AMENDED CLINICAL TRIAL PROTOCOL 12

ACT16248 (formerly RG012-03)

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics of Lademirsen (SAR339375) for Subcutaneous Injection Administered Every Week in Patients with Alport Syndrome
Study Name:	HERA
Document Type:	Clinical Study Protocol
Investigational Medicinal Product:	Lademirsen (SAR339375, formerly RG-012)
Phase of Development:	Phase 2
Indication:	Alport syndrome
Sponsor:	Genzyme Corporation 50 Binney Street Cambridge, Massachusetts, 02142 United States
Protocol Version:	Amended Protocol 12
Protocol Date:	08-Dec-2021
EudraCT Number:	2019-004394-10

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 12	*France*	*08 December 2021, version 1 (electronic 12.0)*
Amended Clinical Trial Protocol 11	*All*	*10 August 2021, version 1 (electronic 11.0)*
Amended Clinical Trial Protocol 10	*All*	*22 January 2021, version 1 (electronic 10.0)*
Amended Clinical Trial Protocol 09	*All*	*11 September 2020, version 1 (electronic 9.0)*
Amended Clinical Trial Protocol 08	*China*	*18 March 2020, version 1 (electronic 8.0)*
Amended Clinical Trial Protocol 07	*Germany*	*20 February 2020, version 1 (electronic 7.0)*
Amended Clinical Trial Protocol 06	*United Kingdom*	*15 January 2020, version 1 (electronic 6.0)*
Amended Clinical Trial Protocol 05	*All*	*07 November 2019, version 1 (electronic 5.0)*
Amended Clinical Trial Protocol 04	*All*	*01 August 2019, version 2 (electronic 4.0)*
Amended Clinical Trial Protocol 03	*All*	*23 April 2019, version 1 (electronic 1.0)*
Clinical Study Protocol version 3.0	*All*	*16 August 2017, version 3.0*
Clinical Study Protocol version 2.0	*All*	*29 June 2017, version 2.0*
Clinical Study Protocol version 1.0	*All*	*01 July 2016, version 1.0*

Amended protocol 12 (08 December 2021)

This amended protocol (amendment 12) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The aim of the amendment is to remove the collection of race for French subjects and, thereby, to implement for French subjects the use of the new CKD-EPI equation that no longer needs race information (Inker et al, N Engl J Med. 2021 Nov 4;385(19):1737-49).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Revised to indicate that this is Amended protocol 12.	To conform with the usual process for protocol amendments.
Protocol Synopsis and 3.2.1 Inclusion criteria	Links to the new Section 10.5.3 for France were added to I04 and I05.	This clarification was added for study conducted in France.

Section # and Name	Description of Change	Brief Rationale
5.1 Screening, 6.2.14 Laboratory assessments, 6.3.1 Estimated GFR, 7.2.5 Efficacy analysis, and 9.3.9 Data protection	Links to the new Section 10.5.3 for France were added.	This clarification was added for study conducted in France.
10.5.3 France	New section was added for study conducted in France.	This was added to clarify that race is not collected for French subjects, and thus to explain how the eGFR is calculated for these subjects.
10.8.1 Amended Protocol 11 (10 August 2021)	New section was created to contain the prior amendment's history, and subsequent sections were renumbered accordingly. Minor formatting updates were applied.	To conform with the usual process for amendment history.
11 References	The Inker, et al. (2021), reference was added as reference 33, and the subsequent reference was renumbered.	This is the reference for the race-free eGFR equation used for French subjects.

In addition, minor editorial, stylistic, and/or grammatical changes were made throughout this document.

NAMES AND ADDRESSES OF:

MONITORING TEAM'S REPRESENTATIVE

Name: Address: Tel: Fax: E-mail:	

PROTOCOL SYNOPSIS

Study Title:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics of Lademirsen (SAR339375) for Subcutaneous Injection Administered Every Week in Patients with Alport Syndrome

Protocol Number: ACT16248 (formerly RG012-03)

Indication: Treatment of renal dysfunction in subjects with Alport syndrome

Study Type: Phase 2, randomized, double-blind, placebo-controlled study with an open-label extension period

Sponsor: Genzyme Corporation

Study Centers: Approximately 20 investigative sites

Study Objectives

Primary Objectives

- To assess the efficacy of lademirsen (SAR339375) in reducing the decline in renal function.
- To assess the safety and tolerability of lademirsen (SAR339375) in subjects with Alport syndrome.

Secondary Objectives:

- To assess plasma pharmacokinetic (PK) parameters. C_{max} will be assessed for the parent compound (lademirsen [SAR339375]), its active major metabolite (RG0005), and the sum of lademirsen (SAR339375) and RG0005 (SUM) following administration of lademirsen (SAR339375). C_{trough} will be assessed in terms of SUM only.
- To assess potential formation of anti-drug antibodies (ADAs) following administration of lademirsen (SAR339375).
- To assess the pharmacodynamic effect of lademirsen (SAR339375) on miR-21 and on changes in renal injury and function biomarkers.

Exploratory Objectives

- To assess the effect of lademirsen (SAR339375) on urine and blood biomarkers in Alport Syndrome subjects.
- Please see Section 10.5.2.1.1 for China-specific exploratory objectives.

Study Endpoints

Efficacy Endpoints:

- Annualized change in estimated glomerular filtration rate (eGFR) from baseline during the placebo-controlled treatment period
- Absolute and percent change in eGFR values from baseline at Weeks 24, and 48
- Number and proportion of subjects who reach end-stage renal disease (ESRD) as defined by an eGFR ≤15 mL/min/1.73 m^2 or initiation of hemodialysis or renal transplantation during the placebo-controlled treatment period
- Absolute and percent change in eGFR values from baseline at Week 96
- Proportion of subjects with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% reduction at Week 24, 48 and 96

Safety Endpoints:

- Incidence and severity of treatment-emergent adverse events (AEs) and serious adverse events (SAEs)
- Observed values and changes from baseline in clinical laboratory parameters (eg, hematology, chemistry, complement, and urinalysis)
- Observed values and changes from baseline in vital signs
- Observed changes from baseline in 12-lead electrocardiogram (ECG)
- Observed changes from baseline in physical examinations
- Incidence and titer of ADAs
- Association of ADAs with adverse events

Pharmacodynamic Endpoints:

- Changes in circulating miR-21 at Weeks 24, 48, and 96
- Change in renal injury and function biomarkers from baseline at Weeks 24, 48, and 96:
  - In blood only: blood urea nitrogen (BUN);
  - In urine only: protein/creatinine ratio, albumin/creatinine ratio, and epidermal growth factor (EGF);
  - In both blood and urine: creatinine, Cystatin C, transforming growth factor-β (TGF-β), and neutrophil gelatinase-associated lipocalin (NGAL).

Exploratory endpoints:

- Changes in exploratory biomarkers, which may include but are not necessarily limited to:
  - In blood only: microRNAs (miRs) other than miR-21;

- In both blood and urine: β-2 microglobulin, and connective tissue growth factor (CTGF);
- In urine only: kidney injury molecule-1 (KIM-1) and calbindin-D28k.

- Please see Section 10.5.2.1.2 for study conduct in China.

