STATISTICAL ANALYSIS PLAN COVER PAGE

Official Title of the study/Protocol Title: AAV8-mediated Low Density Lipoprotein Receptor (LDLR) Gene Replacement in Subjects with Homozygous Familial Hypercholesterolemia (HoFH)

Protocol Number: FHGT002

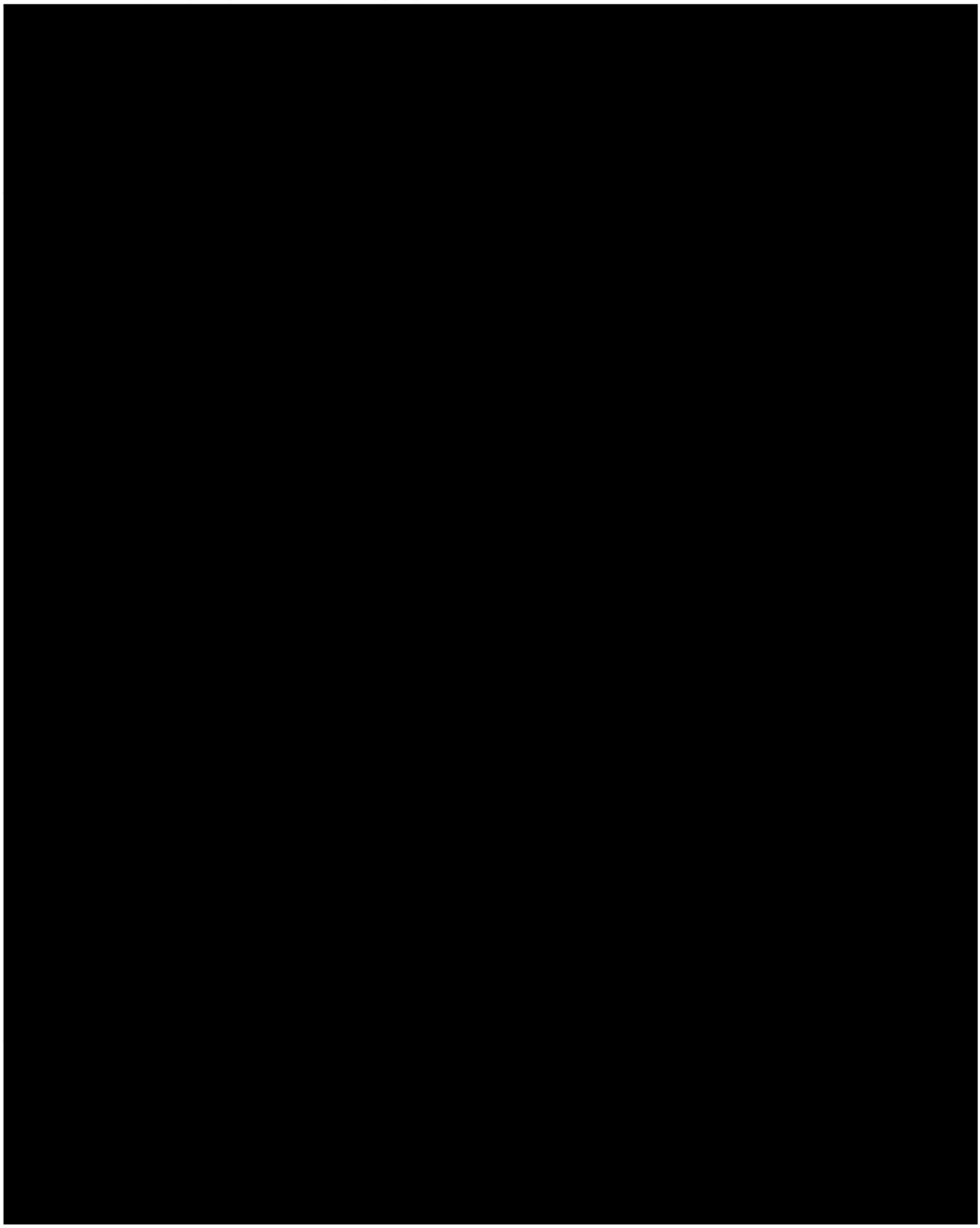
NCT Number: NCT02651675

Document Date: 14 September 2020; Version 2

STATISTICAL ANALYSIS PLAN

AAV8-mediated Low Density Lipoprotein Receptor (LDLR) Gene Replacement in Subjects with Homozygous Familial Hypercholesterolemia (HoFH)

