16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan for Study CT-AMT-060-01

Statistical Analysis Plan

CT-AMT-060-01

A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) administered to adult patients with severe or moderately severe haemophilia B

Protocol: Version 7.0 dated 20APR2021

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1 Introduction

This document describes the planned statistical analyses for uniQure trial id CT-AMT-060-01. Protocol is version 6.0 dated 22DEC2015.

1.1 Abbreviations and definition of Terms

Abbreviations	Meaning of abbreviations in document
AASLD	American Association for the Study of Liver Diseases
AAV5	Adeno-Associated Viral vector serotype 5
ADRG	Analysis Data Reviewers Guide
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CRP	C-Reactive Protein
DOB	Date-of-birth
DNA	Deoxyribonucleic Acid
FAS	Full-Analysis Set
FIX	Coagulation Factor IX
γGT	Gamma-Glutamyl Transferase
HBeAg	Hepatitis B extracellular Antigen
HBsAg	Hepatitis B surface Antigen
HBV DNA	Hepatitis B Virus Deoxyribonucleic Acid
HCV RNA	Hepatitis C Virus Ribonucleic Acid
hFIX	Human coagulation Factor IX
IgG	Immunoglobulin G
IgM	Immunoglobulin M
Il-1β	Interleukin-1beta
IL-2	Interleukin-2
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
INFγ	Interferon gamma
INR	International Normalized Ratio
ITT	Intention-to-treat
IU	International Unit
MedDRA	The Medical Dictionary for Regulatory Activities
PP	Per-Protocol
PT	Prothrombin Time
PRO	Patient-reported outcome
CCI	CCI
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDRG	Study Data Reviewers Guide
CCI	CCI

Terms	Definitions
Screened	Patient who enters the screening phase

1.2 Trial Objectives and Endpoints

Primary objective and primary end point:

The primary objective of the trial is to investigate the safety of systemic administration of AAV5-hFIX, an adeno-associated viral vector containing a codon-optimized human Factor IX gene, to adult patients with severe or moderately severe haemophilia B.

The primary endpoint is defined as frequency and incidence of adverse events.

Secondary objectives and secondary endpoints:

The secondary objectives will be addressing the efficacy and safety of systemic administration of AAV5-hFIX to adult patients with severe or moderately severe haemophilia B.

The secondary objectives in relation to efficacy are stated as:

- To investigate the effect of AAV5-hFIX on FIX activity level
- To investigate the effect of AAV5-hFIX on the use of FIX replacement therapy
- To investigate the effect of AAV5-hFIX on bleeding episodes
- To investigate the effect of AAV5-hFIX on CCI parameters

Correspondingly the secondary efficacy endpoints are as follows:

Confirmatory Secondary Efficacy Endpoint: FIX-replacement-therapy-free FIX activity.

Supportive Efficacy Endpoints:

- Bleeding rate
- Total consumption of FIX replacement therapy
- CCI

The secondary objectives in relation to safety are stated as:

- To monitor shedding of the AAV5 vector in various body matrices
- To monitor the immune responses against AAV5 capsid proteins in response to AAV5-hFIX
- To monitor for immune responses against FIX protein after administration of AAV5-hFIX
- To investigate the effect of AAV5-hFIX on inflammatory markers

Consequently, the secondary safety end points are the following:

- Vector DNA in semen, blood, saliva, nasal secretions, urine and faeces
- Neutralizing antibodies to AAV5
- Total (IgM and IgG) antibodies to AAV5
- AAV5 capsid-specific T cells
- Antibodies to FIX
- FIX inhibitors

- Inflammatory markers IL-1β, IL-2, IL-6, INFγ, MCP-1

2 Trial Design

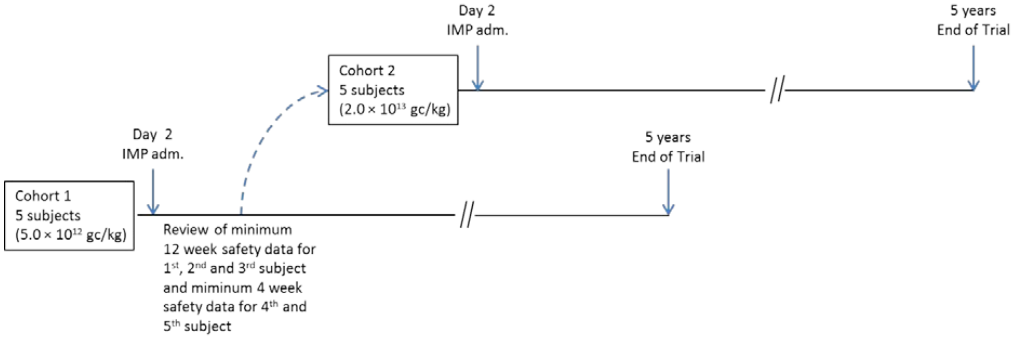
2.1 Trial Procedures – Overview

This trial has an open-label, uncontrolled, single-dose, dose-ascending design and consists of two cohorts, each of 5 patients. Due to the low prevalence of severe and moderately severe haemophilia B patients with a severe phenotype, the trial will be conducted at multiple centres in multiple countries. Since this is a first-in-man single dose escalation trial with a high-risk medicinal product, an adequate information communication system between the sites will be in place (details will be described in the Trial Procedures Manual).

Patients fulfilling the eligibility criteria will be allocated to either Cohort 1 or Cohort 2. Each patient will receive a single dose of IMP (AAV5-hFIX) and will thereafter be followed for five years with respect to safety and with respect to efficacy measured as levels of FIX, bleeding patterns and consumption of FIX replacement therapy. Patients will attend the same visits and undergo the same procedures, regardless of their allocation to Cohort 1 or 2.

Cohort 2 will be initiated based on the recommendation of the data monitoring committee after review of safety data from Cohort 1. These data will include a 12-week follow-up for the first 3 patients dosed as well as four weeks follow-up for the remaining 2 patients in cohort 1 (see figure 2-1). If transaminase elevations requiring corticosteroid treatment have occurred in one or more of the first three patients in Cohort 1, the data monitoring committee may recommend extending the follow-up period, before sponsor decision to initiate Cohort 2 is taken. Inter-cohort stopping criteria are described in the protocol, section 19.2.1

Figure 2-1, Inter-cohort Staggering Interval

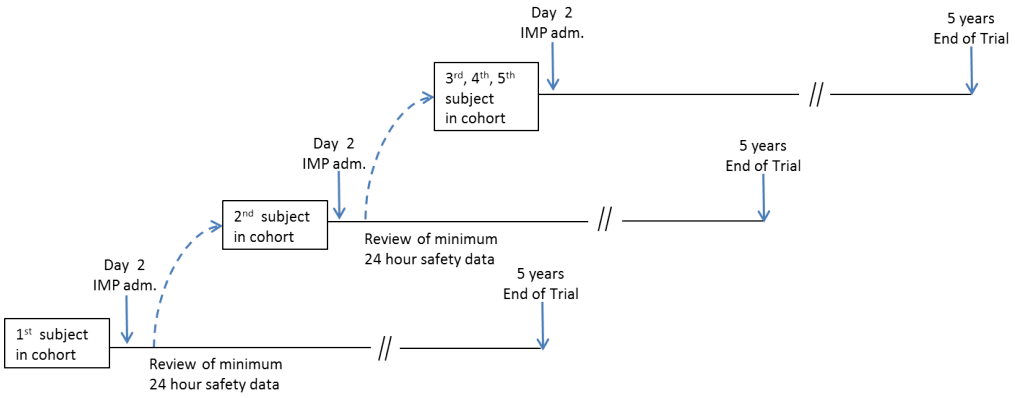


Within each cohort, there will be an observation period between IMP administration to the 1st and 2nd patient and between IMP administration to the 2nd patient and subsequent patient (fig 2-2). Intra cohort stopping criteria are described in the protocol, section 19.2.1.

- After the 1st patient has been dosed in a cohort, the data monitoring committee will evaluate available safety data collected during a period of minimum 24 hours after IMP administration to this first patient. The data monitoring committee will recommend if and when dosing of the 2nd patient can be initiated.
- After the 2nd patient has been dosed in a cohort, the data monitoring committee will evaluate safety data collected during a period of minimum 24 hours after IMP administration to this second patient. The data monitoring committee will recommend if and when dosing of the subsequent 3 patients can be initiated.
- The dosing of the 3rd, 4th and 5th patient within a cohort must be separated by a minimum of 24 hours to ensure observation of any acute reactions.

Details on an adequate information communication system with and between the sites to ensure the timings of patients dosing within a cohort are adhered to will be described in the Trial Procedures Manual.

Figure 2-2, Intra-cohort Staggering Interval



After IMP administration, patients will remain at the clinical site for 24 hours for monitoring of tolerance to IMP and for detection of potential immediate adverse events. Hereafter, patients will be followed with respect to safety and efficacy parameters for 5 years (260 weeks):

- Every week up to week 12
- Every 2nd week from weeks 12 to 26
- Every 13th week from weeks 26 to 156 (6 months to 3 years)
- Every 26th week from weeks 156 to 260 (3 years to 5 years)

Patients on prophylactic FIX replacement therapy will be tapered off their prophylactic FIX replacement therapy in the period from Visit 8 to Visit 14 (weeks 6 – 12). If the investigator determines that FIX replacement therapy should be re-initiated, based on FIX levels or for other reasons, prophylactic FIX replacement therapy may be tapered off again at a later time point. In relation to the withholding of FIX replacement therapy, additional visits may be required for the purpose of additional monitoring of FIX activity levels. For further details, please refer to protocol, section 11.4.

During the entire trial period, blood samples will be drawn regularly for measurements of FIX activity and FIX protein concentration in plasma. For patients on prophylactic FIX replacement therapy, attempts should be made to allow blood sampling at time points where FIX activity and FIX protein concentration are expected to be at lowest justifiable levels. For further information, please refer to protocol, section 12.1.1.

Flowcharts for the trial procedures appear in section 5 of the protocol.

2.2 Determination of Sample Size

No formal sample size calculation is made. The choice of 5 patients in each cohort is considered sufficient to capture commonly occurring adverse events.

2.3 Blinding

The trial is an open-label un-controlled trial where patients are asigned to one of two cohorts. In each cohort one single dose of trial drug (AAV5-hFIX) is administered for each patient. In cohort 1 one single dose of 5.0×10^{12} gc/kg IMP is administered whereas in cohort 2 one single dose of 2.0×10^{13} gc/kg IMP is administered.

2.4 Data Pre-processing

A special problem arises in relation to the data originating from the e-Diary (where the patient registers bleeds and administration of FIX replacement therapy), since it is not possible to correct data once entered in the e-Diary data base. For corrections of erroneous e-Diary data when generating the trial data base the Data Management Notes are used. These notes contain comments related to queries on (amongst other data) e-Diary data, but also contains investigator comments on erroneous data from the e-Diary on bleeds and administration of FIX replacement therapy. The Data Management Notes are not part of the trial data base as such but is locked (in the format of an excel file) together with the trial data base when a formal data base freeze is performed. Each of the specific notes are identified by a unique Id number.

Based on the Data Management Notes Larix will incorporate corrections to the data extracted from the trial data base. The corrections are incorporated employing 'hard coding', when the ADaM datasets are generated and will be documented in the ADRG (Analysis Data Reviewers Guide). The corrections to be included will be discussed and verified with the responsible person at uniQure, and the document maintained concerning these corrections is considered a living document until the programming of the final analyses.

3 Analysis Sets

3.1 Full-Analysis Set

The full-analysis set (FAS) will according to the protocol comprise of all dosed patients and will be used for reporting.

3.2 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set comprises a subset of patients from the FAS population without any major protocol deviations interfering with the analysis of the primary or secondary endpoints.

3.3 Safety Analysis Set

The safety analysis set is the same as FAS.

4 Statistical analyses and presentation of data

4.1 General Considerations

All reporting will be made for the Full Analysis Set. Reporting may also be made for other analysis populations (PP Analysis Set), or subgroups of patients based on for example genotype.

Data will be presented in tables and listings following the principles in ICH E3 guideline regarding (structure and content of clinical reports). On the listings, cohort will appear in a separate column and the listings will be sorted by cohort/dose and patient ID within cohort/dose. In the tables data from each cohort/dose will be presented in separate columns. For selected endpoints data will also be presented graphically.

All data will be listed, including unused and spurious data. Imputation of missing or partial data will not be done unless explicitly described. In the case of imputation of missing data, both the original missing or partial data and the imputed values will be listed. Continuous data will be shown in listings with the same precision as captured.

Summary tables will show the number of non-missing values

Numerical data will be presented in summary tables by number of patients, arithmetic mean, median, standard deviation, minimum and maximum and CV (%). Categorical data will be presented by number and percent of patients as well as the number of events (where applicable).

Patient level summaries (listings) will be presented adjusted for observation time where applicable. This includes but is not limited to the annualized rate of selected signs and symptoms and annualized bleeding rate.

In general, laboratory parameters will be presented by visit and will include categorization of parameters into low/normal/high where applicable. For some of the laboratory parameters a measurement of '< x' (x being a numerical value) are occasionally registered. In such a case a value equal to 0.5*x is used when summary tables are generated, whereas the '< x' will be reported in listings. This recalculation for use in summary tables will also be documented in the ADRG.

The distance in days between a measurement/event and the trial drug administration date is calculated as follows:

- If date(measurement/event) < date(trial drug administration): Distance in days = date(measurement/event) – date(trial drug administration)
- If date(measurement/event) >= date(trial drug administration): Distance in days = date(measurement/event) – date(trial drug administration) + 1

The distance between a FIX activity measurement and the latest FIX replacement therapy administration preceding the FIX activity measurement in question (c.f. section 4.4.2.1) is calculated as follows:

- date(FIX activity measurement) – date(preceding FIX replacement therapy administration) + 1

The date and time of the FIX activity measurement in question and the FIX replacement therapy administrations respectively are used to find the latest FIX replacement therapy administration preceding

the FIX activity measurement in question. In case the dates of the FIX activity measurement in question and a FIX replacement therapy administration are the same and no time is indicated, it is assumed that the FIX replacement therapy administration precedes the FIX activity measurement in question, and the above defined distance therefore becomes equal to 1 (see also section 4.4.2.1).

Duration of an AE in days is calculated (when possible) as date(Resolution) – date(Onset) + 1.

No formal statistical hypothesis will be tested. Two-sided 95% confidence intervals may be calculated but these intervals represent exploratory analyses and will not be related to formal statistical hypothesis tests. No correction for multiplicity will be applied.

