will be monitored during the session to ensure the closed nature of the discussion.

Prior to the meeting, the DMC Data Report and other safety information will have been provided to the DMC via the DMC Secretary for their review.

During the closed session, the DMC members will discuss the provided data summaries and formulate their recommendations to the Sponsor.

DMC members have the right to request detailed information regarding any of the reported individual clinical endpoint events if deemed necessary. The Sponsor Contact and Study Biostatistician will be "on call" during the DMC closed session, in case the DMC requests additional safety information and/or needs to discuss statistical considerations of the provided data; the Study Statistician will maintain confidentiality concerning these discussions.

8.2.3 Open Session II

At the conclusion of the closed session, the open session attendees will be invited to rejoin the meeting/teleconference for a second open session. This second open session will be hosted by the DMC Administrator and will include the DMC members, DMC Secretary, and the Sponsor Contact at a minimum. At this session, the DMC will share their

recommendations with the Sponsor Contact and other Sponsor representatives who are present. Concerns or questions from the DMC may be addressed at this time as well.

8.3 Quorum

For a meeting to proceed, a quorum of three (3) DMC members is required at each safety data review meeting.

At the beginning of the open sessions, the DMC Administrator will confirm the attendance of the quorum. If the quorum is not met, the Chair will confirm that the DMC meeting should not proceed and the DMC Administrator will reschedule the meeting.

The quorum at an ad hoc data review meeting will be three (3) DMC members.

8.4 Voting

All 4 DMC members have voting privileges. To vote, a DMC member must be a participant in the DMC meeting. Voting is by voice and will be recorded by the DMC Chair and in the closed portion of the meeting minutes.

DMC members are responsible for voting on the following:

- All recommendations that will be submitted to the Sponsor (see **Section 8.5**).

A unanimous vote by all members is required for all recommendations to implement a modification to the conduct of the study(ies), to temporarily halt enrollment, or to stop the study(ies).

Any recommendations to modify the study's conduct (e.g., early termination of the study due to alarming safety concerns) must be agreed upon by all members of the DMC and will be made on the basis of the provided study safety data.

A simple voting majority at a meeting will be required for a routine proposal, motion, or recommendation to be made to the Sponsor that does not involve modification to the conduct of the study or discontinuation of the study.

8.5 DMC Recommendations

Based upon their review and discussion of the safety data at each meeting, the DMC has the responsibility to recommend to the Sponsor whether the study should proceed as planned, be modified, or be stopped.

Anticipated recommendations are as follows:

- Continue the studies according to the protocols and current amendments.
- Temporarily stop enrollment in the CT-AMT-061-02 study to investigate a safety issue.
- Modify the study protocol(s) and/or the informed consent.
- Stop the studies due to an urgent situation (serious safety issue).

If the DMC detects a safety signal or has concerns about the provided data in the DMC Data Report or other safety information, they may request additional safety-related information from the Sponsor Contact or designee.

Modifications recommended by the DMC may include, but are not limited to, changes in the exclusion criteria due to NABs (see **Section 10**), other changes in the inclusion/exclusion criteria, frequency of safety monitoring, and instituting changes in the study procedures. While modifications are put into place, enrollment would continue in the CT-AMT-061-02 study unless the DMC also recommends for a temporary stop.

In the case that the DMC recommends to stop the studies or to temporarily halt enrollment in CT-AMT-061-02, the DMC Chair will notify the Sponsor Contact immediately. If the Sponsor needs additional clarification, the Sponsor Contact, or designee, and the DMC members will meet as quickly as possible to discuss the recommendations.

If the DMC recommends to stop the studies, the Sponsor's response would be to place study recruitment on hold pending final decision by the Sponsor. Investigators, Institutional Review Boards (IRBs), and other Regulatory Authorities will be notified by the Sponsor, as appropriate.

8.6 Recommendation Letter

Following each safety data review meeting, the DMC will submit a letter to the Sponsor outlining their recommendations for the study. The DMC Secretary will facilitate the drafting of the letter, based on the DMC recommendations discussed and agreed upon during the closed session. If there is a recommendation for action, the brief rationale for such recommendation will be included in the letter. The DMC Recommendation Letter will be sent to the DMC Chair for review, approval, and signature following the meeting (no later than 1 working day after the DMC meeting). The DMC Secretary will then provide a copy of the final signed Recommendation Letter to the Sponsor Contact, Principal Investigator, and the DMC Administrator on the DMC Chair's behalf via email. If the recommendation letter is not provided to the Sponsor on the same day as the meeting, the DMC Secretary will provide the Sponsor with the DMC members' recommendation decision via email.

The Sponsor will be responsible for communicating to the Investigators, IRBs, and/or other regulatory bodies, as appropriate, a summary of the DMC recommendation(s) and the Sponsor's proposed action.

8.7 DMC Meeting Minutes

Minutes of all meetings will be prepared by the DMC Secretary.