Pharmacokinetic Endpoints:

- Plasma concentrations of lademirsen (SAR339375), RG0005, and SUM in C_{max} samples and SUM only in C_{trough} samples.

Study Design and Methodology

This will be a randomized, double-blind, placebo-controlled, multi-center, Phase 2 study conducted in approximately 45 subjects with Alport Syndrome at multiple investigative centers. At the completion of 48 weeks of double-blind, placebo-controlled treatment, all subjects will enter the 48-week open-label extension period in which all subjects will receive active treatment with lademirsen (SAR339375).

Screening and Baseline Period

Subjects may screen for enrollment after participation in the OBS16374 (formerly RG012-01) ATHENA Natural History Study (ATHENA) or directly in this study. To qualify for this study, subjects must have confirmed Alport Syndrome and meet all eligibility criteria (see below).

Double-Blind, Placebo-Controlled Treatment Period

Eligible subjects will be randomized in a 2:1 ratio to receive every week (QW) subcutaneous (SC) doses of lademirsen (SAR339375) 110 mg or placebo for 48 weeks with stratification by screening eGFR (<60 mL/min/1.73 m^2 versus ≥60 mL/min/1.73 m^2). Once randomized, the subject should be treated within 3 calendar days maximum.

The Schedule of Events for the double-blind, placebo-controlled treatment period is provided in Table 1 and a detailed list of procedures for each study visit is provided see Section 5.2. Study drug injections will be administered by trained, qualified personnel on the Investigator site or, as deemed acceptable by the Investigator, at home or at an alternate location by a trained, qualified healthcare professional. Certain visits outlined in the Schedule of Events (see Table 1) may be performed at home or an alternate location by trained, qualified study personnel, to which the Investigator has delegated responsibility. See Section 5.7 for more details.

Open-Label Treatment Extension Period

Subjects who complete the 48-week double-blind, placebo-controlled treatment period will be rolled over into a 48-week open-label treatment extension period in which all subjects will receive QW active treatment with lademirsen (SAR339375).

The open-label treatment period allows all the subjects to benefit from exposure to lademirsen (SAR339375) after the randomized period of the treatment. In addition, this allows us to gain long-term safety and efficacy data in Alport subjects.

Follow-up Period

Any subject who discontinues early should complete the procedures for an early termination (ET) visit, enumerated in the Schedules of Events tables.

Subjects who complete the open-label treatment extension period or subjects who discontinue early and have completed the early termination visit will enter the post-treatment follow-up period. During the follow-up period, visits will occur at Follow-up Weeks 2, 4, and 10. Follow-up weeks are numbered starting from the last scheduled study visit in the active treatment period (eg, Follow-up Week 2 will occur 2 weeks after Week 96 or after ET). The Schedule of Events for the follow-up period is provided in both Table 1 and Table 2 and a detailed list of procedures for each visit in the follow-up period is provided in Section 5.5.

Safety Management

Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will oversee the safety and overall conduct of this study. The DMC will perform periodic reviews of data during the course of the clinical trial, and on an ad hoc basis for review of emergent safety data, as defined in the DMC Charter for this clinical trial.

In addition to safety monitoring, a non-binding interim futility analysis will be performed to review efficacy data as well. The study may stop additional accrual or follow-up if the threshold for minimum efficacy is not achieved.

Dose Reduction

Before administering each dose of study drug, the Investigator or delegate will review a subject's most recent safety data. A subject's platelet count will be obtained weekly before dose administration. Platelet counts may be measured at a central laboratory and can exceptionally be measured at a local laboratory. The most recent subject's platelet counts, but not older than 10 days, will be reviewed by the Investigator/physician before drug administration.

Following the resolution of a Grade 2 AE or increase in aminotransferases (return to normal or ≤ Grade 1) that does not otherwise trigger a stopping rule (see Section 3.4); the Investigator in consultation with the Sponsor may reduce an individual subject's dose to 110 mg every two weeks (Q2W). Dose reductions should be discussed with the Sponsor Medical Manager before implementation. Once a subject's dose has been reduced, it will not be increased.

Individual Treatment Stopping Criteria

Any Grade 2 AE (except for renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis) not resolved prior to administering the next dose and deemed by the Investigator to be at least "possibly related" to study drug would result in a pausing of dosing (eg, dose not given) until the AE improves to ≤ Grade 1. Injection site reactions (ISRs) will be graded according to Table 6. Any Grade 2 (except erythema/redness) or Grade 3 ISRs which had not resolved or reached Grade 1 ("Mild", eg, limited tenderness, and/or induration, except erythema/redness) prior to the next dose, would result in a pausing of dosing. The continuation of dosing and dose level would be decided upon review between the Investigator and the Sponsor Medical Manager. For further details on dose reduction, see Section 4.5.

Occurrence of any Grade 3 (Severe) or higher AE (except for ISRs and renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis) will result in the cessation of dosing of the subject, unless it can be shown that the event was unrelated to participation in the clinical trial. The DMC will review the circumstances of the AE with the Sponsor and unblind the subject, as appropriate, to evaluate potential relatedness to study drug and will make a recommendation to the Sponsor regarding the further dosing of the subject. After deliberations, DMC will provide guidance to the Sponsor who will implement recommendations and communicate to the site.

With regard to AEs, study drug should be discontinued for subjects who experience any of the following:

- Grade 3 thrombocytopenia (platelet count from <50 000 to 25 000/microL)
- ALT or AST >5 × ULN, or ALT or AST >3 × ULN in association with total bilirubin >2 × ULN
- An unintended weight loss of ≥20% from baseline
- ≥50% decline for eGFR from the last measurement or confirmed ESRD (eGFR ≤15 mL/min/1.73 m^2 or dialysis or renal transplantation is needed).

In case of worsening of eGFR (that do not reach stopping criteria) or urine protein-to-creatinine ratio (UPCR), the Investigator or the Sponsor could repeat the test before the next scheduled one as often as medically needed. The Sponsor needs to be consulted before a decision to discontinue the patient, unless it is a case of emergency.

Study Suspension and Stopping Criteria

The occurrence of two similar Grade 3 (or higher) AEs (except for ISRs and renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis), or any death or two unexpected SAEs considered at least possibly related to participation in the clinical trial, or any TEAE that in the opinion of the Sponsor is of potential clinical significance for subjects safety will result in the recommendation to suspend all dosing

and stop recruitment, then will trigger an ad hoc meeting with the DMC who will be asked to consider the appropriateness of study conduct continuation unchanged, early study termination or modification.

Upon suspension of dosing, a full, unblinded review of the AEs will be performed by the DMC to evaluate the AEs and potential relationship to exposure to the study drug. Following the full, unblinded safety review, one of three outcomes is possible:

- The study may be terminated
- The study design may be amended. For example, the dose of study drug may be reduced for all subjects (to 110 mg SC every other week (the pre-specified dose reduction for a Grade 2 AE), the dose regimen may be changed to reduce the dosing frequency, or inclusion/exclusion criteria may be modified (eg, baseline platelet count or other relevant laboratory or clinical parameter)
- Stopping criteria are at the discretion of the DMC, the study may continue as originally planned, based on clear evidence that the stopping criteria have not been met and measures are in place to ensure subject safety

Study Duration

The planned length of participation in the study for each subject is up to approximately 110 weeks (from screening through completion of follow-up). This includes:

- Screening period of up to 4 weeks
- Double-blind, placebo-controlled treatment period of 48 weeks
- Open-label extension treatment period of 48 weeks
- Post-treatment follow-up period of 10 weeks

Investigational Medicinal Product

Lademirsen (SAR339375) for SC administration is supplied as 110 mg/mL solution in 5 mL glass vial. Each vial will contain a withdrawable volume of 2 mL.