Investigational Product:	AAV8.TBG.hLDLR
Protocol Number:	FHGT002
Development Phase:	Phase I/IIa
Sponsor:	REGENXBIO Inc. 9600 Blackwell Road, Suite 210 Rockville, MD, USA 20850
Original Protocol Date:	November 09, 2015
Protocol V10:	December 14, 2018
SAP Version:	V 2.0
SAP Date:	September 14, 2020



VERSION HISTORY

Version	Version Date	Description
1.0	February 28, 2017	Original signed version
2.0	September 14, 2020	Updated version per protocol amendment 10

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	**Definition**
AAV	Adeno-associated virus
AE	Adverse event
ALT	Alanine aminotransferase
ApoA-I	Apolipoprotein A-I
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic class
BMI	Body Mass Index
CBC	Complete blood count
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FCR	Fractional catabolic rate
GC	Genome copy
GGT	gamma-glutamyl transpeptidase
HDL-C	High density lipoprotein cholesterol
HLA	Human Leukocyte Antigen
hLDLR	Human low density lipoprotein receptor
HoFH	Homozygous familial hypercholesterolemia
INR	International Normalized Ratio
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
Non-HDL-C	Non-HDL cholesterol
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PT	prothrombin time
PTT	partial thromboplastin time

Abbreviation	**Definition**
SAP	Statistical Analysis Plan
SD	Standard deviation
TBG	Thyroxine-binding globulin
TC	Total cholesterol
TG	Triglycerides
TNTC	Too numerous to count
ULN	Upper limit of normal
VLDL-C	Very low density lipoprotein cholesterol
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number FHGT002, version V10, 14 December, 2018. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. STUDY OBJECTIVES

2.1.1 Primary Objective

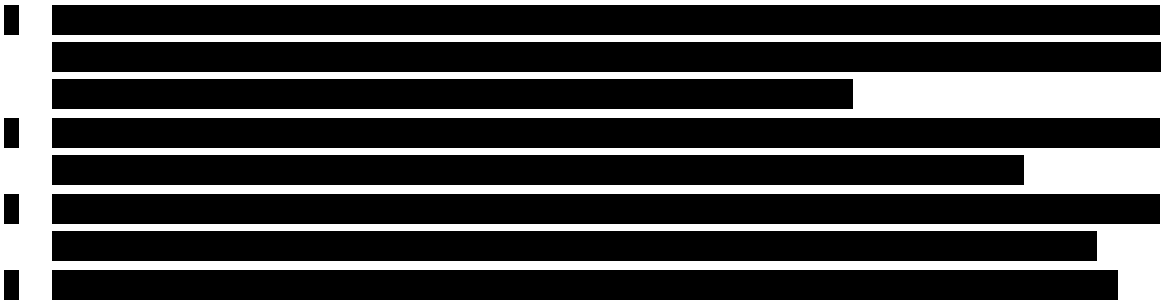
The primary objective of this study is to determine the safety of AAV8.TBG.hLDLR administration in patients with homozygous familial hypercholesterolemia (HoFH) as assessed by the number of reported adverse events (AEs), changes noted on physical examinations, and clinical laboratory parameters assessed up to 24 weeks post vector administration.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the low density lipoprotein cholesterol (LDL-C) reduction achieved with AAV8.TBG.hLDLR administration as defined by percent change in LDL-C at 12 weeks for Cohort 1 compared to Baseline; for Cohort 2 and Expansion Cohort 2 at 18 weeks if the subject is discontinued off steroids for 4 weeks at that timepoint without change to lipid lowering therapy, or earliest timepoint after Week 18 where subject is discontinued off steroid for 4 weeks and has not changed lipid lowering therapies compared to Baseline.
- To assess changes in other lipid parameters at 12 weeks for Cohort 1 compared to Baseline; for Cohort 2 and Expansion Cohort 2 at 18 weeks if the subject is discontinued off steroids for 4 weeks at that timepoint without change to lipid lowering therapy, or earliest timepoint after Week 18 where subject is discontinued off steroid for 4 weeks and has not changed lipid lowering therapies compared to Baseline. Specifically, percent change in total cholesterol (TC), non-high density lipoprotein cholesterol (non-HDL-C), high density lipoprotein cholesterol (HDL-C), fasting triglycerides (TG), very low density lipoprotein cholesterol (VLDL-C), lipoprotein(a) (Lp(a)), apolipoprotein B (apoB), and apolipoprotein A-I (apoA-I).
- To determine the safety of AAV8.TBG.hLDLR administration as assessed by the number of reported adverse events, changes noted on physical examinations and clinical laboratory parameters assessed at multiple time points up to 104 weeks post vector administration.
- To assess vector shedding in plasma and urine.