4.2 Patient Disposition

The data regarding analysis sets (FAS, PP (if defined), withdrawals (and reason for withdrawal), major protocol violations, and previous screening for this trial (yes/no) will be presented in a listing.

The data will also be summarised in a table.

The Sponsor will provide Larix with information on protocol deviations in the format on an excel file according to a pre-specified and agreed structure. Larix will transfer the information to a SAS dataset (SDTM domain DV).

4.3 Demographics and other Baseline Characteristics

4.3.1 Demography

At the screening visit (Visit 1) the date of birth (i.e. the age at the sceening visit),race, ethnic group, height, weight, and BMI are captured. According to inclusion criterion 1 all patients are males. The data (captured at Visit 1) will be listed and also summarised in a table per cohort and overall.

4.3.2 FIX Gene Mutation

At the screening visit available information of FIX gene mutation will be collected. If the information is not available a blood sample for FIX gene sequencing analysis will be collected at visit 1 or at a later time point during the trial. This blood sample can only be collected if a separate informed consent is given by the patient.

The data will be presented in a listing.

4.3.3 Medical History and Concomitant Illnesses

At the screening visit relevant medical history and concomitant illnesses will be registred. Bleeding history will be reported separately (c.f. section 4.3.4). Medical history is any previous medical condition or surgical event that started prior to visit 1 (screening), but is not ongoing at visit 1. A concomitant illness is defined as a medical condition ongoing at visit 1.

The data including coding terms from MedDRA (version 17.1) will be presented in a listing.

4.3.4 History and Status of Bleeding

4.3.4.1 Haemophilia B History

At the screening visit data regarding time of diagnosis, FIX activity at diagnosis, latest measured FIX activity (including the date of this measurement), degree of FIX deficiency, history of FIX inhibitors measured to be >= 0.6 BU/mL (Yes/No), and family members with a history of having FIX inhibitors measured to be >= 0.6 BU/mL (Yes/No) will be registered. Time (in years) from the date of diagnosis until Visit 2 (day 1) will be derived.

The data will be presented in a listing, and summarised in a table.

4.3.4.2 History of FIX Medication and Bleeding

At the screening visit the following historical data regarding bleeding and FIX treatment are collected:

For all patients:
- Number of exposure days of FIX replacement therapy prior to trial entry. An exposure day is a day where the patient received one or more infusion(s) of a FIX product replacement therapy.

For patients receiving prophylactic FIX replacement therapy:
- Number of months on prophylactic FIX replacement therapy for the last 12 months.
- Dose and frequency of dosing; if the patient is on intermittent prophylactic FIX replacement therapy, each regimen followed in the last 12 months should be reported
- Recombinant or plasma FIX product (registered for each treatment regimen)
- Number of treatment requiring bleeding episodes in the last 12 months during each specific prophylactic treatment regimen
- Average number of units to treat a bleed during each specific prophylactic treatment regimen during the last 12 months
- Number of bleeding episodes prior to initiation of prophylactic FIX replacement therapy

For patients receiving on-demand treatment:
- Number of treatment requiring bleeding episodes in the last 12 months during each specific treatment regiment
- Recombinant or plasma FIX product
- Average number of units to treat a bleed during each specific on demand treatment regimen during the last 12 months

All the data will be presented in listings. All data registered in the trial dat base will be included even if not complying strictly with the requirement of having occurred within one year (365 days) before the screening (Visit 1) date.

Furthermore data on use of FIX therapy in the 7 days preceding visit 1 specifically have been registered.

These data will be presented in a listing.

4.3.4.3 Bleeding History from one year prior to screening

In a specific CRF module data regarding all bleeding episodes occuring in the one year period prior to the screening visit wil be registered. For each bleeding the following data will be recorded:

- Date of the bleed
- Type of bleeding (spontaneous, traumatic, unknown)
- If FIX replaceent therapy was used the name of the therapy and the total dose

These data will be listed and summarized as described in section 4.4.2.2 and 4.4.2.3. All data registered in the above mentioned CRF module will be included even if not complying strictly with the requirement of having occurred within one year (365 days) before the screening (Visit 1) date.

4.3.5 Information on Haemophilia B Disease Related Surgeries and Joint Status

4.3.5.1 Information on Haemophilia B Disease Related Surgeries

At the screening visit the following data is collected for disease related surgical history:

- Date of surgery
- Surgical event
- Preventive treatment during surgery: Recombinant or plasma product

The exact same information is also registred for general surgical history.

All data will be presented in listings.

4.3.5.2 Joint Status

At screening the following data are registered:

- Joint status (Haemophilia joint health score version 2.1)
- Number and location of target joints
- Range of motion of joints

All the data will be presented in listings.

4.3.6 Lab Parameters for Evaluation of Patient Eligibility

The presentation of the data at the screening visit related to exclusion criteria 2 (FIX ihibitors as measured by the local laboratory), exclusion criteria 3 (neutralizing antibodies for AAV5), and excluson criteria 4 (serum chemistry) will be described in section 4.5. The data regarding exclusion criteria 5 and 6 are however only measured at the screening visit and these data will be presented in a separate listing. These specific data comprise the following laboratory parameters: HIV, CD4+, HIV viral load, HBsAg, HBeAg, HBVDNA, and HCV RNA.

4.3.7 Administration of IMP

All data registred regarding the administration of IMP at visit 2 will be presented in a listing.

4.4 Efficacy

4.4.1 Primary Efficacy Analysis

None of the efficacy endpoints are considered as primary endpoints. Refer to the next section.

4.4.2 Secondary Efficacy Analyses

4.4.2.1 FIX Levels in Plasma

Blood samples for FIX activity will be collected at all visits. At Visit 2, blood sampling will take place prior to IMP administration.

Throughout the entire trial period (from Visit 1 and onwards) where a patient is on prophylactic FIX replacement therapy, it will be the aim to draw blood samples at time points where FIX activity is expected to be at the lowest levels. To the extent the visit windows allow, the investigator and/or study nurse will collaborate with the patient to schedule visits to take place on days where prophylactic FIX replacement therapy is planned to be administered. At these visits, blood sampling will then take place just prior to administration of prophylactic FIX replacement therapy.

The following FIX activity assays will be applied at the central laboratory:

- one-stage aPTT assay
- chromogenic/amidolytic assay

The data will be presented separately for each activity assay.

Absolute values will be listed and for each measurement the number of days since last FIX replacement therapy administration will be displayed.

The data will also be analysed descriptively by visit and cohort. These summaries will be generated both for a) all FIX measurements data b) FIX-replacement therapy free FIX measurements i.e. only measurement taken more than 10 days after the preceding FIX replacement therapy administration are included.

The procedure for calculating the above distance and defining latest FIX replacement therapy administration preceding the FIX activity measurement in question has been described in section 4.1. It is noted that if the date for a FIX replacement therapy administration is identical to the date of a FIX activity measurement and no time is indicated, then the FIX activity measurement in question is conservatively assumed to be contaminated i.e. as not FIX-replacement therapy free (the distance between the two time points will be calculated to 1 day).

For the one-stage aPTT assay data the patient individual profiles of FIX replacement free measurements in the period from last prophylactic dose (after tapering) until cut-off will also be presented. Regression lines will be presented and 95% confidence intervals will be displayed as part of legend for each patient.

4.4.2.2 Number, Severity and Type of Bleeding Episodes

In relation to the efficacy variables defined in this section and in section 4.4.2.3 a specific subset of the post-treatment period will be considered.

For the interim analyses described in section 5 the end of this specific post treatment will simply be the specified cut-off date. For the final analysis, this will be the end of study date.

The start of this period is defined for each patient as the end of tapering, i.e. the date of the last prophylactic FIX replacement therapy administered. Before the data base freeze for an interim analysis in question (c.f. section 5) this start date will be decided on for each patient. The decisions made in connections with the first formal interim analysis (c.f. section 5) appear in Appendix 2.

As mentioned in section 4.3.4.3 all bleeding episodes occurring in the one year period prior to screening will be registered.

These data will be presented in a listing and also summarized with respect to annualized bleeding rate, and number of episodes. Separate summaries will be generated for all bleeds and for the different types of bleeds (spontaneous, traumatic, unknown, spontaneous+unknown). It is assumed that the bleeding episodes are observed during exactly one year i.e. the observed number bleeds will correspond exactly to the annualized bleeding rate for the 1 year prior to screening data for each patient.

From Visit 1 and throughout the entire trial participation period, patients will be asked to record information on bleeding episodes in an e-diary.

The patient e-diary will include questions regarding each bleeding episode with respect to

- Date and time of onset of bleed
- Date and time of stop of bleed
- Location of bleed (a number of categories have been defined in e-diary/eCRF)
- Circumstances of bleed (spontaneous, traumatic, minor surgery – see definitions in protocol section 12.12)
- FIX replacement treatment of bleed (medication, dose, date and time of administration)
- Other therapy (pain relieving medication compression, ice)
- Investigator's evaluation of severity of bleed
- Evaluation of effect of treatment by patient (excellent, good, moderate, none), see definitions in protocol section 12.1.2)
- Evaluation of effect of treatment by investigator (excellent, good, moderate, none), in case bleeding episode requires hospitalisation or have a fatal outcome. It is noted that this assessment is registered on the (S)AE form.

It is noted that according to the protocol section 12.1.2 a bleeding episode is defined as a recurrent episode (re-bleed) if it is a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after stopping treatment. If a bleed occurs in the same location later than 72 hours after stopping, the bleed is considered as a new bleed.

It is noted that a registration is made in the e-diary for each location for each bleeding episode i.e. if a bleeding episode occurs with more than one location this will be registered with multiple entries (one for each location) in the e-diary. Such multiple entries will be considered as separate bleeding episodes.

All the diary data and evaluations by the patient and investigator will be listed.

All bleeding episodes requiring FIX treatment from the post tapering period (end of prophylactic treatment until cut-off or end of trial) will be summarized in a similar same way as the bleeding episodes from the 1 year prior to screening period, with descriptive summaries of mean observation period and total observation period added. Total observation period (years) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

For this period the annualized bleeding rate is calculated as (number of bleeds * 365.25)/ number of days in the period from last prophylactic dose until cut-off (or end of trial).

4.4.2.3 Prophylactic and On-demand FIX Replacement Therapy

As mentioned in section 4.3.4.3 administration on demand FIX replacement therapy in the 1 year period prior to screening has been registered. All these data will be listed. The on-demand FIX replacement therapy products used and the total dose used will be summarised for each cohort for this 1 year period prior to screening.

From Visit 1 and throughout the entire trial participation period, patients have been asked to document use of FIX replacement therapy in an e-diary. Two different modules in the e-diary will be used for registering prophylactic and on-demand FIX replacement therapy respectively.

The patient e-diary modules will include questions with respect to

- Date/time of administration
- Drug name
- Dose

All data will be presented in listings. The listings will be split two parts: a) the period from screening and until the end of tapering b) the period from end of tapering until end of trial/cut-off date in an interim analysis.

The use of prophylaxis and on-demand treatment in general will be summarized according to product and type (on-demand or prophylaxis). The summaries will be performed by cohort and overall. Furthermore, the total on-demand use for each patient (regardless of product) for the post tapering period will be summarized by cohort. The total dose for each patient will be annualized i.e. the dose will be adjusted for the length of the observation time (end of tapering until end of trial/cut-off date in an interim analysis) for the patient in question.

A listing will be generated combining on a patient level the information for the 1-year period prior to screening and for the post tapering-period including on-demand FIX-replacement therapy (annualized), bleeding episodes and annualized bleeding rates.

4.4.2.4 PRO – CCI

CCI scores will be computed using the CCI user manual. For each of the 8 domains as well as for the physical and mental health total scores descriptive statistics for absolute values and change from baseline will be provided by visits, cohorts and overall. For each domain the progression over time will also be presented, using change from baseline scores.

In case the CCI scores were not determined at the scheduled visit, it will be checked if CCI scores were determined at an adjacent (unscheduled) date , and if so those data will be used as a substitute. These decisions will be documented by Larix and agreed to by the responsible person at uniQure.

4.5 Safety

Safety parameters will be evaluated for the full analysis set.

4.5.1 Adverse Events – Primary Safety Endpoint

All reported adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 17.1).

An AE is considered related with the use of drug if the relationship to IMP is classified as either 'Probably related' or 'Possibly related'. A related AE is referred to as an Adverse Drug Reaction (ADR).

An adverse event is defined as treatment emergent (TEAE) when onset of the event is after the administration of the IMP. In case an AE starts the same day of IMP administration and the exact time is missing, it will be defined as Treatment Emergent AE.

Adverse events for special notification are determined through the eCRF.

In case of missing or incomplete onset dates of AEs the onset date will be imputed such that the event starts as early as possible based on the partial date. Furthermore, if the AE could be treatment emergent based on the missing or incomplete date, then the AE will be regarded as treatment emergent.

Furthermore, missing values for AEs will be treated as missing except for causality and intensity. If causality is missing for a TEAE, the TEAE will be regarded as 'Probably related'. If causality is missing for an AE with onset before administration of trial drug, the AE will be regarded as 'Unlikely related'. If the intensity is missing the intensity of the AE will be regarded as severe. In case seriousness is missing this should be queried again since seriousness cannot be imputed as 'Yes' by default, since this would affect the reconciliation between trial data base and registry of SAEs.

All TEAEs will be tabulated, while pre-treatment AEs will only be listed.

An AE overview summary table will be prepared including the number of patients reporting at least one AE, the percentage of patients (%) with at least one AE, and the number of events (E) reported, for the following categories:

- TEAEs
- Related TEAEs
- Deaths
- Serious TEAEs
- Severe/Moderate/Mild TEAEs
- TEAEs leading to discontinuation of study treatment (defined as action taken='Drug withdrawn' on the AE form)
- TEAEs qualifying for special notification

Treatment-emergent adverse events will be summarized by Dictionary level, i.e., SOC and PT for MedDRA. The table will display the total number of patients reporting at least one AE, the percentage of patients (%) with at least one AE, and the number of events (E) reported. AEs will be presented by SOC and Preferred Term sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- All TEAEs
- All Related TEAEs
- Deaths
- Serious TEAEs
- Severe/moderate/mild TEAEs
- Any TEAEs leading to discontinuation of study treatment

- TEAEs qualifying for special notification

Data listings will be provided for:
- All pretreatment AEs sorted by patient no.
- All TEAEs sorted by patient no.
- All related AEs sorted by patient no.
- Serious AEs sorted by patient no
- AEs leading to discontinuation study treatment
- Deaths sorted by patient no
- TEAEs qualifying for special notification sorted by patient no

4.5.2 Secondary Safety Endpoints

All data described in this section will simply be presented in listings. The listings will include calculated change from baseline (Visit 2, day 1) where applicable.