Placebo matching lademirsen (SAR339375) for SC administration is supplied as sodium chloride and riboflavin (colorant) solution in 5 mL glass vial. Each vial will contain a withdrawable volume of 2 mL.

Study Population

Approximately 45 adult subjects with Alport Syndrome who meet all of the inclusion and none of the exclusion criteria will be enrolled.

Summary of Eligibility Requirements

Inclusion Criteria

I 01. Male or female.

I 02. Confirmed diagnosis of Alport syndrome:

1. Clinical diagnosis (hematuria, family history, hearing loss, ocular change), AND,
2. Genetic confirmation of Alport Syndrome in the subject or the family member, OR,
3. Kidney biopsy showing glomerular basement membrane abnormalities (eg, significant thinning, thickening, irregularity or lucencies) consistent with Alport Syndrome.

I 03. Age 18-55 years old.

I 04. eGFR >35 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2 (based on CKD-EPI) at screening (for study conducted in France, see Section 10.5.3).

I 05. **Renal Function Criteria (subjects must meet at least one of the following CRITERIA A or B or C)**:

A) Prior eGFR Slope Criteria is defined as a decline in eGFR of ≥4 mL/min/1.73 m^2/year (eGFR slope ≤-4 mL/min/1.73 m^2/year) based on a linear regression slope analysis of ≥4 eGFR measurements within 3 years prior to the study and with a minimum of 2-year time span (the last, of the screening measurement, and first eGFR measurements should be separated by at least 2 years). eGFR should be calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (see Figure 1; for study conducted in France, see Section 10.5.3).

B) Proteinuria: UPCR >2000 mg/g or urine albumin-to-creatinine ratio (UACR) >1000 mg/g

C) eGFR (based on CKD-EPI): male 18-23 years old with eGFR <90 mL/min/1.73 m^2 (for study conducted in France, see Section 10.5.3).

I 06. ACE inhibitor and/or ARB dosing regimen should be stable for at least 30 days prior to screening.

I 07. Sexually active female subjects of childbearing potential and sexually mature male subjects must agree to practice true abstinence in line with their preferred and usual lifestyle or to use two acceptable effective methods of contraception for the entire duration of the study and for at least 10 weeks after last dose.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A) Male subjects

Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 10 weeks after the last dose of study intervention:

- Refrain from donating sperm

  Plus either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

B) Female subjects

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

  OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4 during the intervention period and for at least 10 weeks after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during the study and for a period of six weeks. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine as required by local regulations) within 24 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 10.4.
  - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

I 08. Negative drug screen for opiates, cocaine, heroin, phencyclidine, amphetamines (including ecstasy), barbiturates, benzodiazepines, and cannabinoids. At the

Investigator's discretion, subjects prescribed benzodiazepines, cannabinoids, or opiates with positive results on a drug screen may be allowed.

I 09. Negative screening results for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIV) antibody.

- Hepatitis A virus (HAV) screening is not necessary, screenings required above are for identification of chronic diseases.

I 10. Screening hematology, clinical chemistries, coagulation, and urinalysis are not clinically significant, as assessed by the Investigator, and meet the following criteria:

A) Platelets, total white blood cell (WBC) count, and absolute neutrophil count within normal limits

B) Hemoglobin (Hb) ≥11 g/dL

C) Total and direct bilirubin <1.5 x upper limit of normal (ULN), unless elevated bilirubin is associated with a known benign condition (eg, Gilbert's syndrome)

D) Alanine aminotransferase (ALT) <1.5 x ULN

E) Aspartate aminotransferase (AST) <1.5 x ULN

F) Alkaline phosphatase (ALP) <1.5 x ULN

G) Gamma-glutamyl transferase (GGT) <1.5 x ULN

Note: At the discretion of the Investigator, screening laboratory testing may be repeated once to confirm out-of-range (exclusionary) results.

I 11. Agree to report any new prescription medication, dose adjustment to existing medication, over-the-counter medication, or herbal supplement to the Investigator.

I 12. Able to understand all study procedures in the informed consent form (ICF) and willing to comply with all aspects of the protocol.

Exclusion Criteria

E 01. Causes of chronic kidney disease aside from Alport syndrome (including but not limited to other heritable disorders leading to chronic kidney disease, diabetic nephropathy, hypertensive nephropathy, lupus nephritis, IgA nephropathy).

E 02. ESRD as evidenced by ongoing dialysis therapy or history of renal transplantation.

E 03. Any clinically significant illness within 30 days before screening or surgical or medical condition (other than Alport syndrome) that could interfere with the subject's study compliance; confound the study results; impact subject safety; or significantly alter the distribution, metabolism, or excretion of drugs, including but not limited to the following:

- Significant or unstable cardiac disease (unstable angina, myocardial infarction within the last 6 months, symptomatic coronary artery disease, congestive heart failure [New York Heart Association ≥Grade 3], prolonged QT syndrome [torsade de pointes], significant arrhythmia, and/or any other clinically significant ECG abnormalities)
- Uncontrolled seizure disorder (eg, seizure in the last 12 months)
- Chronic infection (eg, tuberculosis)
- Metabolic disease (eg, diabetes mellitus)
- Evidence of urinary obstruction or difficulty in voiding at screening
- History of hypocomplementemia (low complement levels or activity)
- Maintenance medication known to cause QT prolongation

E 04. Weight >110 kg.

E 05. Any history of active malignancy within the last 1 year (history of localized basal cell or squamous cell carcinoma and cervical carcinoma in situ that has been excised/appropriately treated or a fully excised malignant lesion with a low probability of recurrence will not be considered exclusionary).

E 06. History or presence of alcoholism or drug abuse within 2 years before screening or other concurrent social conditions that would potentially interfere with the subject's study compliance, at the discretion of the Investigator.

E 07. Mental impairment or history of or current significant psychiatric disease that may impair ability to provide informed consent or impact compliance with study procedures.

E 08. Participation in a recent investigational study and receipt of an investigational drug or investigational use of a licensed drug within 30 days or 5 half-lives, whichever is longer, prior to screening.

E 09. Prior treatment with Bardoxolone within 90 days prior to screening.

E 10. History or presence of hypersensitivity or idiosyncratic, allergic, or other clinically significant reaction to the study drug (including placebo), inactive ingredients, or related compounds (eg, other oligonucleotide products).

E 11. Any other condition or circumstance that may make the subject unlikely to complete the study or comply with study procedures and requirements, or may pose a risk to the subject's safety and well-being.

E 12. Subjects dependent on the Sponsor or Investigator or employees of the clinical study site or any other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 13. Subjects that are accommodated in an institution because of regulatory or legal order.