[redacted]



3. STUDY OVERVIEW

3.1 Overall Study Design and Treatment Assignment

This is a 104-week Phase I/IIa, multicenter, open-label, single arm, dose escalation study of AAV8.TBG.hLDLR in adults with a clinical presentation consistent with HoFH and carrying 2 mutations in the LDLR gene. Safety will be the primary focus, with a secondary focus on clinical response to AAV8.TBG.hLDLR. The primary safety endpoint is at Week 24. Approximately 12 subjects will be enrolled into one of 3 possible dose cohorts, 2.5×10^{12} genome copies (GC)/kg (Dose 1), 7.5×10^{12} GC/kg (Dose 2), or 2.5×10^{13} GC/kg (Dose 3), and will receive a single dose of AAV8.TBG.hLDLR administered by IV infusion into a peripheral vein (or into an existing AV fistula). Following completion of the primary study period at Week 24, subjects will continue to be assessed (for safety and efficacy) for up to 104 weeks following treatment with AAV8.TBG.hLDLR. At the end of the study, all subjects will be invited to participate in a long-term follow-up study.

In this trial, two groups will assess data accumulated from the trial, an external Data Safety Monitoring Board (DSMB) and the Sponsor's Internal Safety Committee (ISC). The primary role of the independent DSMB is to assess safety at periodic intervals and to provide recommendations on safety and dose escalation. The primary role of the ISC is to monitor safety on an ongoing basis.

The initial Dose 1 cohort of AAV8.TBG.hLDLR will receive 2.5×10^{12} GC/kg. Dosing of subjects will be staggered by at least 4 weeks. A formal review of all safety data will be performed by the DSMB after the 3rd subject is dosed and completes the 4 weeks post-dosing visit, primarily to determine if dose escalation can occur. However, the DSMB could recommend to expand the cohort, lower the dose, or stop the trial.

If the recommendation is to dose escalate, the Dose 2 cohort will be initiated at a dose of 7.5×10^{12} GC/kg (Dose 2). Dosing of subjects will be staggered by at least 4 weeks. A formal review of all safety data will be performed by the DSMB after the 3rd subject is dosed and completes the 4 weeks post-dosing visit, primarily to determine if dose escalation can occur. However, the DSMB could recommend to expand the cohort, lower the dose, or stop the trial. If expansion of Dose 2 cohort is recommended, up to 3 additional subjects will be enrolled and will receive prophylactic corticosteroids. Subject dosing will be staggered by at least 6 weeks. After enrollment of up to 3 subjects in the expanded Dose 2 cohort (or fewer subjects, upon agreement by the DSMB), a review of all the safety data will performed by the DSMB to

determine if dose escalation can occur. After completion of the Dose 2 cohort, the DSMB will need to recommend dose escalation in order for the Dose 3 cohort to be initiated.