4.5.2.1 Vector DNA in Semen, Blood, Saliva, Nasal Secretions, Urine and Faeces

Sampling of the following types of matrix will be performed to determine Vector DNA levels: Blood, saliva, nasal secretions, urine, faeces and semen. Sampling time points are given as: Visits 2-35.

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 shedding 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’. The time to first shedding negative will be flagged on the above-mentioned listings and will also be summarized.

4.5.2.2 Neutralizing Antibodies to AAV5

Blood sampling for measurement of neutralizing antibodies to AAV5 will take place at the time points indicated in the flowchart in the protocol, section 5.

All data will be listed.

4.5.2.3 Total (IgM and IgG) Antibodies to AAV5

Blood sampling for measurement of total (IgG and IgM) antibodies to AAV5 will take place at the time points indicated in the flowchart in the protocol, section 5.

All data will be listed.

4.5.2.4 AAV5 Capsid-specific T cells

Sampling for AAV5 capsid-specific T cells will take place at the time points indicated in the flowchart in the protocol, section 5.

It is noted that the data provided by the laboratory are given in a unit of SFC per 300000 PBMCs. All measurement will therefore be multiplied by a factor 10/3 in order to present the data in unit SFC per 1 million PBMCs.

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

4.5.2.5 Antibodies to FIX

Blood sampling for measurement of anti-FIX antibodies will take place at the time points indicated in the flowchart in the protocol, section 5.

All data will be listed.

4.5.2.6 FIX Inhibitors

Blood sampling for measurement of FIX inhibitors will take place at the time points indicated in the flowchart in the protocol, section 5.

The investigator may instigate that blood samples for FIX inhibitors are taken at additional visits in case (of suspicion) of detection of inhibitors (Nijmegen modified Bethesda assay – Bethesda unit >= 0.6).

A patient is said to suffer from inhibitors (Bethesda Unit ≥0.6) if tested positive for inhibitors at two consecutive test performed preferably within two weeks. If a patient has confirmed inhibitor and continues with no change to treatment type for six weeks and the FIX inhibitor test is negative after that time, the inhibitor is classified as transient.

All data will be listed.

4.5.2.7 Inflammatory Markers IL-1β, IL-2, IL-6, INFγ, MCP-1

Blood sampling for measurement of IL-1β, IL-2, IL-6, INFγ and MCP-1 will take place prior to IMP administration and in the period up to 18 weeks after IMP administration:

- at Visit 2 (prior to IMP administration)
- at Visits 3 - 14 (weekly in weeks 1 - 12)
- at Visits 15 - 17 (bi-weekly in weeks 14, 16, 18).

All data will be listed.

4.5.3 Other Safety Endpoints

4.5.3.1 Physical Examination

A physical examination will be performed at all visits. At Visit 2 (dosing visit with overnight stay) the physical examination will be performed both prior to IMP administration and at the end of the overnight stay (i.e., at 24 hours after IMP administration).
The physical examination will include general appearance and bedside examination of the following body systems: Lymph nodes, mouth and throat, eyes, ears, lungs, abdomen, extremities, musculoskeletal system, neurological system and skin.

The evaluation of each body system will be recorded in the eCRF as “normal” or “abnormal”. Abnormalities will also be recorded in the eCRF.

All data will be presented in listings.

4.5.3.2 Vital Signs and Body Temperature

Blood pressure, pulse, and body temperature will be measured at all visits. At Visit 2 (dosing visit with overnight stay) blood pressure and pulse will be measured prior to IMP administration and at the following approximate time points after IMP administration: 0.5, 1, 2, 3, 4, 6, 8, 12 and at 24 hours.

All data including change from baseline (Visit 2, day 1) will be listed and data will also be presented in plots of individual profiles.

4.5.3.3 Serum Chemistry

At the time points indicated in the flowchart in the protocol, section 5 the following parameters are measured:

Serum electrolytes (sodium, potassium), creatinine, gamma-glutamyltransferase (γGT), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), C-reactive protein (CRP), albumin, total bilirubin and glucose (non-fasting)

All data will be listed. The data will from the parameters amma-glutamyltransferase (γGT), aspartate aminotransferase (AST), alanine transaminase (ALT), CRP, albumin, and total bilirubin will also be presented in plots of individual profiles. On the listing reference range and flag indicating if measurement in question is outside the reference range will appear. The reference range for the parameter in question will also appear on profile plots.

4.5.3.4 Serum Haematology

At the time points indicated in the flowchart in the protocol, section 5 the following parameters are measured:

Haemoglobin, haematocrit, platelet count, red blood cells, white blood cells with differential count (band forms, segment forms, neutrophils, eosinophils, basophils, monocytes, lymphocytes) (all expressed in % as well as in absolute numbers)

All data will be listed. On the listing reference range and flag indicating if measurement in question is outside the reference range will appear.

4.5.3.5 Coagulation Parameters

At the time points indicated in the flowchart in the protocol, section 5 the following parameters are measured:

aPTT, PT (or INR (International normalised ratio), lupus anticoagulant, antithrombin.

All data will be listed. On the listing reference range and flag indicating if measurement in question is outside the reference range will appear.

4.5.3.6 Urine Parameters

At the time points indicated in the flowchart in the protocol, section 5 the following parameters are measured:

pH, protein, blood, leucocyte esterase, glucose.

All data will be listed. On the listing reference range and flag indicating if measurement in question is outside the reference range will appear.

4.5.3.7 FIX Recovery

Measurement of FIX incremental recovery (increase in activity per unit infused (IU/ml per U/kg) at 30 min after infusion of dose of FIX) will be performed at visit 2. Additionally, measurement of FIX incremental recovery should be done at suspicion of FIX inhibitor or at increase in bleeding frequency, as judged by the investigator.

FIX incremental recovery is defined as the difference between the FIX activity at 30 minutes after FIX challenge dose minus the FIX activity prior to FIX challenge dose divided by the dose of the infused FIX.

FIX recovery (C_{max}) is defined as the FIX activity at 30 minutes.

At each occasion a FIX challenge dose of 40 U/kg should be administered while at the clinical trial site. A blood sample should be drawn just prior to FIX dosing and at 30 minutes after FIX dosing. The blood sample should preferably be drawn from a vein different from the vein used in relation to the FIX infusion.

No data regarding the actual dose and date and time for the challenge dose have been registered in the eCRF. The challenge dose will be assumed to be equal to 40IU/kg per protocol in all instances.

The FIX activity used for the calculation of FIX (incremental) recovery will be measured at a central laboratory using the one-stage aPTT assay and the chromogenic/amidolytic assay

The data for each assay will be presented in a listing (blood sampling date, FIX incremental recovery (as defined above), and FIX recovery i.e. Cmax (as defined above)).

4.6 Other Endpoints

4.6.1 Prior and Concomitant Medication

Concomitant treatment is any medication being continued by the patient at trial entry (screening) and any new medication received during the trial.

At every visit the investigator or a qualified designee will ask the patient about concomitant medication.

The following information will be recorded in the eCRF:

- Drug name (generic name preferred)
- Indication
- Dosing regimen (dose, unit, route, frequency)
- Route of administration
- Start date (if started ≥3 months prior to Visit 1, then this can be stated instead of recording the

specific start date)
- Stop date (or ongoing, if ongoing at end trial participation)

Information on FIX replacement therapy will be reported separately.

Concomitant medication data (other than FIX replacement therapy) will be presented through frequency distributions and percentages by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification] and Therapeutic Subgroup (2nd level of the ATC classification). All data will also be presented in listings in which prior medication will be flagged. WHODrug version, September, 2014 will be employed.

4.6.2 FIX Protein Concentration

Blood samples for FIX protein concentration will be collected at all visits. At Visit 2, blood sampling will take place prior to IMP administration.

Throughout the entire trial period (from Visit 1 and onwards) where a patient is on prophylactic FIX replacement therapy, it will be the aim to draw blood samples at time points where FIX protein concentration is expected to be at the lowest levels. To the extent visit windows allow, the investigator and/or study nurse will collaborate with the patient to schedule visits to take place on days where prophylactic FIX replacement therapy is planned to be administered. At these visits, blood sampling will then take place just prior to administration of prophylactic FIX replacement therapy, which will then be administered at the clinic instead of at home.

FIX protein concentration in plasma will be measured via a FIX protein assay at a central laboratory.

All data will be listed.

4.6.3 FIX Activity for Local Monitoring of Patients

At each time point a blood sample for FIX activity measurement is drawn, an additional sample for analysis at the laboratory of the clinical trial site is drawn.

The investigator should arrange with the local coagulation laboratory that analysis results are provided on the same day, or the day after, the blood sampling has taken place. The investigator should enter analysis results in the eCRF.

The analysis method applied at the local coagulation laboratory should be one of the following:
- one-stage APTT assay
- amidolytic/chromogenic assay

The same type of assay should be used consistently for the individual patient throughout the entire trial period.

These data will simply be presented in a listing. On the listing reference range and flag indicating if measurement in question is outside the reference range will appear.

4.6.4 FIX Inhibitors for Local Monitoring of Patients and Eligibility Check

At each time point, a blood sample for FIX inhibitor measurement is drawn (see section 4.5.2.6) an additional sample for analysis at the laboratory of the clinical trial site is drawn. These data will be

presented in a listing.

4.6.5 AST and ALT for Local Monitoring of Patients

At the time points indicated in the protocol, section 12.3.1, Table 4 blood samples have been taken and aspartate aminotransferase (AST), alanine transaminase (ALT) is measured the local laboratory. The results are entered in the eCRF.

These data will be presented in a listing.

4.6.6 BMI

At Visit 1 (Screening Visit), height (without shoes) will be measured and recorded in the eCRF, rounded to the nearest centimetre.

At Visits 1, 2 and 21 - 35, body weight (without overcoat and shoes) will be measured and recorded in the eCRF, rounded to the nearest kilogram.

Body mass index will be calculated automatically, based on eCRF entries of height and body weight.

All the BMI data will be presented in a listing.

4.6.7 Joint Status Post Baseline

The data described in section 4.3.5.2 (collected at Visit 1) will also be collected every 6 months after IMP administration at visits 21, 23, 25, 27, 29, and 31-35. These data will be presented in a listing (c.f. section (4.3.5.2).

4.7 Assignment of visits to assessments not performed at exact visit dates

Joint status (Haemophilia joint health) data:
Subject id PPD had assessments performed on PPD. This date was not registered as an additional visit in the eCRF for subject id PPD. Visit 27 was performed on PPD, and the assessments performed on PPD was entered in Visit 27 in the eCRF. The assessments performed on PPD will be assigned to Visit 27.

Joint status (Haemophilia joint health) data:
Subject id PPD had assessments performed on PPD. This date was not registered as an additional visit in the eCRF for subject id PPD .Visit 31 was performed on PPD, and the assessments performed on PPD was entered in Visit 31 in the eCRF. The assessments performed on PPD will be assigned to Visit 31.

Laboratory data:
Subject id PPD had visit 34 performed on PPD. Due to Covid 19 this was only a telephone visit, so no assessments were performed on that day. On PPD, however, blood samples were taken i.e. laboratory assessments were made. This date was not registered as an additional visit in the eCRF for subject id PPD, but the laboratory assessments performed on PPD were entered in Visit 34 in the eCRF. The assessments performed on PPD will be assigned to Visit 34.

5 Interim Analyses

The sponsor has decided to define a total of two formal interim analyses. Several other data cut-offs will be performed on sponsor request.

First formal interim analysis:

When all enrolled patients have been followed for at least 12 weeks after the IMP administration, i.e. all enrolled patients have attended Visit 14 (Including 14B, if applicable), a formal data base freeze will be performed for the data base including creation of time-stamped SAS datasets in CDISC SDTM format. The data will have the status as “clean data and signed by investigator”. Further details will appear in the Data Management documentation. The time-stamped SAS datasets in CDISC SDTM format will be located on the Larix network on a specific subfolder (‘freeze instance’) for which, Larix Data Management Department is responsible. The ‘DM freeze instance’ (subfolder) will be ‘locked’ after execution of all programs c.f. Larix SOP 205 (‘Study Programming’).

The time-stamped SAS datasets in CDISC SDTM format will be used as the input data for the 12 week interim analyses.

The analyses to be performed will be descriptive analyses and Listing and Table Shells appear in the documents described in section 7. Unless otherwise stated all output for this interim analysis will be based on the Full Analysis Set (FAS). The principles for data cut-off for the first interim analysis are described in Appendix 1.

The analyses will be performed by Larix. The analyses including the creation of time-stamped SAS datasets in CDISC ADaM format will be performed, documented, and located on the Larix network on a specific subfolder (‘freeze instance’) for which Larix Statistics Department is responsible. The ‘STAT freeze instance’ (subfolder) will be ‘locked’ after execution of all programs c.f. Larix SOP 205 (‘Study Programming’).

The actual date for this data cut-off has been defined to be 05AUG2016.

Second formal interim analysis:

When all enrolled patients have been followed for at least 52 weeks after the IMP administration, i.e. all enrolled patients have attended Visit 23, another formal data base freeze will be performed for the data base including creation of time-stamped SAS datasets in CDISC SDTM. The data will have the status as “clean data and signed by investigator”.

The procedures and analyses to be performed will otherwise be as described for the first interim analysis. After the second interim analysis, an interim report will be written by the sponsor.

Several data ‘cut offs’:

The purpose of these data transfers is to provide input to an update of the investigator’s brochure and to provide input for presentations at congresses and meetings with regulators.

The handling of the data for these data transfer will be documented in the Data Management documentation, and the data will have the status as “not finally clean”.

The sponsor will perform and document all analyses performed on the data from this data transfer in relation to the update of the investigator's brochure and presentations at congresses and meetings with regulators.

6 Deviations from Protocol Analysis

The protocol (section 8.2.2 defines FIX replacement therapy free FIX activity as FIX activity measured more than 72 hours after latest FIX replacement therapy. In section 4.4.2.1 the interval of 72 hours has been extended to 10 days.

7 Tables, Listings and Figures

The shell listings, tables, and figures generated appear in the two shell documents (CT_AMT_060_01_Table_Shells_v05.docx and CT_AMT_060_01_Listing_Shells_v05.docx) attached to this SAP. The two documents are considered as being a part of this SAP.