E 14. Prisoners or subjects who are legally institutionalized.

Treatment Assignment

For the double-blind, placebo-controlled treatment period, approximately 45 eligible subjects will be centrally randomized in a 2:1 ratio to lademirsen (SAR339375) 110 mg or placebo SC QW for 48 weeks, with stratification by screening eGFR (<60 mL/min/1.73 m^2 versus ≥60 mL/min/1.73 m^2).

For the open-label extension, all subjects will receive lademirsen (SAR339375) 110 mg SC QW for up to 48 weeks. Subjects who require dose reduction to 110 mg Q2W during the blinded phase of the study will receive lademirsen (SAR339375) as per the same dose that they received in the blinded phase of the study.

Pharmacokinetic Assessment

Plasma PK samples will be collected 4 hours post-dose on Day 1, Week 24, and Week 48 of the Treatment Period, for determination of maximum plasma concentrations (approximate C_{max}) of lademirsen (SAR339375), RG0005, and SUM. In addition, pre-dose plasma PK samples will be collected (up to 4 hours before dose administration) on Day 1 and Weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96 for determination of minimum plasma concentrations (C_{trough}) of SUM (see Table 1). No PK samples will be withdrawn on Weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96 if injection is not administered. In case visit is performed (without injection administered), only pre-dose PK sample will be withdrawn. Time and date of PK sampling, as well as the date of the last prior administration of study drug should be recorded in the electronic case report form (eCRF).

A manual for blood sampling, collection, processing, and shipment will be provided.

Disposition of Samples after Study Completion

Collected blood and urine samples, excluding PK and ADA samples, may be stored and used in the future for the discovery, analysis, verification, and/or validation of other biomarkers or tests for renal disease. PK samples will be disposed of once the clinical study report (CSR) has been finalized. Based on the ADA data from the study, ADA samples may be disposed of upon finalization of the CSR or retained for further assay development and/or characterization of ADA.

For study conduct in China, see Section 10.5.2.3.

Statistical Considerations

Sample Size Determination

An approximate 45 total subjects will be randomized in 2:1 ratio to lademirsen (SAR339375) versus placebo. The sample size will provide approximately 75% power to detect a reduced rate of decline of 5 mL/min/1.73 m^2/year (~50% reduction) in eGFR annualized rate under lademirsen (SAR339375) treatment, in comparison to placebo.

Power calculations were based on simulations. The following model parameters were obtained from preliminary analysis of the ATHENA Natural History Study (OBS16374) data:

- Average linear decline in eGFR of 10 mL/min/1.73 m^2/year in placebo arm
- Standard deviation (SD) for the residual error of eGFR of [redacted] mL/min/1.73 m^2 and SD for random effect of slope to be [redacted] mL/min/1.73 m^2/year
- Mean and SD for intercept to be [redacted] mL/min/1.73 m^2 and [redacted] mL/min/1.73 m^2 correspondingly

In addition, and power calculations were based on a success criterion defined in Section 7.2.5 and 10% dropout rate was assumed.

Analysis populations

The primary efficacy analysis population will be the **Intent-to-Treat (ITT) Population**, defined as all randomized subjects analyzed according to the treatment group allocated by randomization.

The **Safety Population** will include all subjects who receive at least one dose or partial of a dose of the Investigational Medicinal Product (IMP), analyzed according to the treatment actually received.

The **PK Population** will consist of all subjects who receive at least one dose of the IMP and have at least one post-dose PK sample to determine plasma concentrations of lademirsen (SAR339375).

Primary efficacy analysis

Annualized rate of change in eGFR during the placebo-controlled treatment period will be compared between lademirsen (SAR339375) and placebo using a linear mixed effect model. ATHENA Natural History Study (OBS16374) data will be used as prior information supplementing the placebo arm, using a Bayesian approach.

Safety analysis

The safety variables, including adverse events (AEs), laboratory parameters, vital signs, ECG and physical examinations will be summarized using descriptive statistics.

Pharmacokinetic analysis

Measured plasma concentrations (observed PK parameters C_{max} and C_{trough}) for lademirsen (SAR339375), RG0005, and SUM (as applicable) will be summarized using descriptive statistics (eg, mean, standard deviation [SD], median, min-max, and coefficient of variation [%CV]).

[redacted]

[redacted]

[redacted]

Table 1 - Schedule of events for screening and double-blind, placebo-controlled treatment period and follow-up period

	Scr[a]		Double-Blind, Placebo-Controlled Treatment Period[b]																									USV[jj]	ET[c]	Follow-up[d]		
STUDY WEEK	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48[e]**			**2**	**4**	**10**
STUDY DAY		**1[f]**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**			**15**	**29**	**71**
Site Visits[g]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[h]			**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[kk]**		**X**	**X**	
Informed consent[i]	X																															
Demographics	X																															
Medical history[j]	X[g]																															
Family history[k]	X[g]																															
COL4A3/4/5 genotyping[ff]	X[g]																															
Prior medications/ therapy[l]	X[g]																															
Concomitant medications[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[n] and body weight	X	X				X				X						X						X						X	X	X		X
Physical examination[o]	X[g]	X								X						X						X						X	X	X		X
12-lead ECG[ee]	X	X								X						X						X						X	X	X		
Hearing Assessment		X																										X		X		
Drug and alcohol screen	X																															

	Scr[a]		Double-Blind, Placebo-Controlled Treatment Period[b]																									USV[jj]	ET[c]	Follow-up[d]		
STUDY WEEK	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48[e]**			**2**	**4**	**10**
STUDY DAY		**1[f]**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**			**15**	**29**	**71**
Site Visits[g]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[h]			**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[kk]**		**X**	**X**	
HBsAg, HCV, and HIV-1/2 screen	X																															
Subject collects 24-hour urine sample prior to visit[p]	X[e, g]	X								X						X						X						X	X	X			
Spot urine protein-to-creatinine ratio (UPCR)						X		X				X		X				X		X				X		X							
Urinalysis[q]	X	X				X				X						X						X						X	X	X			X
CBC[r]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation panel[s]	X	X				X		X		X		X		X		X		X		X		X		X		X		X	X	X			X
Serum chemistry[t, w]	X[g]	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X			X
Lipid panel[u], hs-CRP	X	X				X				X						X						X						X	X				X
Blood pregnancy[v, w]	X																											X					
Urine pregnancy[v]		X				X		X		X		X		X		X		X		X		X		X		X				X			
PK pre-dose[x]		X				X				X						X						X						X		X			
PK post-dose[x]		X														X												X					
ADA[y]		X	X	X	X	X				X						X						X						X	X	X			X
Complement[z]		X								X						X						X						X		X			X