After initiation of the Dose 3 cohort (2.5×10^{13} GC/kg), the following will occur:

- Dosing of subjects will be staggered by at least 6 weeks. Up to 3 subjects will be enrolled into the cohort.

At any time, if there are safety concerns, the ISC may share safety concerns with the DSMB. The DSMB may recommend to stop the trial, dose additional subject(s) at the current dose, or proceed at a lower dose.

If at any time during dosing an event meets the criteria of a Stopping Rule, dosing of any new subjects will be suspended until a complete review of all safety data by the external DSMB and the ISC has been performed.

At any given DSMB meeting, whether called for by a Safety Review Trigger (SRT) or at the planned DSMB meeting at the conclusion of a dose cohort, the DSMB may recommend stopping the trial, dosing additional subjects at the current dose, proceeding to the next dose cohort, or proceeding at a lower dose. After the final subject has been dosed, a review of all safety data by the DSMB will be performed.

All subjects, including those that were deemed eligible based on their participation in a companion screening protocol, will be invited to undergo a screening visit (Visit 1) to confirm eligibility for this clinical trial. Subjects that agree to participate will be withdrawn from selected lipid-lowering drugs for at least 4 weeks prior to vector administration. An additional Visit 1a may be scheduled as a blood draw either at the study site or by a home healthcare nurse to perform a lipid panel up to 2 weeks prior to the dosing visit (Visit 3).

All subjects will be admitted at the research inpatient unit the day of or the day before vector administration and eligibility and willingness to participate in the trial will be appropriately re-confirmed. Following AAV8.TBG.hLDLR administration, safety assessments and laboratory draws will occur for 24 hours post dosing as per Table 16.1 in protocol, after which the subject will be discharged from the research unit. Subject will return to the Research Unit for a safety visit 48 hours post-dosing. Blood will be drawn weekly for safety testing from Week 2 to Week 12. Based on the experience accumulated with subjects dosed under earlier versions of this protocol, prophylactic corticosteroids will be administered to any future dosed subjects starting 1 day prior to dosing through the end of Week 13.

After week 14, subjects will undergo study site visits at Weeks 18, 24, 36, and 52 for the active study and at Weeks 78 and 104 during the follow up period. Additional laboratory assessments will occur at least biweekly between Week 14 and Week 24. Both liver function tests (LFTs) and LDL-C collected locally either at local lab or by health care nurse will be recorded in the Clinical Database. Long-term follow-up will be conducted via a separate protocol. All visits and follow-up will be indexed to the date of the vector infusion.

3.2 Study Endpoints

3.2.1 Primary Endpoints: Safety

Safety assessment up to Week 24 is the primary objective of this Phase I/IIa study. Safety assessments will be performed before and at multiple time points after vector administration. Safety endpoints will include reported adverse events, changes noted on physical examinations and laboratory parameters from assessments listed below..

3.2.1.1 Laboratory Assessments

- Biochemical Profile: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, lactate dehydrogenase (LDH), creatinine, creatinine phosphokinase, calcium, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin. Gamma glutamyl transferase (GGT) will be measured at screening and only as clinically indicated through the study.
- Complete Blood Count (CBC): white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Hemoglobin A1c (HbA1c)
- Coagulation: prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT), at screening and baseline, and as needed throughout the study.
- Urinalysis: urinary color, turbidity, pH, glucose, bilirubin, ketones, red blood cells (RBCs), protein, and WBCs.
- Vector concentration: AAV8 concentration in plasma and urine, measured as vector genomes by polymerase chain reaction (PCR).

3.2.1.2 Adverse Events of Special Interest

Based on the pre-specified laboratory and clinical assessments described above, the number of subjects who have the following will be presented:

- Liver injury
  - Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Grade 2 or higher lab result for bilirubin (>1.5 × upper limit of normal (ULN)) or liver enzymes (AST > 3 × ULN, ALT > 3 × ULN, alkaline phosphatase > 2.5 × ULN).
- Hepatotoxicity (i.e., meet criteria for "Hy's law")
  - ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and no other reason can be found to explain the changes observed.