8 Change Log

Edition	Effective on	Reason for revision
01	19JUN2015	1st Edition
02	28APR2016	Signature Page: PPD replacing PPD and PPD replacing PPD. Section 5 revised: Three specific data 'cut-off' are defined.
03	07JUN2017	Second interim analysis: Spelling errors corrected. Signature page updated Section 3: analysis sets updated Section 4.3.4.3 has been added Section 4.4.2.1: Reorganized. Sections 4.4.2.2: Reorganized and data regarding the 1 year prior to screening period has been added. Sections 4.4.2.3: Reorganized and data regarding the 1 year prior to screening period has been added. Section 4.5.1: Added paragraph on imputation rules for adverse events. Added definition of TEAEs leading to discontinuation of study treatment. Section 4.5.2.1: Definition of time to first shedding has been added. Section 4.5.3: Added out of range to lab sections Section 4.6.1: Added prior medication Section 4.6.5 has been added. Section 5: Details about interim analysis added Section 7: The lists of outputs have been replaced by a reference to two shell documents. Appendices 1 and 2 have been added.
04	11APR2018	Section 8 Change Log corrected as follows: - Reference to Edition 1.0 changed to Edition 01 - Reference to Edition 2.0 26APR2016 changed to Edition 02 28APR2016 - Changes for Edition 3.0 07JUL2016 merged together with changes for Edition 03 07JUN2017. Signature Page: PPD replacing PPD and PPD replacing PPD. Section 2.4: Use of Data Management Notes for correction of e-Diary data has been added. Section 4.1: Statements added regarding handling of laboratory measurements registered as '< x' and calculation of duration and distances between dates. Section 4.2: Statements added regarding Protocol Deviations. Section 4.3.1: Emphasizing that Visit 1 (screening) data are used. Section 4.3.4.3: Emphasizing that all data registered in the particular e-CRF module in question are presented. Section 4.2.4.1: Additional details on definition of contaminated

		FIX activity measurements. Section 4.2.4.4: Added specific handling of two assessments with respect to visit assignment. Section 4.5.1: Adding handling of AE causality if missing for AEs occurring before IMP administration. Section 4.5.3.7: Updated to be aligned with how the listing is actually generated. Section 7: Reference to shell documents changed and the shell documents have been updated.
05	27MAY2021	Front page: Refence to protocol changed to version 7.0 dated 20APR2021. Section 4.7 'Assignment of visits to assessments not performed at exact visit dates' added. Section 7: reference to shell documents changed to version 5.0 of the two shell documents.

Appendix 1 Cut-off definition

The reporting for the Interim analyses will be based upon all data up to and including the cut-off date 05 August 2016 or 12 May 2017, respectively. Since the trial is continuing, it is necessary to define what data will be included in the interim analysis. Hence cut-offs must be defined. The cut-off will be performed in the ADAM dataset. No cut-off will be made in the study databases or in the integrated SDTM-database.

OBS: Raw-data and SDTM data will contain all data from the database also data after the cut-off date. Data after the cut-off date is not signed by the Investigator and should not be used for any analysis).

The following cut-off rules will apply:

CUTOFFDT = 05AUG2016/12MAY2017

Dataset	**Description of actions to ensure no data after cut-off date in ADaM**
ADSL - Patient demographics, baseline and other key characteristics	Cut-off date added to dataset in variable CUTOFFDT.
ADAE – Adverse Event Analysis Dataset	All events where start date (ASTDT) <= CUTOFFDT No change of data, i.e. end dates after CUTOFFDT may occur and updates to end dates/outcome may occur anytime up to final extraction of data.
ADBL – Bleeding Episode Dataset	All events where start date (ASTDT) <= CUTOFFDT No change of data, i.e. end dates after CUTOFFDT may occur and updates to end dates/outcome may occur anytime up to final extraction of data.
ADCM – Concomitant Medication Analysis Dataset	All medications where start date (ASTDT) <= CUTOFFDT No change of data, i.e. end dates after CUTOFFDT may occur and updates to end dates may occur anytime up to final extraction of data.
ADEX – FIX treatment dataset	All records
ADHH – Hemophilia History Dataset	All records
ADHJHS – Hemophilia Joint Health Score Dataset	All assessments where Analysis Date (ADT) < CUTOFFDT
ADLB – Laboratory Tests Analysis Dataset	All assessments where Analysis Date (ADT) <= CUTOFFDT
ADMH – Medical History Analysis Dataset	All records
ADPE – Physical Examination Analysis Dataset	All assessments where Analysis Date (ADT) <= CUTOFFDT
ADQS – Questionnaire Scores Analysis Dataset	All records where Analysis Date (ADT) <= CUTOFFDT
ADVS – Vital Signs Analysis Dataset	All assessments where Analysis Date (ADT) <= CUTOFFDT

Appendix 2 Definition of Start of Post-Tapering Period

Below the start date of the post tapering period as defined for the first formal interim analysis (c.f. section 5) is presented for each patient:

Cohort	Pat. Id	Last PPX FIX adm = start of post tapering period	Comments
1	PPD	PPD	All FIX replacement therapy registered in the eCRF after PPD as either Regular or On-demand are to be considered as On-demand.
1	PPD	PPD	
1	PPD	PPD	
1	PPD	PPD	
1	PPD	PPD	
2	PPD	PPD	
2	PPD	PPD	
2	PPD	PPD	The is an on-demand patient.
2	PPD	PPD	Note that the start of the relevant post treatment period is after the cut-off date (PPD) for the first interim analysis c.f. section 5
2	PPD	PPD	

CT-AMT-060-01

A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIXco) administered to adult patients with severe or moderately severe haemophilia B

Sponsor:	uniQure biopharma B.V.
Investigational Medicinal Product:	AAV5-hFIX (adeno-associated viral vector containing a codon-optimized human factor IX Gene)
Indication:	Haemophilia B
Phase:	I-II
Author:	PPD Larix A/S
Date of issue:	27 MAY 2021
Version:	Final 05

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14.1 Demographic Data

Table 14.1.1 Patient disposition

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Screened			xx
Full Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)

N: Number of patients in Full Analysis Set.
n: Number of patients with the reported population.
(%): Percentage of patients in Full Analysis Set.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.1.2 Reason for discontinuation - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Reason for discontinuation			
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow Up	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued due to AE	xx (xx.x)	xx (xx.x)	xx (xx.x)

N: Number of patients in Full Analysis Set.
n: Number of patients with the reported population.
(%): Percentage of patients in Full Analysis Set.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.1.3 Demographics - FAS

	Cohort 1 (N=x)	**Cohort 2 (N=x)**	**Total (N=x)**
Age (years)			
n	x	x	x
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x
Min ; Max	xx; xx	xx; xx	xx; xx
Race, n (%)			
n	x	x	x
Black Or African American	x(xx.x)	x(xx.x)	x(xx.x)
White	x (xx.x)	x (xx.x)	x (xx.x)
Ethnic Group, n (%)			
n	x	x	x
Hispanic Or Latino	x (xx.x)	x (xx.x)	x (xx.x)
Not Hispanic Or Latino	x (xx.x)	x (xx.x)	x (xx.x)
Height (cm)			
n	x	x	x
Mean (SD)	xxx.x (x.x)	xxx.x (x.x)	xxx.x (x.x)
Median	xxx.x	xxx.x	xxx.x
Min ; Max	xxx; xxx	xxx; xxx	xxx; xxx

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with data. (%): Percentage of patients of FAS. SD: Standard Deviation.
All patients are males.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.1.3 Demographics - FAS

	Cohort 1 (N=x)	**Cohort 2 (N=x)**	**Total (N=x)**
Weight (kg)			
n	x	x	x
Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)	xx.xx (x.xx)
Median	xx.xx	xx.xx	xx.xx
Min ; Max	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x
BMI (kg/m^2)			
n	x	x	x
Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)	xx.xx (x.xx)
Median	xx.xx	xx.xx	xx.xx
Min ; Max	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with data. (%): Percentage of patients of FAS. SD: Standard Deviation.
All patients are males.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.1.4 Haemophilia B history - FAS

	Cohort 1 (N=x)	Cohort 2 (N=x)	Total (N=x)
FIX replacement therapy, n (%)			
n	x	x	x
Prophylactic	x (xx.x)	x (xx.x)	x (xx.x)
On demand	x (xx.x)	x (xx.x)	x (xx.x)
Degree of FIX deficiency as per diagnosis, n (%)			
n	x	x	x
Severe	x (xx.x)	x (xx.x)	x (xx.x)
Moderately Severe	x (xx.x)	x (xx.x)	x (xx.x)
FIX activity level at diagnosis time, n (%)			
n	x	x	x
<1%	x (xx.x)	x (xx.x)	x (xx.x)
1%	x (xx.x)	x (xx.x)	x (xx.x)
1.5%	x (xx.x)	x (xx.x)	x (xx.x)
Result of latest FIX activity level, n (%)			
n	x	x	x
<1%	x (xx.x)	x (xx.x)	x (xx.x)
1%	x (xx.x)	x (xx.x)	x (xx.x)
2%	x (xx.x)	x (xx.x)	x (xx.x)

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with data. (%): Percentage of patients of FAS. SD: Standard Deviation.
Prior exposure days are estimate/best guess as given by patient and registered in eCRF.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.1.4 Haemophilia B history – FAS

	Cohort 1 (N=x)	**Cohort 2 (N=x)**	**Total (N=x)**
Subject history of FIX inhibitors, n (%)			
n	x	x	x
Yes	x (xx.x)	x (xx.x)	x (xx.x)
No	x (xx.x)	x (xx.x)	x (xx.x)
Family history of FIX inhibitors, n (%)			
n	x	x	x
Yes	x (xx.x)	x (xx.x)	x (xx.x)
No	x (xx.x)	x (xx.x)	x (xx.x)
Prior exposure of FIX replacement therapy (days)			
n	x	x	x
Mean (SD)	xxxx (xxxx)	xxxx (xxxx)	xxxx (xxxx)
Median	xxxx	xxxx	xxxx
Min ; Max	xxx; xxxx	xxx; xxxx	xxx; xxxx

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with data. (%): Percentage of patients of FAS. SD: Standard Deviation.
Prior exposure days are estimate/best guess as given by patient and registered in eCRF.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

14.2 Efficacy Data

Table 14.2.1 Summary of FIX in plasma - Data from central laboratory - One Stage aPTT assay - FAS

	Cohort 1 (N = x)	**Cohort 2 (N = x)**	**Total (N = x)**
One-stage aPTT for FIX activity (%)			
Visit 1			
n	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx	xx.xx
Min ; Max	x.x ; xx.x	x.x ; xx.x	x.x ; xx.x
CV (%)	xx.x	xx.x	xx.x
Visit 2, Day 1, Pre-dose			
n	x	x	x
Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)	xx.xx (x.xx)
Median	xx.xx	xx.xx	xx.xx
Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
CV (%)	xx.x	xx.x	xx.x
Visit 2, Day 1			
n	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (x.xx)	xx.xx (x.xx)
Median	xx.xx	xx.xx	xx.xx
Min ; Max	x.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
CV (%)	xx.x	xx.x	xx.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. CV: Coefficient of Variation. LLOQ: LLOQ/2.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
No adjustment has been performed for time since most recent administration of FIX replacement therapy, which implies some data could be contaminated with exogenous FIX.
At Visit 2, Day 1 the pre-challenge dose measurement data are tabulated; the 30-min post challenge dose data are presented in the listings.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.1 Summary of FIX in plasma - Data from central laboratory - One Stage aPTT assay - FAS

	Cohort 1 (N = x)	**Cohort 2 (N = x)**	**Total (N = x)**
Visit 3			
n	x	x	x
Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)	xx.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x ; xx.x	x.x ; xx.x	x.x ; xx.x
CV (%)	xx.x	xx.x	xx.x
Visit 4			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x ; xx.x	x.x ; xx.x	x.x ; xx.x
CV (%)	xx.x	xx.x	xx.x
…			
Continue until visit 23			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. CV: Coefficient of Variation. LLOQ: LLOQ/2.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
No adjustment has been performed for time since most recent administration of FIX replacement therapy, which implies some data could be contaminated with exogenous FIX.
At Visit 2, Day 1 the pre-challenge dose measurement data are tabulated; the 30-min post challenge dose data are presented in the listings.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.2 Summary of FIX-replacement-therapy-free FIX in plasma - Data from central laboratory - One Stage aPTT assay - FAS

	Cohort 1 (N = x)	**Cohort 2 (N = x)**	**Total (N = x)**
One-stage aPTT for FIX activity (%)			
Visit 1			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Visit 2, Day 1			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Visit 3			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Continue until visit 26			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. CV: Coefficient of Variation. LLOQ: LLOQ/2.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only assessments performed more than 10 days after most recent FIX-replacement therapy administration included.
At Visit 2, Day 1 the pre-challenge dose measurement data are tabulated; the 30-min post challenge dose data are presented in the listings.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.3 Summary of FIX in plasma - Data from central laboratory - Chromogenic/Amidolytic assay - FAS

	Cohort 1 (N = x)	**Cohort 2 (N = x)**	**Total (N = x)**
Chromogenic/amidolytic assay for FIX activity (%)			
Visit 1			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Visit 2, Day 1, Pre-dose			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Visit 2, Day 1			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Continue until visit 26			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. CV: Coefficient of Variation. LLOQ: LLOQ/2.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
No adjustment has been performed for time since most recent administration of FIX replacement therapy, which implies some data could be contaminated with exogenous FIX.
At Visit 2, Day 1 the pre-challenge dose measurement data are tabulated; the 30-min post challenge dose data are presented in the listings.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.4 Summary of FIX-replacement-therapy-free FIX in plasma - Data from central laboratory - Chromogenic/Amidolytic assay - FAS

	Cohort 1 (N = x)	**Cohort 2 (N = x)**	**Total (N = x)**
Chromogenic/amidolytic assay for FIX activity (%)			
Visit 1			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Visit 2, Day 1			
n	x	x	x
Mean (SD)	x.xx(x.xx)	x.xx(x.xx)	x.xx(x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x
CV (%)	x.x	x.x	x.x
Continue until visit 26			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. CV: Coefficient of Variation. LLOQ: LLOQ/2.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only assessments performed more than 10 days after most recent FIX-replacement therapy administration included.
At Visit 2, Day 1 the pre-challenge dose measurement data are tabulated; the 30-min post challenge dose data are presented in the listings.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.5 Summary of pre-treatment use of FIX replacement therapy - On-Demand - Period: One year prior to screening - FAS