	Scr[a]		Double-Blind, Placebo-Controlled Treatment Period[b]																									USV[jj]	ET[c]	Follow-up[d]		
STUDY WEEK	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48[e]**			**2**	**4**	**10**
STUDY DAY		**1[f]**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**			**15**	**29**	**71**
Site Visits[g]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[h]			**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[kk]**		**X**	**X**	
Markers of inflammation[ii]		X								X						X						X						X	X	X			X
microRNA-21 (miR 21)		X								X						X						X						X		X			X
Renal biomarkers[aa]		X								X						X						X						X	X	X			
Plasma/serum for storage (for study conduct in China, see Section 10.5.2.3)		X								X						X						X						X		X			
Exploratory biomarkers[bb]		X								X						X						X						X		X			
Assignment to treatment group[gg]		X																															
IRT contact	X	X				X		X		X		X		X		X		X		X		X		X		X		x					
Assessment of ISRs[cc, dd]		To be completed weekly																															
Study drug administration		To be completed weekly																															
1 day post injection follow-up[dd]		To be completed weekly																															
Record adverse events	To be assessed and reported throughout the study																																

	Scr[a]		Double-Blind, Placebo-Controlled Treatment Period[b]																									USV[jj]	ET[c]	Follow-up[d]		
STUDY WEEK	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48[e]**			**2**	**4**	**10**
STUDY DAY		**1[f]**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**			**15**	**29**	**71**
Site Visits[g]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[h]			**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[kk]**		**X**	**X**	
Product Complaint[hh]	To be assessed and reported throughout the study																															

Abbreviations: ADA, anti-drug antibodies; CBC, complete blood count; *COL4A3/4/5*, type IV collagen alpha chain genes 3, 4, and 5; ECG, electrocardiogram; ET, early termination; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; ISR, injection site reaction; PK, pharmacokinetics; Scr, Screening; USV, unscheduled visit; IRT, Interactive Response Technology; UPCR, urine protein-to-creatinine ratio

a Screening data may be collected at more than 1 visit.

b After Day 1, the visits will be done every 7 days. During the active treatment period, the visit window is ±2 days for each visit. Subjects who complete the double-blind, placebo-controlled treatment period will be rolled over directly into the open-label treatment extension (see Table 2). Subjects who complete the double-blind, placebo-controlled treatment period but who will not continue with the open-label treatment extension will enter the follow-up period, which is the same for all subjects.

c Except for complete blood count (CBC), serum and urine chemistry, and coagulation panel, laboratory tests scheduled for the early termination (ET) visit do not need to be completed if the tests were completed as part of a study visit within 4 weeks of the last visit. ET will be done 7 days ±2 days after the last study visit.

d Follow-up days and weeks are numbered starting from the last scheduled visit in the active treatment period. Thus, for subjects who discontinue early, Follow-up Week 2 is 2 weeks after the ET visit. The visit window is ±3 days for all follow-up visits.

e For subjects who complete the double-blind, placebo-controlled treatment period and will enter the open-label treatment extension, the Week 48 visit will serve as the baseline visit of the open-label extension.

f Day 1 is the baseline visit.

g See Section 5 for visit windows, and Section 5.2 for odds visit details.

h Option for Investigator to delegate visit assessments to be performed at an alternate location, including the subject's home, conducted by trained, qualified study personnel. During the last 6 months of the double-blind period, the subject will be trained on self-administration of the study drug and will be observed in self-administration technique.

i Informed consent will be obtained prior to performing any study-related procedures.

j Prior and ongoing illnesses, surgeries, use of tobacco/alcohol/recreational drugs, and allergic reactions/hypersensitivity.

k Family history relevant to Alport syndrome and renal disease.

l Prior medication/therapy is any medication or therapy given within 30 days before study entry (eg, before signing the informed consent form [ICF]), as well as ongoing medication or therapy.

m Any medication taken after signing the ICF will be collected at each visit.

n Systolic and diastolic blood pressure measurements, pulse rate, body temperature, and respiratory rate. Vital signs collection will be performed prior to drug administration throughout the study; specifically on Day 1 and W48, vital signs will be done at 0.5 to 1 hour pre- and 4 hours post-dose.

o Complete examination at screening, baseline, Week 24, Week 48, ET, and Follow-up Week 10. Limited (symptom-directed) examination at Weeks 12 and 36. Height should be measured at screening.

p 24-hour urine chemistry panel (albumin, creatinine, sodium, total protein).

q Urinalysis: assessment of colour and appearance, and dipstick test for specific gravity, erythrocytes, pH, protein, glucose, ketones, leukocyte esterase, nitrate, bilirubin, and urobilinogen will be done locally. Microscopic examination of urine sediment, microalbuminuria, urine creatinine, and urine protein will be a laboratory test.

r Full hematology panel performed weekly during treatment period and at each visit timepoint during the follow up period: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

s Coagulation panel: prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR), and fibrinogen.

t Total protein, glucose, Cystatin C, creatinine for calculation of estimated glomerular filtration rate (eGFR), uric acid, lactate dehydrogenase, sodium, potassium, chloride, bicarbonate, calcium, iron, phosphate, blood urea nitrogen (BUN), and hepatic function panel (albumin, total bilirubin, direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]). In the event of elevated aminotransferases (ALT or AST) >3 xULN, see Section 10.3.2 for guidance on additional monitoring. If subject experienced low protein <1 g the investigation will be done by the Investigator as per local practice. In case of worsening of eGFR, the Investigator could repeat the eGFR before the next scheduled test.

u Total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

v For women of child bearing potential, a blood pregnancy and a monthly urine pregnancy test will be performed; in case the urine test is positive, injections will be stopped and a blood test will be performed to confirm the pregnancy.

w Serum chemistry will be done centrally except for exceptional circumstances, and urine pregnancy can be done locally.

x PK sampling time points on Day 1, Week 24 and Week 48 will be pre-dose (up to 4 hours before dose administration) and 4 hours post-dose. PK samples on other visits (Week 4, Week 12 and Week 36) will be pre-dose only (up to 4 hours before dose administration). No PK samples will be withdrawn on W4, W12, W24, W36, and W48, if injection is not administered and visit not performed. In case visit is performed (without injection administered), only pre-dose PK sample will be withdrawn. Time and date of PK sampling, as well as the date of the last prior administration of study drug should be recorded in the electronic case report form (eCRF).

y All ADA samples should be collected pre-dose (up to 4 hours before dose administration).

z Complement C3, C3a, C4, and Bb will be measured on Day 1 in samples obtained 0.5 hour pre-dose and 0.5, and 4 hours post-dose. On other visits, complement C3, C3A, c4, AND Bb will be measured pre-dose only.

aa Blood Urea Nitrogen, Albumin/creatinine ratio, urine Cystatin C: Urine Neutrophil Gelatinase Associated Lipocalin (NGAL), blood and urine transforming growth factor-β (TGF-β), and EGF see Section 6.4 and Section 10.5.2.2 (for study conduct in China). In addition Urine protein/creatinine ratio will be performed every 4 weeks, either using spot urine or 24h-h urine collection (at D1, W12, W24, W36, W48, and ET). In case of worsening of UPCR, the Investigator could repeat the UPCR before the next scheduled test.

bb May include but are not necessarily limited to the following: additional blood microRNAs, Kidney Injury Molecule-1, β-2 Microglobulin, and urine connective tissue growth factor (CTGF); and urine calbindin-D28k. For study conduct in China, see Section 10.5.2.2.

cc Study drug administration and ISR assessment and reporting will be performed after each injection.

dd Subjects will be monitored for at least 2 hours after the first injection at baseline to ensure subject safety. In subsequent injections, the healthcare professional will monitor the subject's injection site for 15 minutes. The study staff will contact the subjects 1 day post injection to check on any occurrence of ISR and associated symptoms.

ee 12-lead ECG will be performed before IMP administration during the study treatment period.

ff Genotyping is not needed for randomization except for patient for whom historical data for genetic confirmation of Alport syndrome and a kidney biopsy showing glomerular basement membrane abnormalities consistent with Alport Syndrome are not available at screening visit.

gg Day 1 should be within 3 calendar days maximum after assignment to treatment group.

hh Please refer to Section 6.2.9.

ii Markers of inflammation: quantitative immunoglobulin (γ-globulin, IgG, IgM).

jj At unscheduled visits, only blood samples that are needed for abnormal laboratory value follow up will be collected. ECGs will only be performed in case an abnormality potentially has an impact on the continuity of the study drug administration, as deemed by the Investigator.

kk The USVs may be done at alternative location visit (as described in footnote *h*), except when abnormal safety parameters are linked to physical examination.