Additionally, ALT or AST elevations that may trigger initiation or adjustment of corticosteroid therapy will be flagged and reported.

3.2.2 Secondary Endpoints

The secondary efficacy endpoints are based on a detailed assessment of the percent change in lipid parameters. The secondary efficacy endpoints timepoint is defined as below.

For Cohort 1: 12 weeks following administration of AAV8.TBG.hLDLR compared to Baseline.

For Cohort 2 and Expansion Cohort 2: at 18 weeks if the subject is discontinued off steroids for 4 weeks at that timepoint without change to lipid lowering therapy, or earliest timepoint after Week 18 where subject is discontinued off steroid for 4 weeks and has not changed lipid lowering therapies following administration of AAV8.TBG.hLDLR compared to Baseline.

This will include:

- Percent changes in LDL-C
- Percent changes in TC, VLDL-C, HDL-C, non-HDL-C, TG, apoA-I, apoB, and Lp(a)

Efficacy will primarily be defined using LDL-C measured by beta quantification and separate analyses will be done using LDL-C (direct) and calculated LDL-C (Freidewald equation). The baseline LDL-C value will be determined using qualified LDL-C drawn prior to administration of AAV8.TBG.hLDLR. Qualified LDL-C draws will be those taken after sufficient washout of selected lipid lowering medications has occurred and pre-apheresis in subjects receiving apheresis (i.e., the day of apheresis). Baseline LDL-C value will be calculated as the average of up to 2 of the most recent qualified fasting LDL-C levels obtained during stable lipid lowering treatment before administration of AAV8.TBG.hLDLR. The 2 most recent LDL-C values should be no more than approximately 4 weeks apart. Baseline LDL-C values based on both beta-quantification and direct methods will be based on the same visit dates. Similar methods to define the baseline value will be applied to other lipid parameters. Lipid lowering treatment must be stable as per inclusion/exclusion criteria by the time of the first laboratory assessment.

The secondary safety endpoints are safety assessments stated in Section 3.2.1 that are measured after vector administration up to the 104 week post dosing visit.

[redacted]

[redacted]

4. STATISTICAL METHODOLOGY

4.1 General Statistical Considerations

4.1.1 Baseline, Endpoint, and Other Statistical Considerations

Baseline LDL-C value will be calculated as the average of up to 2 of the most recent qualified fasting LDL-C levels obtained during stable lipid lowering treatment before administration of AAV8.TBG.hLDLR. The 2 most recent LDL-C values should be no more than approximately 4 weeks apart.

Baseline LDL-C values based on both beta-quantification and direct methods will be based on the same visit dates.

Similar methods to define the baseline value will be applied to other lipid parameters.

Baseline of measures other than lipid parameters is defined as the last measurement prior to the administration of AAV8.TBG.hLDLR.

LDL-C calculated will be derived using Freidewald formula as following:

LDL-C (mg/dL) = TC (mg/dL) -HDL-C (mg/dL) – TG (mg/dL)/5.

All data will be presented in subject data listings. Categorical variables will be summarized using frequencies and percentages, and continuous variables will be summarized using descriptive statistics (number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum). Graphical displays will be presented as appropriate.

Safety, PD, and efficacy endpoints will be reported by dose cohort and may also be reported for all dose cohorts combined.

4.1.2 Analysis Day

Analysis day will be calculated from the date of AAV8.TBG.hLDLR administration. The day of AAV8.TBG.hLDLR administration will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0. The analysis day will be calculated as:

- For days prior to the dose date, Analysis Day = Date - Date of AAV8.TBG.hLDLR Administration
- For days on/after the dose date, Analysis Day = Date - Date of AAV8.TBG.hLDLR Administration + 1

4.1.3 Analysis Visits

Analysis visit is a timing variable to be used for analyses involving visits. Analysis window will be used to determine the analysis visit which a measurement should be mapped to. For this study, the target date and window specified per protocol will be used to map measurements.