Use of on-demand FIX replacement therapy	Cohort 1 (N=x) n (%)	Cohort 2 (N=x) n (%)	Total (N=x) n (%)
Any medication	x (xx.x)	x (xx.x)	x (xx.x)
Benefix	x (xx.x)	x (xx.x)	x (xx.x)
Haemonine	x (xx.x)	x (xx.x)	x (xx.x)
Mononine	x (xx.x)	x (xx.x)	x (xx.x)
…			
Etc.			
Repeat for all medications reported			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with at least one dose of medication.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.6 Summary of post-treatment use of FIX replacement therapy - Prophylaxis - Period: From Dosing To cut-off - FAS

Use of prophylactic FIX replacement therapy	Cohort 1 (N=x) n (%)	Cohort 2 (N=x) n (%)	Total (N=x) n (%)
Any medication	x (xx.x)	x (xx.x)	x (xx.x)
Benefix	x (xx.x)	x (xx.x)	x (xx.x)
Haemonine	x (xx.x)	x (xx.x)	x (xx.x)
Mononine	x (xx.x)	x (xx.x)	x (xx.x)
…			
Etc.			
Repeat for all medications reported			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with at least one dose of medication.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

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Table 14.2.7 Summary of post-treatment use of FIX replacement therapy - On-Demand - Period: From Dosing To cut-off - FAS

Use of on-demand FIX replacement therapy	Cohort 1 (N=x) n (%)	Cohort 2 (N=x) n (%)	Total (N=x) n (%)
Any medication	x (xx.x)	x (xx.x)	x (xx.x)
Benefix	x (xx.x)	x (xx.x)	x (xx.x)
Haemonine	x (xx.x)	x (xx.x)	x (xx.x)
Mononine	x (xx.x)	x (xx.x)	x (xx.x)
…			
Etc.			
Repeat for all medications reported			

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with at least one dose of medication.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.8 Summary of FIX replacement therapy dose - Period: One year prior to screening - FAS

	Cohort 1 (N=x)	**Cohort 2 (N=x)**	**Total (N=x)**
FIX Infusions (IU/year)			
n	x	x	x
Mean (SD)	xxx (xxx)	xxx (xxx)	xxx (xxx)
Median	xxx	xxx	xxx
Min ; Max	xxx ; xxx	xxx ; xxx	xxx ; xxx

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with at least one dose of medication.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
FIX infusions is the total sum of FIX administrated as prophylaxis and On-demand.

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Table 14.2.9 Summary of FIX replacement therapy dose - Period: From tapering-off to cut-off - FAS

	Cohort 1 (N=x)	**Cohort 2 (N=x)**	**Total (N=x)**
Annualized FIX Infusions (IU/year)			
n	x	x	x
Mean (SD)	xxx (xxx)	xxx (xxx)	xxx (xxx)
Median	xxx	xxx	xxx
Min ; Max	xxx ; xxx	xxx ; xxx	xxx ; xxx

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with at least one dose of medication.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
FIX infusions is the total sum of FIX administrated as prophylaxis and On-demand.

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Table 14.2.10 Summary of bleeding episodes and annualized bleeding rates - All bleeds - Period: One year prior to screening - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x; x	x; x	x; x
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.11 Summary of bleeding episodes and annualized bleeding rates - Spontaneous bleeds - Period: One year prior to screening - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x; x	x; x	x; x
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.

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Table 14.2.12 Summary of bleeding episodes and annualized bleeding rates - Traumatic bleeds - Period: One year prior to screening - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x; x	x; x	x; x
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.

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Table 14.2.13 Summary of bleeding episodes and annualized bleeding rates - Unknown bleeds - Period: One year prior to screening - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x; x	x; x	x; x
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.

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Table 14.2.14 Summary of bleeding episodes and annualized bleeding rates - Spontaneous and unknown bleeds - Period: One year prior to screening - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x; x	x; x	x; x
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x; x.x	x.x; x.x	x.x; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.

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Table 14.2.15 Summary of bleeding episodes and annualized bleeding rates - All bleeds - Period: From tapering-off to cut-off - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	xx	xx	xx
Bleeds per patient (min; max)	x ; x	x ; x	x ; x
Mean observation period (days)	xxx	xxx	xxx
Total observation period (days)	xxx	xxx	xxx
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x ; x.x	x.x ; x.x	x.x ; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

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Table 14.2.15 Summary of bleeding episodes and annualized bleeding rates - All bleeds - Period: From tapering-off to cut-off - FAS

	Cohort 1 (N=x) n (%)	Cohort 2 (N=x) n (%)	Total (N=x) n (%)
Severity, n*			
Severe	x	x	x
Mild/Moderate	x	x	x
Location, n*			
Right - Joint, Ankle	x	x	x
Right - Joint, Elbow	x	x	x
Right - Joint, Finger(S)	x	x	x
Right - Joint, Knee	x	x	x
Right - Joint, Toe(S)	x	x	x
Right - Joint, Wrist	x	x	x
Right - Muscle, Hip, Leg Or Foot	x	x	x
Left - Joint, Elbow	x	x	x
Left - Joint, Knee	x	x	x
Continued for left...	x	x	x
Muscle, Back Incl Buttocks	x	x	x
Other	x	x	x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

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Table 14.2.16 Summary of bleeding episodes and annualized bleeding rates - Spontaneous bleeds - Period: From tapering-off to cut-off - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x ; x	x ; x	x ; x
Mean observation period (days)	xxx	xxx	xxx
Total observation period (days)	xxx	xxx	xxx
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x ; x.x	x.x ; x.x	x.x ; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

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Table 14.2.16 Summary of post treatment bleeding episodes and annualized bleeding rates - Period: From last prophylactic dose to cut-off - Spontaneous bleeds - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Severity, n*			
Severe	x	x	x
Mild/Moderate	x	x	x
Location, n*			
Right - Joint, Elbow	x	x	x
Right - Joint, Finger(S)	x	x	x
Right - Joint, Knee	x	x	x
Right - Joint, Wrist	x	x	x
Left - Joint, Elbow	x	x	x
Continued for left...	x	x	x
Other	x	x	x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

Table 14.2.17 Summary of bleeding episodes and annualized bleeding rates - Traumatic bleeds - Period: From tapering-off to cut-off - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x ; x	x ; x	x ; x
Mean observation period (days)	xxx	xxx	xxx
Total observation period (days)	xxx	xxx	xxx
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x ; x.x	x.x ; x.x	x.x ; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

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Table 14.2.17 Summary of post treatment bleeding episodes and annualized bleeding rates - Period: From last prophylactic dose to cut-off - Traumatic bleeds - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Severity, n*			
Severe	x	x	x
Mild/Moderate	x	x	x
Location, n*			
Right - Joint, Ankle	x	x	x
Right - Joint, Elbow	x	x	x
Right - Joint, Knee	x	x	x
Right - Joint, Toe(S)	x	x	x
Right - Muscle, Hip, Leg Or Foot	x	x	x
Left - Joint, Elbow	x	x	x
Left - Joint, Knee	x	x	x
Continued for left...	x	x	x
Muscle, Back Incl Buttocks	x	x	x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.18 Summary of bleeding episodes and annualized bleeding rates - Unknown bleeds - Period: From tapering-off to cut-off - FAS

As 14.2.17

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.19 Summary of bleeding episodes and annualized bleeding rates - Spontaneous and unknown bleeds - Period: From tapering-off to cut-off - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Number of patients with bleed, n (%)	x (xx.x)	x (xx.x)	x (xx.x)
Number of bleeds	x	x	x
Bleeds per patient (min; max)	x ; x	x ; x	x ; x
Mean observation period (days)	xx	xx	xx
Total observation period (days)	xxx	xxx	xxx
Annualized bleeding rate			
n	x	x	x
Mean (SD)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Median	x.xx	x.xx	x.xx
Min ; Max	x.x ; x.x	x.x ; x.x	x.x ; x.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.19 Summary of post treatment bleeding episodes and annualized bleeding rates - Period: From last prophylactic dose to cut-off - Spontaneous and unknown bleeds - FAS

	Cohort 1 (N=x) n (%)	**Cohort 2 (N=x) n (%)**	**Total (N=x) n (%)**
Severity, n*			
Severe	x	x	x
Mild/Moderate	x	x	x
Location, n*			
Right - Joint, Elbow	x	x	x
Right - Joint, Finger(S)	x	x	x
Right - Joint, Knee	x	x	x
Right - Joint, Wrist	x	x	x
Left - Joint, Elbow	x	x	x
Continued for left...	x	x	x
Other	x	x	x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation. n*: Number of bleeds.
Severity: Assessment by investigator.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Only bleeds requiring on demand FIX infusion are included.
Total observation period (yrs) for each cohort is calculated as the sum of the observation periods of all patients in that cohort.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.2.20 Summary of CCI domains and total scores - FAS

	Cohort 1 (N = x)		Cohort 2 (N = x)		Total (N = x)	
	Absolute value	**Change from Baseline**	**Absolute value**	**Change from Baseline**	**Absolute value**	**Change from Baseline**
PF (Physical Functioning)						
Visit 1						
n	x		x		x	
Mean (SD)	xx.xx (xx.xx)		xx.xx (xx.xx)		xx.xx (xx.xx)	
Median	xx.xx		xx.xx		xx.xx	
Min ; Max	xx.x ; xx.x		xx.x ; xx.x		xx.x ; xx.x	
Visit 21						
n	x	x	x	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
Visit 23						
n	x	x	x	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients with the parameter. SD: Standard Deviation.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
CCI : CCI : CCI version 2 is used.
Data collected at additional visits will be presented in listings.

UniQure/AMT/CT-AMT-060-01/ current - program/tablename.rtf/ddmmmyyy

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events - FAS

	Cohort 1 (N=x) n (%) E	**Cohort 2 (N=x) n (%) E**	**Total (N=x) n (%) E**
All TEAEs	x (xx.x) x	x (xx.x) x	x (xx.x) x
Mild TEAEs	x (xx.x) x	x (xx.x) x	x (xx.x) x
Moderate TEAEs	x (xx.x) x	x (xx.x) x	x (xx.x) x
Severe TEAEs	x (xx.x) x	x (xx.x) x	x (xx.x) x
Probably Related TEAEs (ADRs)	x (xx.x) x	x (xx.x) x	x (xx.x) x
Possibly Related TEAEs (ADRs)	x (xx.x) x	x (xx.x) x	x (xx.x) x
Unlikely Related TEAEs (ADRs)	x (xx.x) x	x (xx.x) x	x (xx.x) x
Serious TEAEs (SAEs)	x (xx.x) x	x (xx.x) x	x (xx.x) x
Deaths	x (xx.x) x	x (xx.x) x	x (xx.x) x
TEAEs leading to discontinuation	x (xx.x) x	x (xx.x) x	x (xx.x) x
TEAEs for special notification	x (xx.x) x	x (xx.x) x	x (xx.x) x

TEAE: Treatment Emergent Adverse Event. ADR. Adverse Drug Reaction.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.2 Frequency and Incidence of TEAEs by MedDRA SOC and PT - FAS

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any TEAEs	x (xx.x) x	x (xx.x) x	x (xx.x) x
Musculoskeletal and connective tissue disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Arthralgia	x (xx.x) x	x (xx.x) x	x (xx.x) x
Musculoskeletal pain	x (xx.x) x	x (xx.x) x	x (xx.x) x
Back pain	x (xx.x) x	x (xx.x) x	x (xx.x) x
Pain in extremity	x (xx.x) x	x (xx.x) x	x (xx.x) x
Neck pain	x (xx.x) x	x (xx.x) x	x (xx.x) x
Joint swelling	x (xx.x) x	x (xx.x) x	x (xx.x) x
Tenosynovitis	x (xx.x) x	x (xx.x) x	x (xx.x) x
Infections and infestations	x (xx.x) x	x (xx.x) x	x (xx.x) x
Nasopharyngitis	x (xx.x) x	x (xx.x) x	x (xx.x) x
Sinusitis	x (xx.x) x	x (xx.x) x	x (xx.x) x
Influenza	x (xx.x) x	x (xx.x) x	x (xx.x) x
Rhinitis	x (xx.x) x	x (xx.x) x	x (xx.x) x
…	x (xx.x) x	x (xx.x) x	x (xx.x) x
…	x (xx.x) x	x (xx.x) x	x (xx.x) x
…	x (xx.x) x	x (xx.x) x	x (xx.x) x
…	x (xx.x) x	x (xx.x) x	x (xx.x) x
…	x (xx.x) x	x (xx.x) x	x (xx.x) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.3 Frequency and Incidence of Related TEAEs by MedDRA SOC and PT - FAS

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any Related TEAEs	x (xx.x) x	x (xx.x) x	x (xx.x) x
Investigations	x (xx.x) x	x (xx.x) x	x (xx.x) x
Hepatic enzyme increased	x (xx.x) x	x (xx.x) x	x (xx.x) x
Transaminases increased	x (xx.x) x	x (xx.x) x	x (xx.x) x
Alanine aminotransferase increased	x (xx.x) x	x (xx.x) x	x (xx.x) x
General disorders and administration site conditions	x (xx.x) x	x (xx.x) x	x (xx.x) x
Pyrexia	x (xx.x) x	x (xx.x) x	x (xx.x) x
Drug ineffective	x (xx.x) x	x (xx.x) x	x (xx.x) x
Psychiatric disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Anxiety	x (xx.x) x	x (xx.x) x	x (xx.x) x
Reproductive system and breast disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Prostatitis	x (xx.x) x	x (xx.x) x	x (xx.x) x
Skin and subcutaneous tissue disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Rash	x (xx.x) x	x (xx.x) x	x (xx.x) x
Cardiac disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Palpitations	x (xx.x) x	x (xx.x) x	x (xx.x) x

FAS: Full Analysis Set. TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities (version 17.1). SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in FAS. n: Number of patients with events. (%): Percentage of patients in Full Analysis Set with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.3 Frequency and Incidence of Related TEAEs by MedDRA SOC and PT – FAS

System Organ Class Preferred Term	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Nervous system disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Headache	x (xx.x) x	x (xx.x) x	x (xx.x) x
Cardiac disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Palpitations	x (xx.x) x	x (xx.x) x	x (xx.x) x
Musculoskeletal and connective tissue disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Joint swelling	x (xx.x) x	x (xx.x) x	x (xx.x) x
Skin and subcutaneous tissue disorders	x (xx.x) x	x (xx.x) x	x (xx.x) x
Rash	x (xx.x) x	x (xx.x) x	x (xx.x) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1
Events classified as Possibly Related or Probably Related are included in output.