Table 2 - Schedule of events for open-label treatment extension period and follow-up period

	Open-Label Treatment Extension Period[a]																										USV[aa]	ET[b]	Follow-up[c]		
STUDY WEEK	**48**	**49**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**			**2**	**4**	**10**
STUDY DAY	**337**	**344**	**351**	**365**	**379**	**393**	**407**	**421**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**			**15**	**29**	**71**
Site Visits[d]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[e]		**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[bb]**		**X**	**X**	
Concomitant medications	X			X		X		X		X		X		X		X		X		X		X		X		X	X	X			X
Vital signs[f] and body weight	X			X				X						X						X						X	X	X			X
Physical examination[g]	X							X						X						X						X	X	X			X
12-lead ECG[v]	X							X						X						X						X	X	X			
Hearing Assessment	X																									X		X			
Spot urine protein-to-creatinine ratio (UPCR)	X			X		X				X		X				X		X				X		X							
Subject collects 24-hour urine sample prior to visit[h]	X							X						X						X						X	X	X			
Urinalysis[i]	X			X				X						X						X						X	X	X			X
CBC[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation panel[j]	X			X		X		X		X		X		X		X		X		X		X		X		X	X	X			X
Serum chemistry[k, n]	X			X		X		X		X		X		X		X		X		X		X		X		X	X	X			X
Lipid panel[l], hs-CRP	X			X				X						X						X						X	X	X			X
Blood pregnancy[m]	X																														

	Open-Label Treatment Extension Period[a]																										USV[aa]	ET[b]	Follow-up[c]		
STUDY WEEK	**48**	**49**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**			**2**	**4**	**10**
STUDY DAY	**337**	**344**	**351**	**365**	**379**	**393**	**407**	**421**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**			**15**	**29**	**71**
Site Visits[d]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[e]		**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[bb]**		**X**	**X**	
Urine pregnancy[m]				X		X		X		X		X		X		X		X		X		X		X		X		X			
ADA[o, p]	X							X						X						X						X	X	X			X
PK pre-dose[x]	X							X						X						X						X		X			
PK post-dose	X																														
Complement[q]	X							X						X						X						X		X			X
Markers of inflammation[z]	X							X						X						X						X	X	X			X
microRNA-21 (miR 21)	X							X						X						X						X		X			X
Renal function/injury biomarkers[r]	X							X						X						X						X	X	X			
Exploratory biomarkers[s]	X							X						X						X						X		X			
Record adverse events	To be assessed and reported throughout the study																														

	Open-Label Treatment Extension Period[a]																									USV[aa]	ET[b]	Follow-up[c]		
STUDY WEEK	**48**	**49**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**			**2**	**4**	**10**
STUDY DAY	**337**	**344**	**351**	**365**	**379**	**393**	**407**	**421**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**			**15**	**29**	**71**
Site Visits[d]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Alt. location option[e]		**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X[bb]**		**X**	**X**	
Product Complaint[y]	To be assessed and reported throughout the study																													
IRT contact	X			X		X		X		X		X		X		X		X		X		X		X		X					
Assessment of ISRs[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
1 day post injection follow-up[cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Study drug administration[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						

Abbreviations: ADA, anti-drug antibodies; CBC, complete blood count; ECG, electrocardiogram; ET, early termination; hs-CRP, high-sensitivity C-reactive protein; ISR, injection site reaction; PK, pharmacokinetics, USV, unscheduled visit; IRT, Interactive Response Technology; UPCR, urine protein-to-creatinine ratio

a The visits will be done every 7 days. During the active treatment period, the visit window is ±2 days for each visit.

b With the exception of complete blood count (CBC), serum and urine chemistry, and coagulation panel, laboratory tests scheduled for the early termination (ET) visit do not need to be completed if the tests were completed as part of a study visit within 4 weeks. ET will be done 7 days ±2 days after the last study visit.

c Follow-up days and weeks are numbered starting from the last scheduled visit in the active treatment period. Thus, for subjects who complete the open-label treatment extension, Follow-up Week 2 is 2 weeks after the ET visit or Week 96. The visit window is ±3 days for all follow-up visits.

d These study visits are required to be on site visits.

e Option for Investigator to delegate visit assessments to be performed at an alternate location, including the subject's home, conducted by trained, qualified study personnel. Upon completion of training during the last 6 months of double-blind period, the Investigator may decide if self-administration at home is possible, please see Section 4.4.

f Systolic and diastolic blood pressure measurements, pulse rate, body temperature, and respiratory rate. Vital signs should be measured before blood is drawn and respiratory rate will be determined by observation for at least 30 seconds. At Week 48, vital signs will be done at 0.5 to 1 hour pre and 4 hour post-dose.

g Complete physical examination at Weeks 48, 72, and 96; ET; and Follow-up Week 10. Limited (symptom-directed) physical examination at Weeks 60 and 84.

h 24-hour urine chemistry panel (albumin, creatinine, sodium, total protein).

i Urinalysis: assessment of colour and appearance, and dipstick test for specific gravity, erythrocytes, pH, protein, glucose, ketones, leukocyte esterase, nitrate, bilirubin, and urobilinogen will be done locally. Microscopic examination of urine sediment, microalbuminuria, urine creatinine, and urine protein will be a laboratory test.

j Coagulation panel: prothrombin time, activated partial thromboplastin time (aPTT), international normalized ratio (INR), and fibrinogen.

k Total protein, glucose (in fasting condition as per site habit), Cystatin C, creatinine for calculation of estimated glomerular filtration rate (eGFR), uric acid, lactate dehydrogenase, sodium, potassium, chloride, bicarbonate, calcium, iron, phosphate, blood urea nitrogen (BUN), and hepatic function panel (albumin, total bilirubin, direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]). In the event of elevated aminotransferases (ALT or AST) >3 xULN, see Section 10.3.2 for guidance on additional monitoring.

l Total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

m For women of child bearing potential, a blood pregnancy and a monthly urine pregnancy test will be performed; in case the urine test is positive, injections will be stopped and a blood test will be performed to confirm the pregnancy.

n Serum chemistry will be done centrally except for exceptional circumstances, and urine pregnancy can be done locally.