Data collected at a scheduled visit will be used as the data at the corresponding analysis visit even if the visit is out-of-window. If a scheduled visit is missing, measurement taken at a unscheduled visit fall into the analysis window will be used as the measurement for that specific visit. If multiple measurements fall into the same visit window, the last one will be selected.

If both central and local laboratory measurements fall into the same visit window, measurement from central laboratory should be selected for that specific visit. The measurements from local laboratory will be used only if there are no central laboratory measurements available within that visit window.

In subject data listings, the visit label will be presented as collected, analysis visit label will be used for by-visit summary and analysis purposes.

4.1.4 Handling of Missing or Partial Dates

This section applies to impute missing or partial AE/concomitant medication start and end dates.

The goal for imputing partially missing data is to select the most conservative date within the possible range specified by the non-missing data. The imputation rules are as following:

Date	Type of Missing Date	Handling of Missing Date
Event Start Date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied.
	Only YYYY is available	Use the first day of YYYY to impute the missing month and date parts of the start date. In the situation where AAV8.TBG.hLDLR was administered in the same year, the start date will be

		imputed as date of AAV8.TBG.hLDLR administration.
	YYYY and MM are available, but DD is missing	Use the first day of MM to impute the missing date part of the start date. In the situation where AAV8.TBG.hLDLR was administered in the same month and year, the start date will be imputed as date of AAV8.TBG.hLDLR administration.
Event End Date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied. The event will be considered ongoing at the end of study.
	Only YYYY is available	Use the last day of YYYY to impute the missing month and date parts of the end date
	YYYY and MM are available, but DD is missing	Use the last day of MM to impute the missing date part of the end date

In the case where the imputed start date is later than the reported stop date, the imputed date will be set equal to the stop date.

In all listings, missing or partial dates should be left as they have been recorded.

4.2 Analysis Populations

Safey Population: The Safety Population includes all subjects who receive any treatment dose. All analyses will be performed based on the Safety Population.

4.3 Subject Data and Study Conduct

4.3.1 Subject Disposition

The number of subjects enrolled, the number of subjects treated, the number of subjects who complete the study, and the number of subjects who withdraw from the study, along with the reasons for their withdrawal, will be summarized by dose cohort and by the study overall. In addition, the total number of subjects screened and the number of screen failures, along with the reason for screen failure, will be summarized.

4.3.2 Protocol Deviations

Protocol deviations will be presented in data listing.

4.3.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by dose cohort, as well as for the study overall.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, body weight, height, and body mass index (BMI). Continuous variables (e.g., age, weight, and BMI) will be summarized by descriptive statistics (n, mean, SD, minimum, median, and maximum). Categorical variables (e.g., gender, race, and ethnicity) will be summarized by the number and percentage of subjects in corresponding categories.

Past and current medical history will be summarized by treatment group using the system organ class (SOC) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Deviations from inclusion/exclusion criteria as well as subject's status will be listed.

4.3.4 Prior and Concomitant Medications

All medications administered during the study will be listed and coded using the most current version of the World Health Organization (WHO) Drug Reference List. A listing of all concomitant medications including the reported term, preferred term, and Anatomical Therapeutic Chemical (ATC) class, start and stop dates, and other relevant data will be provided.

For summary purposes, medications will be considered prior medications if they were taken prior to AAV8.TBG.hLDLR administration and concomitant medications if they were taken at any time after AAV8.TBG.hLDLR administration (i.e. started prior to the AAV8.TBG.hLDLR administration date and were ongoing or started after the administration date). Medications could be considered both prior and concomitant.

The number and percentage of subjects taking prior and concomitant medications will be summarized by cohort, ATC, and preferred term.