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.4 Frequency and Incidence of Deaths by MedDRA SOC and PT - FAS

As 14.3.1.3

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.5 Frequency and Incidence of Serious TEAEs by MedDRA SOC and PT - FAS

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any Serious TEAEs	x (x.xx) x	x (x.xx) x	x (x.xx) x
Investigations	x (x.xx) x	x (x.xx) x	x (x.xx) x
Hepatic enzyme increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Alanine aminotransferase increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
General disorders and administration site conditions	x (x.xx) x	x (x.xx) x	x (x.xx) x
Pyrexia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Nervous system disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Myelopathy	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.6 Frequency and Incidence of TEAEs of Mild Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any mild TEAEs	x (x.xx) x	x (x.xx) x	x (x.xx) x
Infections and infestations	x (x.xx) x	x (x.xx) x	x (x.xx) x
Nasopharyngitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Eye infection	x (x.xx) x	x (x.xx) x	x (x.xx) x
Influenza	x (x.xx) x	x (x.xx) x	x (x.xx) x
Sinusitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Respiratory tract infection	x (x.xx) x	x (x.xx) x	x (x.xx) x
Rhinitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Oral herpes	x (x.xx) x	x (x.xx) x	x (x.xx) x
Musculoskeletal and connective tissue disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Musculoskeletal pain	x (x.xx) x	x (x.xx) x	x (x.xx) x
Arthralgia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Back pain	x (x.xx) x	x (x.xx) x	x (x.xx) x
Joint swelling	x (x.xx) x	x (x.xx) x	x (x.xx) x
Groin pain	x (x.xx) x	x (x.xx) x	x (x.xx) x
Tenosynovitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Pain in extremity	x (x.xx) x	x (x.xx) x	x (x.xx) x
Neck pain	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mild.rtf/10jan2018

Table 14.3.1.6 Frequency and Incidence of TEAEs of Mild Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Nervous system disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Headache	x (x.xx) x	x (x.xx) x	x (x.xx) x
Dizziness	x (x.xx) x	x (x.xx) x	x (x.xx) x
Nervous system disorder	x (x.xx) x	x (x.xx) x	x (x.xx) x
Hypoaesthesia	x (x.xx) x	x (x.xx) x	x (x.xx) x
General disorders and administration site conditions	x (x.xx) x	x (x.xx) x	x (x.xx) x
Pyrexia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Influenza like illness	x (x.xx) x	x (x.xx) x	x (x.xx) x
Peripheral swelling	x (x.xx) x	x (x.xx) x	x (x.xx) x
Investigations	x (x.xx) x	x (x.xx) x	x (x.xx) x
Hepatic enzyme increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Transaminases increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Platelet count decreased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Alanine aminotransferase increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Psychiatric disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Sleep disorder	x (x.xx) x	x (x.xx) x	x (x.xx) x
Anxiety	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mild.rtf/10jan2018

Table 14.3.1.6 Frequency and Incidence of TEAEs of Mild Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Gastrointestinal disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Abdominal pain lower	x (x.xx) x	x (x.xx) x	x (x.xx) x
Diarrhoea	x (x.xx) x	x (x.xx) x	x (x.xx) x
Irritable bowel syndrome	x (x.xx) x	x (x.xx) x	x (x.xx) x
Dyspepsia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Injury, poisoning and procedural complications	x (x.xx) x	x (x.xx) x	x (x.xx) x
Ulna fracture	x (x.xx) x	x (x.xx) x	x (x.xx) x
Joint injury	x (x.xx) x	x (x.xx) x	x (x.xx) x
Abdominal injury	x (x.xx) x	x (x.xx) x	x (x.xx) x
Tooth fracture	x (x.xx) x	x (x.xx) x	x (x.xx) x
Cardiac disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Tachycardia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Palpitations	x (x.xx) x	x (x.xx) x	x (x.xx) x
Skin and subcutaneous tissue disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Actinic keratosis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Rash	x (x.xx) x	x (x.xx) x	x (x.xx) x
Vascular disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mild.rtf/10jan2018

Table 14.3.1.6 Frequency and Incidence of TEAEs of Mild Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Haematoma	x (x.xx) x	x (x.xx) x	x (x.xx) x
Reproductive system and breast disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Prostatitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Ear and labyrinth disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Cerumen impaction	x (x.xx) x	x (x.xx) x	x (x.xx) x
Immune system disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Hypersensitivity	x (x.xx) x	x (x.xx) x	x (x.xx) x
Renal and urinary disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Renal colic	x (x.xx) x	x (x.xx) x	x (x.xx) x
Blood and lymphatic system disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Splenomegaly	x (x.xx) x	x (x.xx) x	x (x.xx) x
Eye disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Blepharitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Respiratory, thoracic and mediastinal disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mild.rtf/10jan2018

Table 14.3.1.6 Frequency and Incidence of TEAEs of Mild Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Chronic obstructive pulmonary disease	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mild.rtf/10jan2018

Table 14.3.1.7 Frequency and Incidence of TEAEs of Moderate Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any moderate TEAEs	x (x.xx) x	x (x.xx) x	x (x.xx) x
Infections and infestations	x (x.xx) x	x (x.xx) x	x (x.xx) x
Pulpitis dental	x (x.xx) x	x (x.xx) x	x (x.xx) x
Bronchitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Cellulitis	x (x.xx) x	x (x.xx) x	x (x.xx) x
Musculoskeletal and connective tissue disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Musculoskeletal stiffness	x (x.xx) x	x (x.xx) x	x (x.xx) x
Back pain	x (x.xx) x	x (x.xx) x	x (x.xx) x
Arthralgia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Injury, poisoning and procedural complications	x (x.xx) x	x (x.xx) x	x (x.xx) x
Muscle strain	x (x.xx) x	x (x.xx) x	x (x.xx) x
Upper limb fracture	x (x.xx) x	x (x.xx) x	x (x.xx) x
General disorders and administration site conditions	x (x.xx) x	x (x.xx) x	x (x.xx) x
Drug ineffective	x (x.xx) x	x (x.xx) x	x (x.xx) x
Pyrexia	x (x.xx) x	x (x.xx) x	x (x.xx) x
Psychiatric disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mod.rtf/10jan2018

Table 14.3.1.7 Frequency and Incidence of TEAEs of Moderate Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Anxiety	x (x.xx) x	x (x.xx) x	x (x.xx) x
Nervous system disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Nervous system disorder	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_mod.rtf/10jan2018

Table 14.3.1.8 Frequency and Incidence of TEAEs of Severe Severity by MedDRA SOC and PT - Full analysis set

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any severe TEAEs	x (x.xx) x	x (x.xx) x	x (x.xx) x
Nervous system disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Myelopathy	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - tab_ae.sas/tab_ae_teae_sev.rtf/10jan2018

Table 14.3.1.9 Frequency and Incidence of TEAEs Leading to Discontinuation by MedDRA SOC and PT - FAS

As 14.3.1.8

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

Table 14.3.1.10 Frequency and Incidence of TEAEs Qualifying for Special Notification by MedDRA SOC and PT - FAS

SOC PT	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any TEAEs qualifying for special notification	x (x.xx) x	x (x.xx) x	x (x.xx) x
Investigations	x (x.xx) x	x (x.xx) x	x (x.xx) x
Transaminases increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Hepatic enzyme increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
Alanine aminotransferase increased	x (x.xx) x	x (x.xx) x	x (x.xx) x
General disorders and administration site conditions	x (x.xx) x	x (x.xx) x	x (x.xx) x
Drug ineffective	x (x.xx) x	x (x.xx) x	x (x.xx) x
Psychiatric disorders	x (x.xx) x	x (x.xx) x	x (x.xx) x
Anxiety	x (x.xx) x	x (x.xx) x	x (x.xx) x

TEAE: Treatment Emergent Adverse Event. MedDRA: Medical Dictionary for Regulatory Activities. SOC: System Organ Class. PT: Preferred Term.
N: Number of patients in Full Analysis Set (FAS). n: Number of patients with events. (%): Percentage of patients in FAS with Adverse Event. E: Number of Adverse Events.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Adverse Events coded with MedDRA version 17.1

UniQure/AMT/CT-AMT-060-01/current - program/tablename.rtf/ddmmmyyy

14.3.7 Other Safety Observations Displays

Table 14.3.7.1 Summary of concomitant medications (Other than FIX replacement therapy) by therapeutic grouping - Full analysis set

ATC level 1 ATC level 2	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any medication	x (xxx) x	x (xxx) x	x (xxx) x
Alimentary Tract And Metabolism	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Acid Related Disorders	x (xxx) x	x (xxx) x	x (xxx) x
Drugs Used In Diabetes	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Constipation	x (xxx) x	x (xxx) x	x (xxx) x
Antidiarrheals, Intestinal Antiinflammatory/Antiin	x (xxx) x	x (xxx) x	x (xxx) x
Antiemetics And Antinauseants	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Functional Gastrointestinal Disorders	x (xxx) x	x (xxx) x	x (xxx) x
Vitamins	x (xxx) x	x (xxx) x	x (xxx) x
Stomatological Preparations	x (xxx) x	x (xxx) x	x (xxx) x
Nervous System	x (xxx) x	x (xxx) x	x (xxx) x
Analgesics	x (xxx) x	x (xxx) x	x (xxx) x
Psycholeptics	x (xxx) x	x (xxx) x	x (xxx) x
Anesthetics	x (xxx) x	x (xxx) x	x (xxx) x
Cardiovascular System	x (xxx) x	x (xxx) x	x (xxx) x
Agents Acting On The Renin-Angiotensin System	x (xxx) x	x (xxx) x	x (xxx) x
Lipid Modifying Agents	x (xxx) x	x (xxx) x	x (xxx) x
Beta Blocking Agents	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). ATC Class: Anatomical Therapeutic Chemical Classification.
n: Number of patients with the medication. (%): Percentage of patients with the medication in FAS. E: Number of Medications.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Medication coded with WHO DD version 143E

UniQure/AMT/CT-AMT-060-01/current - tab_cm.sas/tab_cm_sum.rtf/10jan2018

Table 14.3.7.1 Summary of concomitant medications (Other than FIX replacement therapy) by therapeutic grouping - Full analysis set

ATC level 1 ATC level 2	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Diuretics	x (xxx) x	x (xxx) x	x (xxx) x
Calcium Channel Blockers	x (xxx) x	x (xxx) x	x (xxx) x
Antiinfectives For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Antibacterials For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Antivirals For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Vaccines	x (xxx) x	x (xxx) x	x (xxx) x
Systemic Hormonal Preparations, Excl. Sex Hormones	x (xxx) x	x (xxx) x	x (xxx) x
Corticosteroids For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Musculo-Skeletal System	x (xxx) x	x (xxx) x	x (xxx) x
Antiinflammatory And Antirheumatic Products	x (xxx) x	x (xxx) x	x (xxx) x
Muscle Relaxants	x (xxx) x	x (xxx) x	x (xxx) x
Blood And Blood Forming Organs	x (xxx) x	x (xxx) x	x (xxx) x
Antihemorrhagics	x (xxx) x	x (xxx) x	x (xxx) x
Blood Substitutes And Perfusion Solutions	x (xxx) x	x (xxx) x	x (xxx) x
Respiratory System	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Obstructive Airway Diseases	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). ATC Class: Anatomical Therapeutic Chemical Classification.
n: Number of patients with the medication. (%): Percentage of patients with the medication in FAS. E: Number of Medications.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Medication coded with WHO DD version 143E

UniQure/AMT/CT-AMT-060-01/current - tab_cm.sas/tab_cm_sum.rtf/10jan2018

Table 14.3.7.1 Summary of concomitant medications (Other than FIX replacement therapy) by therapeutic grouping - Full analysis set

ATC level 1 ATC level 2	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Nasal Preparations	x (xxx) x	x (xxx) x	x (xxx) x
Sensory Organs	x (xxx) x	x (xxx) x	x (xxx) x
Ophthalmological And Otological Preparations	x (xxx) x	x (xxx) x	x (xxx) x
Genito Urinary System And Sex Hormones	x (xxx) x	x (xxx) x	x (xxx) x
Urologicals	x (xxx) x	x (xxx) x	x (xxx) x
***** ATC1 not coded *****	x (xxx) x	x (xxx) x	x (xxx) x
***** ATC2 not coded *****	x (xxx) x	x (xxx) x	x (xxx) x
Antineoplastic And Immunomodulating Agents	x (xxx) x	x (xxx) x	x (xxx) x
Antineoplastic Agents	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). ATC Class: Anatomical Therapeutic Chemical Classification.
n: Number of patients with the medication. (%): Percentage of patients with the medication in FAS. E: Number of Medications.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Medication coded with WHO DD version 143E

UniQure/AMT/CT-AMT-060-01/current - tab_cm.sas/tab_cm_sum.rtf/10jan2018

Table 14.3.7.2 Summary of time to first shedding negative (days) - Vector DNA - Full analysis set

	Cohort 1 (N=x)	Cohort 2 (N=x)	Total (N=x)
Vector DNA Blood (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Faeces (copies/mg)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Nasal Secretion (copies per swab)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Saliva (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients who have met the criterion for shedding negative.
First shedding negative is defined for a specific matrix when 3 consecutive negative samples have been detected for the patient for that particular type of matrix.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - tab_shed_neg.sas/tab_shed_neg.rtf/10jan2018

Table 14.3.7.2 Summary of time to first shedding negative (days) - Vector DNA - Full analysis set

	Cohort 1 (N=x)	Cohort 2 (N=x)	Total (N=x)
Vector DNA Semen (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Urine (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients who have met the criterion for shedding negative.
First shedding negative is defined for a specific matrix when 3 consecutive negative samples have been detected for the patient for that particular type of matrix.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - tab_shed_neg.sas/tab_shed_neg.rtf/10jan2018

14.3.7 Other Safety Observations Displays

Table 14.3.7.1 Summary of concomitant medications (Other than FIX replacement therapy) by therapeutic grouping - Full analysis set