o After the Week 96 sample, additional ADA samples will only need to be collected at Follow-up and ET, if the Week 96 sample was confirmed positive for ADA.

p ADA samples will be collected pre-dose (up to 4 hours before dose administration), see Section 5.5, follow up visit Week 10.

q Complement C3, C3a, C4, and Bb will be measured pre-dose.

r Blood urea nitrogen (BUN); albumin/creatinine ratio, urine Cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL), blood and urine transforming growth factor-β (TGF-β) and EGF. For study conduct in China, see Section 10.5.2.2. In addition Urine protein/creatinine ratio will be performed every 4 weeks, either using spot urine or 24h-h urine collection (at W48, W60, W72, W84, W96, and ET). In case of worsening of UPCR, the Investigator could repeat the UPCR before the next scheduled test.

s May include but are not necessarily limited to the following: additional blood microRNAs, kidney injury molecule-1 (KIM-1), β-2 microglobulin, and urine connective tissue growth factor (CTGF); and urine calbindin-D28k. For study conduct in China, see Section 10.5.2.2.

t Study drug administration and ISR assessment and reporting will be performed after each injection.

u Subjects will be monitored for at least 2 hours after injection at Week 48 to ensure subject safety. In the subsequent injections:

- In case of home injection the healthcare professional will continue to monitor the subject's injection site for 15 minutes. The study staff will contact the subjects 1 day post injection to check on any occurrence of ISR and associated symptoms,
- When lademirsen (SAR339375) is self-administered, study drug administration should be done after blood sampling. The Investigator or delegate will call the subject on the planned day of injection and will collect and review safety assessments (AEs, concomitant medication). The study staff will contact the subjects 1 day post injection to check on any occurrence of ISR and associated symptoms.

v 12-lead electrocardiogram (ECG) will be performed before IMP administration during the study treatment period.

w Full hematology panel performed weekly during treatment period and at each visit timepoint during follow up period: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

x Pre-dose plasma PK samples will be collected (up to 4 hours before dose administration). No PK samples will be withdrawn on W60, W72, W84 and W96 if injection is not administered and visit not performed. In case visit is performed (without injection administered), only pre-dose PK sample will be withdrawn.

y Please refer to Section 6.2.9.

z Markers of inflammation: quantitative immunoglobulin (γ-globulin, IgG, IgM).

aa At unscheduled visits, only blood samples that are needed for abnormal laboratory value follow up will be collected. ECGs will only be performed in case an abnormality potentially has an impact on the continuity of the study drug administration, as deemed by the Investigator.

bb The USVs may be done at alternative location visit (as described in footnote *h*), except when abnormal safety parameters are linked to physical examination.

cc The study staff will contact the subjects 1 day post injection to check on any occurrence of ISR and associated symptoms, and will schedule the next injection with the subject.

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1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Alport syndrome

Alport syndrome is an inherited form of kidney disease characterized by progressive glomerulonephritis, leading to glomerulosclerosis, tubulo-interstitial disease, and organ failure (1, 2, 3). Alport syndrome is caused by mutations in genes coding for the capillary basement membrane protein collagen IV. The prevalence of mutations in the collagen IV family of genes is estimated to be 1 in 5000 individuals (4). Multiple mutations have been identified in each of 3 distinct collagen IV alpha genes (*COL4A3*, *COL4A4,* and *COL4A5*) that encode different collagen IV alpha chains (the α3(IV), α4(IV), and α5(IV) chains, respectively). Each chain is a key component of the collagen IV α3/α4/α5 network critical for maintaining the structure and integrity of the glomerular basement membrane. Mutations in these genes result in enhanced glomerular permeability that is also strongly linked to the development of interstitial fibrosis. The majority of subjects diagnosed with Alport syndrome have mutations in *COL4A5*, a gene located on the X-chromosome, and Alport syndrome has also been known as X-linked Alport syndrome (XLAS) or X-linked nephritis. *COL4A3* and *COL4A4* are located on chromosome 2, and mutations in either of those genes can lead to autosomal recessive Alport syndrome (ARAS) or, rarely, autosomal dominant Alport syndrome (ADAS) (5, 6). The clinical data describing XLAS and ARAS in the literature are summarized in the lademirsen (SAR339375) Investigator's Brochure.

Although the type of mutation may affect the rate of disease progression, all subjects with Alport syndrome eventually develop end-stage renal disease ESRD requiring dialysis or renal transplantation, and subjects with Alport syndrome are thought to account for approximately 2.5% of all renal transplants in the US. Although renal transplantation has been shown to increase the survival of subjects with Alport syndrome (7), it is associated with significant morbidity, even if successful in preventing death. In the US, there are no approved agents to delay time to ESRD for subjects with Alport syndrome. Numerous agents have been investigated for their ability to reduce proteinuria and improve other symptoms associated with Alport syndrome. These agents include cyclosporine (8, 9), angiotensin-converting enzyme (ACE) inhibitors (10), angiotensin II Type I receptor blockers (ARBs) (11, 12), and mineralocorticoid receptor antagonists (13, 14). Only ACE inhibitors have been shown to extend the time to dialysis in treated subjects over that of family relatives with Alport syndrome who were not receiving ACE inhibitors (10). Thus, an urgent need remains for the development of new therapeutics that can reduce the degree of fibrosis and renal inflammation, improve renal function, and delay dialysis for subjects with Alport syndrome.

1.1.2 Lademirsen (SAR339375)

Lademirsen (INN, USAN), also referred to as SAR339375, RG-012 or RG456070, is an octadecasodium salt of a 19-base, single-stranded, chemically modified oligonucleotide. Lademirsen (SAR339375) is formulated as an aqueous solution in 0.3% sodium chloride and will be administered by the subcutaneous (SC) route.

The mechanism of action through which lademirsen (SAR339375) is expected to treat renal dysfunction in subjects with Alport syndrome is pharmacological inhibition of microRNA-21 (miR-21). miR-21 is a ubiquitously expressed and highly conserved microRNA in vertebrates. Mice deficient in miR-21 develop normally and have no overt abnormality. However, in response to stress, miR-21 is upregulated, and this upregulation contributes to fibrosis and disease progression, as demonstrated using both genetic deletion and pharmacologic inhibition of miR-21 in multiple rodent disease models. For example, in response to kidney injury in wild-type mice, miR-21 is activated and represses multiple target mRNAs, including peroxisome proliferator-activated receptor alpha (PPARα), which exaggerates tissue damage by causing fibrosis (15). In contrast, mice deficient in miR-21 or wild-type mice treated with miR-21 anti-miRs do not show repression of PPARα and suffer less interstitial fibrosis and loss of renal function in response to kidney injury (15). The current hypothesis is that lademirsen (SAR339375) modulates multiple mRNAs involved in maintaining mitochondrial function, such as PPARα, Fads6, and Mpv17l.

miR-21 is upregulated in a wide variety of human disease states, including fibrosis of multiple organs (15, 16, 17, 18, 19). Notably, miR-21 is upregulated in human kidneys in various chronic kidney disease states, especially those characterized by accumulation of renal fibrosis. The results in rodent models suggest that inhibition of miR-21 is a viable therapeutic approach for treating conditions involving renal fibrosis, including Alport syndrome.