4.4 Safety Endpoint Analyses: Primary and Secondary

Safety assessments will be performed before and at multiple time points after vector administration up to the 104 week post dosing visit. The primary endpoint analyses will be performed using safety assessments through Week 24. The secondary endpoint analyses will be performed using safety assessments after Week 24.

Safety endpoint variables will be summarized using descriptive statistics as defined in section 4.1 for continuous variables and frequency and percentage for categorical variables.

4.4.1 Adverse Events

All AEs will be recorded from the time the subject signs the informed consent form to the end of the study (Week 104). Long-term follow-up will be conducted via a separate protocol (starting after 104 weeks post vector administration) for up to 5 years' cumulative duration in this study plus the follow-up study. All AEs will be coded to system organ class and preferred term using MedDRA version 23.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that start or worsen during or after administration of AAV8.TBG.hLDLR.

AEs occurring prior to a treatment dose will be listed and presented separately from those that occur during or after receiving a treatment dose.

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any TEAEs (overall and by maximum severity)
- Any treatment related TEAEs
- Any study procedure related TEAEs
- Any advese events of special interest
- Any serious AEs (SAEs)
- Any AEs leading to study discontinuation
- Any AEs leading to death

Counts and percentages of subjects will also be presented by system organ class and preferred term for TEAEs, SAEs and treatment related TEAEs. TEAEs started prior to/at Week 24 and after Week 24 will be summarized separately. AEs are considered to start prior to/at Week 24 if (AE onset date – first dose date + 1)/7 <=24. All AEs will be coded using MedDRA. AEs leading to study discontinuation and death will be listed separately.

In cases of missing or incomplete dates, the missing component(s) will be imputed as stated in Section 4.1.4.

Actual data values as they appear in the original electronic case report form (eCRF) will be presented in the data listings.

4.4.2 Liver Injury and Hepatotoxicity

Counts and percentages of subjects who have the following at any of the post baseline visit will be presented:

- Liver injury
    - Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Grade 2 or higher lab result for bilirubin (>1.5 × upper limit of normal (ULN)) or liver enzymes (AST > 3 × ULN, ALT > 3 × ULN, alkaline phosphatase > 2.5 × ULN).
- Hepatotoxicity (i.e., meet criteria for “Hy’s law”)
    - ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and no other reason can be found to explain the changes observed.

Data collected in both central and local labs at scheduled and unscheduled visits will be used to determine whether the subjects experienced liver injury and hepatotoxicity.
Additionally, ALT or AST elevations that may trigger initiation or adjustment of corticosteroid therapy will be flagged and reported in a listing.
The time to onset of liver injury or hepatotoxicity from the date of AAV8.TBG.hLDLR administration will also be summarized descriptively by dose cohort and by the study overall.

4.4.3 Clinical Laboratory Tests

Observed values and changes from baseline (as applicable) through Week 104 will be summarized descriptively by dose cohort, by visit and by the study overall for each biochemical profile, CBC, coagulation, and urinalysis parameter stated in Section 3.2.1.1. In addition, the incidence of subjects who meet predefined criteria for clinically significant abnormal values (or abnormal change) will also be summarized by dose cohort and by the study overall.

4.4.4 Vector Concentration

Observed values of AAV8 concentration in plasma and urine, measured as vector genomes by PCR will be summarize descriptively by dose cohort and the study overall.

4.4.5 Physical Examination Findings

Counts and percentages of subjects who have abnormal, indeterminate, normal, not evaluable and unknown physical examination findings will be presented by dose cohort and visit time so the normal/abnormal finding can be followed from baseline to post-baseline visits through Week 104. Physical examination results will be listed.

4.5 Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoints are based on a detailed assessment of the percent change in lipid parameters at the secondary efficacy endpoints timepoint.

Summary statistics of lipid parameters results and percent change from baseline will be provided by dose cohort at each time point. Lipid parameters include: LDL-C measured by beta quantification, LDL-C direct, LDL-C calculated (Freidewald equation), TC, VLDL-C, HDL-C, non-HDL-C, TG, apoA-I, apoB, and Lp (a).