The DMC minutes for open and closed meeting sessions will be circulated to the DMC members for comments within 5 business days after a meeting. If comments/confirmation are not received within 5 business days, except for a pre-specified reason from a DMC member, it will be assumed there are no comments. At the same time, the minutes for the open sessions will be circulated to the Sponsor for comments. If the DMC has a recommendation for action, this will be outlined in the open session minutes with any rationale. The DMC Secretary will incorporate the comments and then route the final minutes to the DMC members for approval signatures.

Each DMC member will be provided with final copies of the complete summary meeting minutes by the DMC Secretary and the Sponsor will be provided with a final copy of the open session meeting minutes with DMC recommendations.

At the end of the study, the DMC Secretary will forward to the Sponsor Contact a complete set of summary meeting minutes (including both open and closed sessions).

8.8 Ad hoc Meetings

An emergency meeting of the DMC may be called at any time by the Chair should questions of subject safety arise. The request will be sent to the DMC Administrator, who will then schedule and organize the meeting and meeting materials. Further data review meetings in addition to those already planned may be required based on study enrollment extending beyond the planned duration of the 2 trials.

Ad hoc specialists can be invited to DMC meetings as recommended by the DMC or uniQure.

9. AMT-061 DOSE CONFIRMATION FOR PHASE III TRIAL

At their first safety data review meeting, the DMC will confirm if the dose of 2 x 10^{13} gc/kg AMT-061 used in the Phase IIb study CT-AMT-061-01 is suitable for administration in the Phase III study CT-AMT-061-02, in addition to reviewing the study safety.

In addition to safety data, the DMC will be provided with the 6 week interim efficacy data from CT-AMT-061-01 to review prior to the meeting. The DMC will evaluate response to treatment with a single dose of 2 x 10^{13} gc/kg of AMT-061 in terms of FIX activity levels and assess whether observed FIX activity levels are ≥5%.

Following their review, the DMC has the responsibility to provide a recommendation to Sponsor concerning the dose of 2 x 10^{13} gc/kg AMT-061, either confirming this dose is suitable for use in the Phase III study or to suggest further evaluation. If the DMC determines that the observed response is not within the expected range, or they do not observe enough consistency of effect to proceed to Phase 3 dosing, they can elect to recommend up to three more subjects be treated at the same dose or recommend a second dose be studied.

Anticipated recommendations concerning the dose of AMT-061 are as follows:

- Proceed with dosing in CT-AMT-061-02 with a single treatment of 2 x 10^{13} gc/kg AMT-061
- Treat 1, 2, or 3 additional subjects at the dose of 2 x 10^{13} gc/kg AMT-061 and reevaluate the data
- Evaluate a second dose of AMT-061

This recommendation will be in addition to a safety recommendation as per **Section 8.5**.

10. NEUTRALIZING ANTIBODIES

The DMC will assess whether there is an impact of pre-existing NAB titers on clinical outcome following treatment with AMT-061. Should the DMC determine that there is a recognizable impact of a certain titer and above, they can recommend institution of an exclusion criterion based on these titers for further enrollment in the study.

The DMC will review data after every set of approximately 10 subjects enrolled depending on enrollment rates (enrollment will not stop during this review). Review of this data will be

included in the safety data review meetings or in NAB-specific data review meetings, depending on the timing of the review due to the rate of enrollment. NAB review meetings may be combined and include multiple set of 10 subjects due to a high rate of enrollment. Ad hoc meetings may be called if there is a safety concern, impacted outcomes, or need for a protocol amendment. During their review, the DMC will provide one of the following assessments:

- No clear impact, continue with prospective analysis
- There are impacted outcomes (safety and/or efficacy), institution of a data-driven cut-point
- Protocol amendment needed

An enactment of a NAB titer cut-off mid-trial is recommended if all of the following criteria are met:

- Two patients with NAB titers and FIX <5%
- No patients with NAB titers equal or greater to NAB titers in patients with FIX ≥5%
- No patients without NAB titer and FIX <5%

11. DATA REPORTS FOR REVIEW BY THE DMC

For each data review meeting, the DMC Data Reports will be provided to each DMC member by the DMC Secretary via a suitable secure method for their prior review. The report will be delivered approximately 10 business days before each DMC meeting.

The DMC Data Report for the DMC includes the tables, figures, and listings (TFLs) to be reviewed by the DMC members at the scheduled and/or ad hoc meetings. Mock-ups of the report format and content (i.e., TFL shells) are provided for CT-AMT-061-01 in **Appendix 4** and for CT-AMT-061-02 in **Appendix 5**. The Sponsor and DMC members will review and approve the format and content of the mock-up DMC Data Report prior to the first DMC data review meeting.

The following descriptive summaries and listings will be included in the DMC Data Report based on the cumulative data in the study.

- Baseline demographic tables and results of the number of subjects screened, randomized or discontinued (with reasons for discontinuation) for the study
- List of frequent AEs (>5%) listed in order of frequency, from high to low and summarized of all SAEs and AEs leading to study discontinuation
- Summaries of all potentially clinically significant (PCS) laboratory results and vital signs
- Summaries of increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- NAB titer
- Capsid-specific T-cells
- FIX activity levels

A subset of these outputs will be provided for DMC review after every set of approximately 10 subjects enrolled, for assessment of the impact of NABs. This subset of outputs will be identified in the DMC Data Report shells.