ATC level 1 ATC level 2	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Any medication	x (xxx) x	x (xxx) x	x (xxx) x
Alimentary Tract And Metabolism	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Acid Related Disorders	x (xxx) x	x (xxx) x	x (xxx) x
Drugs Used In Diabetes	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Constipation	x (xxx) x	x (xxx) x	x (xxx) x
Antidiarrheals, Intestinal Antiinflammatory/Antiin	x (xxx) x	x (xxx) x	x (xxx) x
Antiemetics And Antinauseants	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Functional Gastrointestinal Disorders	x (xxx) x	x (xxx) x	x (xxx) x
Vitamins	x (xxx) x	x (xxx) x	x (xxx) x
Stomatological Preparations	x (xxx) x	x (xxx) x	x (xxx) x
Nervous System	x (xxx) x	x (xxx) x	x (xxx) x
Analgesics	x (xxx) x	x (xxx) x	x (xxx) x
Psycholeptics	x (xxx) x	x (xxx) x	x (xxx) x
Anesthetics	x (xxx) x	x (xxx) x	x (xxx) x
Cardiovascular System	x (xxx) x	x (xxx) x	x (xxx) x
Agents Acting On The Renin-Angiotensin System	x (xxx) x	x (xxx) x	x (xxx) x
Lipid Modifying Agents	x (xxx) x	x (xxx) x	x (xxx) x
Beta Blocking Agents	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). ATC Class: Anatomical Therapeutic Chemical Classification.
n: Number of patients with the medication. (%): Percentage of patients with the medication in FAS. E: Number of Medications.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Medication coded with WHO DD version 143E

UniQure/AMT/CT-AMT-060-01/current - tab_cm.sas/tab_cm_sum.rtf/10jan2018

Table 14.3.7.1 Summary of concomitant medications (Other than FIX replacement therapy) by therapeutic grouping - Full analysis set

ATC level 1 ATC level 2	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Diuretics	x (xxx) x	x (xxx) x	x (xxx) x
Calcium Channel Blockers	x (xxx) x	x (xxx) x	x (xxx) x
Antiinfectives For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Antibacterials For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Antivirals For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Vaccines	x (xxx) x	x (xxx) x	x (xxx) x
Systemic Hormonal Preparations, Excl. Sex Hormones	x (xxx) x	x (xxx) x	x (xxx) x
Corticosteroids For Systemic Use	x (xxx) x	x (xxx) x	x (xxx) x
Musculo-Skeletal System	x (xxx) x	x (xxx) x	x (xxx) x
Antiinflammatory And Antirheumatic Products	x (xxx) x	x (xxx) x	x (xxx) x
Muscle Relaxants	x (xxx) x	x (xxx) x	x (xxx) x
Blood And Blood Forming Organs	x (xxx) x	x (xxx) x	x (xxx) x
Antihemorrhagics	x (xxx) x	x (xxx) x	x (xxx) x
Blood Substitutes And Perfusion Solutions	x (xxx) x	x (xxx) x	x (xxx) x
Respiratory System	x (xxx) x	x (xxx) x	x (xxx) x
Drugs For Obstructive Airway Diseases	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). ATC Class: Anatomical Therapeutic Chemical Classification.
n: Number of patients with the medication. (%): Percentage of patients with the medication in FAS. E: Number of Medications.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Medication coded with WHO DD version 143E

UniQure/AMT/CT-AMT-060-01/current - tab_cm.sas/tab_cm_sum.rtf/10jan2018

Table 14.3.7.1 Summary of concomitant medications (Other than FIX replacement therapy) by therapeutic grouping - Full analysis set

ATC level 1 ATC level 2	Cohort 1 (N=x) n (%) E	Cohort 2 (N=x) n (%) E	Total (N=x) n (%) E
Nasal Preparations	x (xxx) x	x (xxx) x	x (xxx) x
Sensory Organs	x (xxx) x	x (xxx) x	x (xxx) x
Ophthalmological And Otological Preparations	x (xxx) x	x (xxx) x	x (xxx) x
Genito Urinary System And Sex Hormones	x (xxx) x	x (xxx) x	x (xxx) x
Urologicals	x (xxx) x	x (xxx) x	x (xxx) x
***** ATC1 not coded *****	x (xxx) x	x (xxx) x	x (xxx) x
***** ATC2 not coded *****	x (xxx) x	x (xxx) x	x (xxx) x
Antineoplastic And Immunomodulating Agents	x (xxx) x	x (xxx) x	x (xxx) x
Antineoplastic Agents	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). ATC Class: Anatomical Therapeutic Chemical Classification.
n: Number of patients with the medication. (%): Percentage of patients with the medication in FAS. E: Number of Medications.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg
Medication coded with WHO DD version 143E

UniQure/AMT/CT-AMT-060-01/current - tab_cm.sas/tab_cm_sum.rtf/10jan2018

Table 14.3.7.2 Summary of time to first shedding negative (days) - Vector DNA - Full analysis set

	Cohort 1 (N=x)	Cohort 2 (N=x)	Total (N=x)
Vector DNA Blood (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Faeces (copies/mg)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Nasal Secretion (copies per swab)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Saliva (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients who have met the criterion for shedding negative.
First shedding negative is defined for a specific matrix when 3 consecutive negative samples have been detected for the patient for that particular type of matrix.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

UniQure/AMT/CT-AMT-060-01/current - tab_shed_neg.sas/tab_shed_neg.rtf/10jan2018

Table 14.3.7.2 Summary of time to first shedding negative (days) - Vector DNA - Full analysis set

	Cohort 1 (N=5)	Cohort 2 (N=5)	Total (N=10)
Vector DNA Semen (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x
Vector DNA Urine (copies/mL)			
n	x (xxx) x	x (xxx) x	x (xxx) x
Mean (SD)	x (xxx) x	x (xxx) x	x (xxx) x
Median	x (xxx) x	x (xxx) x	x (xxx) x
Min ; Max	x (xxx) x	x (xxx) x	x (xxx) x

N: Number of patients in Full Analysis Set (FAS). n: Number of patients who have met the criterion for shedding negative.
First shedding negative is defined for a specific matrix when 3 consecutive negative samples have been detected for the patient for that particular type of matrix.
Cohort 1: AAV5-hFIX 5.0 x 10^12 gc/kg, Cohort 2: AAV5-hFIX 2.0 x 10^13 gc/kg

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Figures to be generated – no shells

Figure 14.2.21 FIX activity over time - One Stage aPTT assay - Cohort 1 - Period: From tapering-off to cut-off – FAS
Figure 14.2.22 FIX activity over time - One Stage aPTT assay - Cohort 2 - Period: From tapering-off to cut-off off – FAS

Figure 14.3.5.1 Individual profile plot of T-cell (AAV5-capsid) ELISPOT ((SFC)/million PBMCs) - Cohort 1 - Period: From IMP to cut-off – FAS
Figure 14.3.5.2 Individual profile plot of T-cell (AAV5-capsid) ELISPOT ((SFC)/million PBMCs) - Cohort 2 - Period: From IMP to cut-off – FAS
Figure 14.3.5.3 Individual profile plot of Vector DNA blood (copies/mL) - Cohort 1 - Period: From IMP to cut-off – FAS
Figure 14.3.5.4 Individual profile plot of Vector DNA blood (copies/mL) - Cohort 2 - Period: From IMP to cut-off – FAS
Figure 14.3.5.5 Individual profile plot of Vector DNA faeces (copies/mg) - Cohort 1 - Period: From IMP to cut-off – FAS
Figure 14.3.5.6 Individual profile plot of Vector DNA faeces (copies/mg) - Cohort 2 - Period: From IMP to cut-off – FAS
Figure 14.3.5.7 Individual profile plot of Vector DNA nasal (copies per swab) - Cohort 1 - Period: From IMP to cut-off – FAS
Figure 14.3.5.8 Individual profile plot of Vector DNA nasal (copies per swab) - Cohort 2 - Period: From IMP to cut-off – FAS
Figure 14.3.5.9 Individual profile plot of Vector DNA saliva (copies/mL) - Cohort 1 - Period: From IMP to cut-off – FAS
Figure 14.3.5.10 Individual profile plot of Vector DNA saliva (copies/mL) - Cohort 2 - Period: From IMP to cut-off – FAS
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CT-AMT-060-01

A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIXco) administered to adult patients with severe or moderately severe haemophilia B

Sponsor:	uniQure biopharma B.V.
Investigational Medicinal Product:	AAV5-hFIX (adeno-associated viral vector containing a codon-optimized human factor IX Gene)
Indication:	Haemophilia B
Phase:	I-II
Author:	PPD Larix A/S
Date of issue:	27MAY2021
Version:	Final version 05

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“The following sections (pg#107-111) have been removed:

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- Listing 16.1.1.1 Patient disposition (Pg#108)
- 16.2.1 Discontinued patients (Pg#109)
- Listing 16.2.1.1 Discontinued patients (Pg#110)
- Listing 16.2.1.2 Screening failures (Pg#111)

16.2.2 Protocol deviations

Listing 16.2.2.1 Protocol deviations

NO DATA FOUND FOR THIS LISTING

UniQure/AMT/CT-AMT-060-01/current - lst_emptylist.sas/lst_prodev.rtf/ddmmmyyyy

16.2.3 Patients excluded from the efficacy analysis

Listing 16.2.3.1 Patients excluded from the efficacy analysis

NO DATA FOUND FOR THIS LISTING

UniQure/AMT/CT-AMT-060-01/current - lst_emptylist.sas/lst_PatientExc.rtf/ddmmmyyyy

“The following sections (pg#116-194) have been removed:

- 16.2.4 Demographic Data (Pg#116)
- Listing 16.2.4.1 Demographics and baseline characteristics -Full analysis set (Pg#117)
- Listing 16.2.4.2 FIX gene sequencing data -Full analysis set (Pg#118)
- Listing 16.2.4.3 Medical history and concomitant illnesses -Full analysis set (Pg#119)
- Listing 16.2.4.4 General surgical history -Full analysis set (Pg#120)
- Listing 16.2.4.5 Haemophilia B disease related surgical history -Full analysis set (Pg#121)
- Listing 16.2.4.6 Haemophilia B history -Full analysis set (Pg#122)
- Listing 16.2.4.7 Use of FIX medication during last 7 days prior to visit 1 -Full analysis set (Pg#123)
- Listing 16.2.4.8 History of FIX replacement therapy and bleeding history prior to visit 1 (Prophylaxis regimen) -Full analysis set (Pg#124)
- Listing 16.2.4.9 History of FIX replacement therapy and bleeding history prior to visit 1 (On-demand regimen) -Full analysis set (Pg#125)
- Listing 16.2.4.10 Data on joint status at screening -Full analysis set (Pg#126)
- Listing 16.2.4.11 Data on joint status at screening -HJHS score by location -Full analysis set (Pg#127)
- Listing 16.2.4.11 Data on joint status at screening -HJHS score by location -Full analysis set (Pg#128)
- Listing 16.2.4.13 Data on joint status at week 52 -HJHS score by location -Full analysis set (Pg#129)
- Listing 16.2.4.14 Data on joint status at week 52 -HJHS score -Total -Full analysis set (Pg#130)
- Listing 16.2.4.15 Laboratory parameters related to exclusion criteria 5 and 6 -Full analysis set (Pg#131)
- 16.2.5 Compliance and/or Drug Concentration Data (if available) (Pg#132)
- Listing 16.2.5.1 Administration of IMP -Full analysis set (Pg#133)
- 16.2.6 Individual Efficacy Response data (Pg#134)
- Listing 16.2.6.1 Data on bleeding episodes -Bleeding diary and AE form – Period: Screening until dosing -Full analysis set (Pg#135)
- Listing 16.2.6.2 Data on bleeding episodes -Bleeding diary and AE form -Period: From Dosing To cut-off -Full analysis set (Pg#136)
- Listing 16.2.6.3 Bleeding episodes during 1 year period before visit 1 -Full analysis set (Pg#137)
- Listing 16.2.6.4 FIX protein concentration (µg/L) data -Full analysis set (Pg#138)
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- Listing 16.2.6.6 Incremental recovery -Full analysis set (Pg#140)
- Listing 16.2.6.7 FIX activity (%) -Local monitoring data -Full analysis set (Pg#141)
- Listing 16.2.6.8 FIX replacement therapy after tapering-off -Full analysis set (Pg#142)
- Listing 16.2.6.9 FIX replacement therapy before tapering-off -Full analysis set (Pg#143)
- Listing 16.2.6.10 Prescribed FIX replacement therapy -Full analysis set (Pg#144)
- Listing 16.2.6.11 On-demand FIX replacement therapy during 1 year period before visit 1 (Pg#145)
- Listing 16.2.6.12 FIX replacement therapy, bleeding episodes and annualized bleeding rates -Full analysis set (Pg#146)
- Listing 16.2.6.13 SF-36 Item numbers and texts (Pg#147-148)

16.1.9.2 Data Monitoring Committee (DMC)

Data Monitoring Committee Charter

Trial ID:	CT-AMT-060-01
EudraCT No.:	2013-005579-42
Trial Phase:	I/II
Trial Title:	A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) administered to adult patients with severe or moderately severe haemophilia B
Trial Indication:	Haemophilia B
Investigational Medicinal Product (IMP):	AAV5-hFIX (adeno-associated viral vector containing a codon-optimized human factor IX gene)
Date:	30 December 2014
Version:	Final 1.0
Sponsor:	uniQure biopharma B.V. Meibergdreef 61 1105 BA Amsterdam The Netherlands

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List of Abbreviations

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AAV5	Adeno-Associated Viral vector serotype 5
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
cDNA	complementary Deoxyribonucleic Acid
CTP	Clinical Trial Protocol
DMC	Data Monitoring Committee
FIX	Factor IX
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IRB	Institutional Review Board
SAE	Serious Adverse Event

List of Terms

Term	Definition
AAV5-hFIX	Adeno-associated viral vector containing a codon-optimized human factor IX gene

1. DMC Members' Approval of Data Monitoring Committee Charter

PPD
(External independent, medically qualified expert)

PPD	PPD	PPD
		Date

PPD
(External independent, medically qualified expert)

PPD	Signature	Date

PPD
(External independent, medically qualified expert)

PPD	Signature	Date

PPD
(External independent statistician)

PPD	Signature	Date

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PPD Signature Date

PPD
(External independent, medically qualified expert)

PPD PPD PPD

PPD
(External independent statistician)

PPD PPD PPD Date

2. Sponsor's Approval of Data Monitoring Committee Charter

Sponsor's responsible PPD

PPD

PPD

uniQure biopharma B.V.