Lipid parameters will be presented in data listings.

[redacted]

[redacted]

[redacted]

4.7 Vital Signs and Electrocardiogram Findings

Observed values and changes from baseline (as applicable) through Week 104 will be summarized descriptively by dose cohort and by the study overall for vital signs. In addition, the incidence of subjects who meet pre-defined criteria for clinically significant abnormal values (or abnormal change) will also be summarized by dose cohort and by the study overall. Results fall in following criteria will be considered as clinically significant abnormal values:

- Heart rate <50 bpm or >120 bpm
- Heart rate change from baseline >30 bpm increase or decrease
- Systolic blood pressure <95 mmHg or >180 mmHg
- Systolic blood pressure change from baseline >30 mmHg increase or decrease
- Diastolic blood pressure <50 mmHg or >110 mmHg
- Diastolic blood pressure change from baseline >20 mmHg increase or decrease

For electrocardiogram (ECG), counts and percentages of subjects who have clinically significant and not clinically significant overall interpretation will be presented by dose cohort and visit through Week 104.

Vital signs and ECG results will be listed.

4.8 Interim Analysis

No interim analysis is planned.

5. SAMPLE SIZE DETERMINATION

The sample size chosen for this study is not based on statistical considerations, as HoFH is a very rare disease. Approximately 12 subjects are planned to be treated.

6. PROGRAMMING SPECIFICATIONS

Statistical analyses will be performed using SAS® (Cary, NC) version 9.3 or above. The programming specifications, including the mock-up analysis tables, figures, and data listings,

as well as the derived database specifications, will be prepared in stand-alone documents. The programming specification documents will be finalized prior to database lock.

7. CHANGES FROM PROTOCOL

Study was terminated before the enrollment of Cohort 3 per REGENXBIO's decision. Data from only Cohort 1, 2, and Expansion Cohort 2 will be included in the analysis.

The following objective and endpoints are updated in the SAP.

	Original	Updated	Rational
Analysis Timepoint	After all subjects have completed the primary study period (i.e., through Week 24), analyses will be performed for all safety, pharmacodynamic (PD), and efficacy endpoints for primary period. After all subjects have completed the end of study period (through Week 104), analyses will be performed for all safety, PD, and efficacy endpoints.	Primary study period analysis is incoportated in the final analysis.	Study is terminated before all planned subjects (Cohort 3 not enrolled) reach the Week 24 primary study period.
[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]		
Local lab for LDL-C	Assessment of Absolute and Percent change of LDL-C using all available data, including local labs through 104 weeks.	Not included	Local lab LDL-C is not collected in this study.
Time point for secondary efficacy endpoint	at Week 18 if the subject is discontinued off steroids for 4 weeks at that timepoint without change to lipid lowering therapy, or earliest timepoint after Week 18 where subject is discontinued off steroid for 4 weeks and has not changed lipid lowering therapies following administration of AAV8.TBG.hLDLR compared to Baseline.	The secondary efficacy endpoints timepoint are defined as below. For Cohort 1: 12 weeks following administration of AAV8.TBG.hLDLR For Cohort 2 and Expansion Cohort 2: at Week 18 if the subject is discontinued off steroids for 4 weeks at that timepoint without change to lipid lowering therapy, or earliest timepoint after Week 18 where subject is discontinued off steroid for 4 weeks and has not changed lipid lowering therapies following administration of AAV8.TBG.hLDLR compared to Baseline.	To clarify original lanauage in the protocol regarding the timepoint of assessment.
[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]		
Follow up and analysis on Apheresis	For those subjects who are receiving lipid apheresis treatment, the number of subjects who experienced a change in frequency of apheresis treatments, including discontinuation, at any time during the study.	For those subjects who are receiving lipid apheresis, the frequency of apheresis treatments, the volume and duration of the treatments at any time during the study will be listed.	Due to the different version of the protocol, apheresis treatment are not followed consistently for all subjects.