12. DMC CLOSURE

The responsibilities of the DMC will end when both clinical trials have closed. The DMC may be closed during a formal DMC meeting with all DMC members.

The DMC Secretary will provide an archived copy of all maintained files (recommendation letters, DMC data reports, open and closed meeting minutes) to the Sponsor after the study database is locked and the DMC activities have concluded.

13. REFERENCES

1. Food and Drug Administration Final Guidance: Guidance for clinical study sponsors on the establishment and operation of clinical study data monitoring committees. March, 2006.
2. World Health Organization. Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards. 2005.
3. European Medicines Agency. Guideline on Data Monitoring Committees. January, 2006.

APPENDIX 1 DMC MEMBERS

Name, Degrees:	PPD (PPD)
Role/Title:	PPD, University of Rochester School of Medicine & Dentistry PPD, Mary M. Gooley Hemophilia Treatment Center
Address:	Rochester, New York, USA
E-mail:	PPD Tel: PPD
Name, Degrees:	PPD
Role/Title:	PPD, National Hemophilia Center and the Institute of Thrombosis & Hemostasis PPD, Amalia Biron Research Institute of Thrombosis & Hemostasis, Sheba Medical Center
Address:	Tel Hashomer, Israel
E-mail:	PPD Tel: PPD
Name, Degrees:	PPD
Role/Title:	PPD PPD, Emory University
Address:	Atlanta, Georgia, USA
E-mail:	PPD Tel: PPD
Name, Degrees:	PPD
Role/Title:	PPD, Nationwide Children's Hospital
Address:	Columbus, Ohio, USA
E-mail:	PPD Tel: PPD

APPENDIX 2 DMC SUPPORT PERSONNEL

Sponsor Contact[1]	Name, Degree(s):	PPD		
	Title:	PPD, Clinical Development		
	Organization:	uniQure		
	E-mail:	PPD	Tel:	PPD PPD (cell)
DMC Administrator	Name, Degree(s):	PPD		
	Title:	PPD, Medical Writing and Clinical Safety Monitoring, Clinical Safety Associate		
	Organization:	Everest Clinical Research Corporation		
	E-mail:	PPD	Tel:	PPD
DMC Secretary	Name, Degree(s):	PPD		
	Title:	PPD, Clinical Safety Monitoring		
	Organization:	Everest Clinical Research Corporation		
	E-mail:	PPD	Tel:	PPD

1 Primary Sponsor Contact for the DMC through the DMC Administrator or DMC Secretary (e.g., receiving the DMC Recommendations Letter from the DMC Chair).

APPENDIX 3 DMC MEETING PLAN

Meeting Chair: PPD			Minutes By: PPD
Meeting		**Date/Time**	**Meeting Purposes and Objectives**
1	Kick-off Meeting	PPD	Initial meeting: • Review of the studies. • Review and approve DMC Charter.
2	Data Review Meeting: Dose Confirmation and Safety Review	Tentatively: PPD (once interim analysis data is available from CT-AMT-061-01)	Open Session I: • Overview of study progress. Closed Session: • Review of the DMC Data Report • Evaluation of the safety and tolerability of study treatment • Evaluation of the FIX activity data to confirm the AMT-061 dose for CT-AMT-061-02 • Determination of DMC Recommendations to the Sponsor Open Session II: • DMC shares recommendations
3-9	Data Review Meetings: Safety Review	During subject enrollment: approximately every 6 months. Once all subjects enrolled, every 12 months until study completion	Open Session I: • Overview of study progress. Closed Session: • Review of the DMC Data Report • Evaluation of the safety and tolerability of study treatment • Determination of DMC Recommendations to the Sponsor Open Session II: • DMC shares recommendations
	Data Review Meetings: NAB Review	During subject enrollment: approximately every 10 subjects dosed. May be combined with Safety Data Review Meeting	Open Session I: • Overview of study progress. Closed Session: • Review of the NAB DMC Data Report • Determination of DMC Recommendations to the Sponsor Open Session II: DMC shares recommendations
	Ad hoc Meetings (if required)	TBD	DMC may meet if required to discuss and communicate any safety concerns noted between scheduled safety data review meetings.

APPENDIX 4 DMC DATA REPORT SHELLS FOR CT-AMT-061-01

The DMC Data Report TFL shells for CT-AMT-061-01 will be provided in a separate document.

APPENDIX 5 DMC DATA REPORT SHELLS FOR CT-AMT-061-02

The DMC Data Report TFL shells for CT-AMT-061-02 will be provided in a separate document.

Signature Page

CT-AMT-061-01 - Statistical Analysis Plan - Statistical methods

Signed By	Date (GMT)
PPD	PPD
Approved-Internal Approval	

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