PPD

PPD

Date

3. Purpose

The Data Monitoring Committee (DMC) is a committee established by uniQure, composed of individuals with appropriate and relevant experience to assess safety data of subjects participating in the clinical trial, CT-AMT-060-01.
The purpose of this charter is to define how the DMC will operate prior to and during the conduct of the clinical trial, CT-AMT-060-01.

4. Trial Design

Trial CT-AMT-060-01 has an open-label, uncontrolled, single-dose, dose-ascending design and consists of two cohorts. The trial will be conducted at multiple centres in multiple countries in male patients, aged ≥18 years, with severe haemophilia B or moderately severe haemophilia B with a severe bleeding phenotype defined as:

- Known coagulation Factor IX (FIX) deficiency with plasma FIX activity level < 1% (severe) or plasma FIX activity level ≥ 1% and ≤ 2% (moderately severe) and
- currently on prophylactic FIX replacement therapy for a history of bleeding, or
- currently on on-demand therapy with a current or past history of frequent bleeding (defined as four or more bleeding episodes in the last 12 months or chronic haemophilic arthropathy [pain, joint destruction, and loss of range of motion] in one or more joints).

Patients should have had more than 150 previous exposure days of treatment with FIX protein.

The Investigational Medicinal Product (IMP) is a recombinant adeno-associated viral vector of serotype 5 (AAV5) containing the codon-optimized hFIX complementary Deoxyribonucleic Acid (cDNA) under the control of a liver-specific promoter. The IMP is identified as AAV5-hFIX. The pharmaceutical form of AAV5-hFIX is solution for intravenous infusion.

Subjects will be allocated to one of two cohorts with the following planned dose levels:
- Cohort 1 (5 subjects): AAV5-hFIX 5.0×10^{12} gc/kg
- Cohort 2 (5 subjects): AAV5-hFIX 2.0×10^{13} gc/kg

Subjects will receive the IMP on only one occasion and will thereafter be followed for five years with respect to safety and with respect to efficacy measured as levels of FIX, bleeding patterns and consumption of FIX replacement therapy.

5. Responsibilities and Tasks of the DMC

The primary responsibilities of the DMC are to:

- periodically review and evaluate accumulated safety data from trial CT-AMT-060-01 throughout the entire trial period, and
- identify potential safety signals, and
- make recommendations to uniQure concerning trial continuation, protocol modifications, additional analyses or trial suspension based on available safety data

The DMC chair will:

- Chair the DMC meetings
- Ensure written statements/recommendations and minutes are approved and stored
- Request additional data and/or analysis and/or ad hoc experts to be called for

The DMC member acting as independent external statistician will:

- Prepare data packages to the DMC and Sponsor
- Provide data package via secure website to DMC
- Assist the DMC in evaluating data and serve as interface with sponsor to if additional data or analyses are required.
- Be member of the DMC.
- Ensure that Sponsor provide presentation at open sessions for trial developments, as needed.
- Arrange DMC meetings
- Arrange meetings between Sponsor and DMC if the DMC provides a recommendation which different from “dosing and trial design should continue as planned” (see Section 6.2.4)

All DMC members (excluding the external independent statistician) will:

- evaluate available safety data from the first subject in each cohort prior to allowing dosing of the second subject in that particular cohort (see Section 5.1.2)
- evaluate available safety data from the second subject in each cohort prior to allowing dosing of the subsequent 3 subjects in that particular cohort (see Section 5.1.2)
- evaluate available safety data from subjects in Cohort 1 prior to allowing dosing of subjects in Cohort 2 (see Section 5.1.3)

These evaluations will take place at Gateway Meetings (see Section 6.3).

In relation to these evaluations, the DMC will adhere to Trial Stopping Rules (see Section 5.1.1).

To strengthen its evaluations, the DMC may recommend specific interim analyses to be performed during the course of the trial.

5.1 Trial Stopping Rules and Decisions on dosing next Subject(s)

5.1.1 Trial Stopping Rules

As the trial is a one-dose trial, stopping rules are relevant only for the recruitment period. Independently of any changes to the recruitment, subjects who have already been dosed will be followed as per protocol to the end of trial.

The following events will lead to decision to pause dosing, i.e. stop subject recruitment to allow for evaluation and assessment of the implications of the event for further subject dosing:

1. A more than fivefold increase in ALT, AST or both in one or more subjects after IMP administration which is not manageable by steroid rescue treatment implemented according to AASLD guidelines (see clinical trial protocol for CT-AMT-060-01).
2. An SAE judged as probably or possibly related to the IMP and which pose either an immediate risks to subject's health or is likely to adversely affect the subject's health long term. This includes events classified as adverse events qualifying for special as listed in the clinical trial protocol, if these are judged as probably or possibly related to the IMP. The development of an inhibitor towards FIX in one subject is not a cause for stop of subject recruitment, however the development of an FIX inhibitor in more than one subject should lead to pausing of dosing and further investigations of causal relationship
3. Death of a subject, after having received the IMP, that is judged as related to the IMP
4. The occurrence of a malignancy at any point after gene transfer that is judged as probably or possibly related to the IMP.

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5.1.2 Decision to dose the next Subject(s) within a Cohort

The DMC will evaluate the available safety data collected during a period of minimum 24 hours after IMP administration to the 1st subject in a cohort and recommend if and when dosing of the 2nd subject in the cohort can be initiated. Similarly, after the 2nd subject has been dosed in a cohort, the DMC will evaluate available safety data collected during a period of minimum 24 hours after IMP administration to this second subject and recommend if and when dosing of the subsequent 3 subjects in the cohort can be initiated.

5.1.3 Decision to start Cohort 2

The DMC will evaluate all available safety data collected during the period of a minimum of 12 weeks after IMP administration in the first 3 subjects of Cohort 1 and for a minimum of 4 weeks after IMP administration in subjects 4 and 5 of Cohort 1.

If none of the events listed in Section 5.1.1 have occurred, the DMC may recommend to initiate Cohort 2. If one or more of these events have occurred, the DMC may recommend

dosing to be paused while the event(s) is/are further investigated including the implications for further dosing and dose level.

6. DMC Meetings

6.1 Kick-off Meeting

A kick-off meeting will be held before screening of the first subject. During this meeting the following will be presented and discussed:

- Background information and mechanism of action of AAV5-hFIX
- The presently known safety profile of AAV5-hFIX
- Clinical Trial Protocol (CTP) and CTP amendments, if any

The kick-off meeting must be attended by all DMC members and by representatives of uniQure. Sponsor's Drug Safety Expert (DSE), or delegate, will send, in a timely manner, all documents necessary to prepare for this meeting to all participants.

The purpose of the kick-off meeting is to:

- Review, discuss and approve the DMC Charter, including the role and responsibilities of the DMC. The DMC members may in the context of this discussion propose changes to the DMC Charter; however, uniQure is responsible for final decisions relating to the charter
- Review, discuss and train on the IMP and CTP, and associated documents (e.g. patient information sheets, the IB, comments from Independent Ethics Committee(s) (IECs)/ Institutional Review Board(s) (IRBs),reviews, relevant literature, and other research-related document(s))
- Establish the frequency of the DMC meetings, including decisions related to the organization of the meeting (e.g. face-to-face meetings, teleconferences)
- Pre-book date and time for next meeting to be held.
- Review guidelines for assessing the clinical trial progress and safety data, the clinical trial modification and/or termination guidelines, and if applicable, for efficacy based on plans specified in the CTP.
- Develop procedures for conducting business (e.g. voting rules, attendance).

Sponsor's DSE, or delegate, will prepare the minutes, as applicable, of this kick-off meeting and ensure distribution of these, as relevant.

Sponsor's responsible chief medical officer, or delegate, will ensure finalization of the DMC Charter and the approval of this by sponsor's responsible chief medical officer and the DMC Chair. 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.

6.2 Periodic DMC Meetings

The DMC will meet at periodic intervals to review cumulative safety data. The DMC meetings will take form as

- Gateway meetings (see Section 6.3)
- Bi-annual meetings (see Section 6.4)
- Other meetings (see Section 6.5)

For all meetings, the principles regarding meeting preparation, format of meetings, minutes of meetings and DMC recommendations, described in Sections 6.2.1 - 6.2.4, will be followed.

6.2.1 Preparation of Periodic DMC Meetings

The external independent statistician will prepare a data package with all relevant safety data available and distribute this among DMC members and sponsor representatives.
The agenda for each meeting will include:

- Review of data available
- Discussion of the need for additional data
- Decision of DMC recommendation

6.2.2 Format of Meetings

Each DMC meeting following the kick-off meeting will, as necessary, be divided into two sessions: An open session and a closed session (both typically held as teleconferences). At least 3 members of the DMC, including the DMC Chair, must be participating in the closed session in order to have quorum.

Open Sessions
During open sessions, the DMC may request the attendance of sponsor's DSE, sponsor's responsible chief medical officer, investigator(s) and/or representatives of uniQure's clinical trial team, and/or independent consultant(s) to provide specific clarification or to respond to issues that have arisen. 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 enrolment data, individual adverse event data and data on baseline characteristics.

Closed Sessions
During the closed sessions hosted by the external independent statistician, only DMC members must be present. During the closed sessions, the DMC must decide what recommendation(s) it will present to uniQure.

6.2.3 Meeting Minutes

Minutes from the open sessions are prepared by the external independent statistician and approved by the DMC Chair. Minutes from the closed sessions are prepared by the DMC Chair assisted by the external independent statistician.

It is the goal that draft meeting minutes of open and closed sessions are prepared within 2 working days after the meeting. Draft meeting minutes are forwarded to all DMC members for their review, enabling final approved minutes within 7 calendar days after the meeting. Minutes of open and closed sessions are approved by the DMC Chair.

6.2.4 DMC Recommendation(s)

DMC recommendations (regarding trial continuation, protocol modifications, additional analyses, or trial to be terminated) will be communicated to sponsor's DSE and sponsor's responsible chief medical officer. The recommendation(s) provided by the DMC to uniQure should be in writing and provided to uniQure immediately after the finalization of DMC meeting minutes. The recommendation and the related documentation should be filed in the Trial Master File (TMF).

The recommendation should include a brief ticking:

a) No change recommended – dosing and trial design should continue as planned
b) Stopping or adjusting dose and/or trial design
c) Stopping the trial immediately
d) Putting the trial on hold while investigating issue

Furthermore, if recommendation b), c) or d) is ticked, a detailed explanation of this recommendation should be given. Additionally, a meeting should be set up between the DMC and Sponsor (arranged by the DMC member acting as external independent statistician).

uniQure's decision(s) to follow DMC recommendations will be documented in writing, signed by uniQure's DSE and Sponsor's responsible chief medical officer, and will be communicated by uniQure to:

- Investigator(s)
- IEC(s)/IRB(s)
- Competent authorities(s).

The communication to investigators, IEC(s)/IRB(s) and competent authorities will be organized by Sponsor's Clinical Trial Manager.

6.3 Gateway Meetings

Regular safety data evaluation meetings (i.e. gateway meetings) will take place to accommodate, as a minimum, the gateway decisions described in Section 5.1.2 and 5.1.3.

An overview of gateway meetings is given in **Table 6-1**. These meetings will usually be held as telephone conferences.

During these sessions safety data (see **Table 6-1**) will be discussed and a recommendation for actions to be taken, if any, will be agreed upon. This recommendation is written as part of the meeting minutes.

Table 6-1, Overview of DMC Gateway Meetings and minimum available Data

Purpose of Meeting	Timing of Meeting	Expected Data to be Available (as a minimum)
Gateway meeting for allowing dosing of 2nd subject in Cohort 1	≥24 hours after dosing of 1st subject in Cohort 1	Available vital signs, C-reactive protein, SAEs and AEs from 1st subject.
Gateway meeting for allowing dosing of 3rd, 4th and 5th subjects in Cohort 1	≥24 hours after dosing of 2nd subject in Cohort 1	Available vital signs, C-reactive protein, SAEs and AEs from 2nd subject. Available vital signs, SAEs, AEs and safety laboratory data (such as liver parameters and inflammatory markers) from the 1st subject
Gateway meeting for allowing dosing of 1st subject in Cohort 2	≥12 weeks after dosing of 1st, 2nd and 3rd subject of Cohort 1 and ≥4 weeks after dosing of 4th and 5th subjects of Cohort 1	Available vital signs, SAEs, AEs and safety laboratory data (such as liver parameters and inflammatory markers) Data from 1st - 5th subject, Cohort 1
Gateway meeting for allowing dosing of 2nd subject in Cohort 2	≥24 hours after dosing of 1st subject in Cohort 2	Available vital signs, SAEs, AEs and safety laboratory data (including liver parameters. inflammatory markers) from 1st - 5th subject, Cohort 1 Available vital signs, C-reactive protein, SAEs and AEs from 1st subject, Cohort 2.
Gateway meeting for allowing dosing of 3rd, 4th and 5th subjects in Cohort 2	≥24 hours after dosing of 2nd subject in Cohort 2	Available vital signs, SAEs, AEs and safety laboratory data (including liver parameters. inflammatory markers) Data from 1st - 5th subject, Cohort 1 Available vital signs, C-reactive protein, SAEs and AEs from 2nd subject, cohort 2. Available vital signs, SAEs,

		AEs and safety laboratory data (such as liver parameters and inflammatory markers) from the 1st subject, cohort 2.

6.4 Bi-annual Meetings

In addition to gateway meetings, the DMC will meet bi-annually throughout the course of the trial until trial closure.

At bi-annual meetings, the DMC will review cumulative safety data collected on all subjects dosed. The assessment by the DMC of those data, will be considered in design of future trials

6.5 Other Meetings

The DMC members, if considered relevant, may call for additional telephone conferences or face-to-face meetings at any time.

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

7. DMC Closure

The responsibilities of the DMC will end when the clinical trial has been closed. The DMC may be closed during a formal DMC meeting with all DMC members.

All documentation concerning the DMC and communication with the DMC must be filed and archived in the TMF. The DSE or delegate is responsible for filing all documents that are generated during the conduct of the clinical trial. At the closure of the clinical trial, the documents which have not been transferred on an ongoing basis from the DMC to uniQure must be forwarded to uniQure.

8. DMC Members

Three external, independent and medically qualified experts and one external, independent statistician are planned to participate in the DMC (see **Table 8-1**).

Table 8-1, DMC Members

Role	Name and Title	Working Address
PPD	PPD PPD	PPD PPD
PPD	PPD PPD	PPD
PPD	PPD PPD	PPD PPD
PPD	PPD PPD	PPD PPD

Signature Page

CT-AMT-060-01 - Statistical Analysis Plan - statistical-methods

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

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