1.1.3 Nonclinical experience

The efficacy of lademirsen (SAR339375) has been evaluated in a number of different in vivo models using a variety of endpoints, including improvement in survival, renal function, pathology, and modulation of relevant biomarkers that reflect phenotypic improvement. Lademirsen (SAR339375) produced improvement in multiple endpoints in mouse models with renal damage and fibrosis:

- In the unilateral ureteral obstruction (UUO) model, lademirsen (SAR339375) increased miR-21 target mRNAs such as PPARα and decreased renal fibrosis measured via *COL1A1* and *COL3A1* gene expression.
- In the IR/Nx model, lademirsen (SAR339375) reduced albumin-to-creatinine ratio (ACR) and prolonged survival after removal of the healthy kidney.

In the *COL4A3* mutant model, which produces a phenotype that parallels human Alport syndrome, lademirsen (SAR339375) improved the disruption in glomerular basement membrane that leads to loss of tubular epithelial cell viability, reduced development of both interstitial and glomerular fibrosis/sclerosis, reduced loss of podocytes, decreased infiltration of inflammatory

cells, improved renal function, and increased survival by up to 44%. Lademirsen (SAR339375) was efficacious in increasing survival at dose levels of 12.5 to 50 mg/kg once weekly and 25 mg/kg every 2 weeks (Q2W). Moreover, lademirsen (SAR339375) in combination with the ACE inhibitor ramipril, a common treatment in Alport syndrome subjects, produced better efficacy than either treatment alone. The toxicity of lademirsen (SAR339375) has been evaluated in mice and monkeys, and the pharmacokinetic (PK) and toxicokinetic (TK) properties of lademirsen (SAR339375), including its absorption, distribution, metabolism, and elimination characteristics, have been investigated in mice, rabbits, and cynomolgus monkeys. To enable the planned Phase 2 clinical study, Genzyme Corporation has completed Good Laboratory Practice (GLP)–compliant chronic toxicity studies of 26 weeks in mice and 39 weeks in monkeys, as well as definitive embryofetal development studies (in mice and rabbits), a fertility and early-embryonic-development-to-implantation study (in mice), and the full battery of genotoxicity tests.

The chronic toxicity study in mice tested SC doses of 0, 50, 100, and 300 mg/kg/week for 26 weeks. Lademirsen (SAR339375) administered to male and female mice at 100 and 300 mg/kg/week resulted in mortality. Fourteen of 118 animals at 300 mg/kg/week were found dead or euthanized between Weeks 22 and 27. At 100 mg/kg/week, 6 of 118 animals died or were sacrificed early; the majority of deaths occurred after ≥23 weeks of dosing. Although the deaths of several of these animals may be attributed to other causes, a relationship between the remaining deaths and lademirsen (SAR339375) cannot be excluded. Dose levels of ≥100 mg/kg/week were also associated with body weight decreases, decreases in red blood cell (RBC) mass and serum chemistry parameters including albumin, total protein, total cholesterol, and triglycerides. Other findings included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Microscopic findings were observed in the kidney, liver, spleen, thymus, adrenals, mesenteric lymph nodes, and testes, often with correlating gross observations and/or organ weight changes. At 50 mg/kg/week, no mortality occurred, and lademirsen (SAR339375)-related effects were limited to minimal changes in body weight (males only), decreases in platelet counts, and minimal changes in target organs. Although recovery was not assessed at 50 mg/kg/week, full or partial reversibility of the majority of these findings was evident at 100 mg/kg/week.

The chronic toxicity study in monkeys tested SC doses of 0, 3, 10, 30, and 100 mg/kg/week for 39 weeks. Lademirsen (SAR339375) administered at 30 mg/kg/week and 100 mg/kg/week was associated with mortality (death or early euthanasia) in 2 of 16 animals and 6 of 16 animals, respectively. These unscheduled deaths were typically preceded by body weight loss and/or serum albumin concentrations below 2.0 g/dL. Test article-related findings at 30 and/or 100 mg/kg/week included hunched posture, thin appearance, ataxia, shaking, eyelid closure, and in appetence in 100 mg/kg animals and a few 30 mg/kg females. Additionally, lademirsen (SAR339375)-related decreases in body weight and/or decreased body condition score were apparent in 30 and/or 100 mg/kg males and females, and required veterinary intervention. These dose levels were also associated with decreases in indices of RBCs (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]). In addition, lower platelet counts were observed during the dosing and/or recovery period in several animals at 30 or 100 mg/kg/week, including 1 animal with a platelet count as low as 15 x 10^9/L. At these dose levels, mean activated partial thromboplastin time (aPTT) also showed

dose-dependent and sometimes statistically significant increases at 4 hours post-dosing on some dosing days, with reversal by 48 hours. Changes in the serum chemistry data included consistently and often statistically significantly lower mean albumin and albumin/globulin ratios throughout the dosing phase and into the recovery period, primarily in animals dosed at 30 or 100 mg/kg/week and to a lesser extent in animals dosed at 10 mg/kg/week. Other noteworthy findings include elevated urea nitrogen, creatinine, inorganic phosphorus, and potassium and lower sodium and chloride values in a few animals dosed at 100 mg/kg/week. Microscopic findings were observed in the liver, kidney, spleen, thymus, adrenal gland, brain (choroid plexus), bone marrow, and lymph nodes, often with correlating gross observations and/or organ weight changes. Although the majority of these findings were partially to fully reversed upon cessation of dosing, renal findings persisted and included fibroplasia.

The no-observed-adverse-effect levels (NOAELs) in the chronic mouse and monkey studies were 50 mg/kg/week and 3 mg/kg/week, respectively. These and other previously conducted Investigational New Drug (IND)-enabling toxicology studies have shown that lademirsen (SAR339375) produces toxicities generally consistent with those reported for this class of oligonucleotides (20, 21, 22, 23, 24, 25, 26).

The development of anti-drug antibodies (ADA) was seen with chronic dosing of lademirsen (SAR339375) in monkeys and appears generally consistent with class effects of oligonucleotides (27). ADA will be monitored in this clinical study.

Overall, the findings of the nonclinical program indicate that the species and dose regimens evaluated are appropriate to support the planned dosing of up to 110 mg lademirsen (SAR339375) QW for up to 96 weeks in humans. For additional information on the nonclinical program, including calculation of safety margins, refer to the Investigator's Brochure.

1.1.4 Clinical experience to date

For additional information on lademirsen (SAR339375) clinical experience, refer to the Investigator's Brochure.

1.1.4.1 Study RG012-02

Safety, tolerability, and PK were evaluated in a Phase 1 study in which single ascending SC doses of lademirsen (0.5, 1.0, 2.0, 4.0, and 8.0 mg/kg) were administered to healthy adult subjects (males and females between 18 and 55 years of age). Pharmacokinetics of the parent compound (lademirsen [SAR339375]), its active metabolite (RG0005), and the sum of lademirsen (SAR339375) and RG0005 (SUM) were evaluated.

Lademirsen (SAR339375) was well tolerated, with an adverse event (AE) profile consistent with that anticipated for a second-generation oligonucleotide. All 40 subjects who enrolled successfully completed the study. There were no serious AEs or deaths, and all AEs were considered mild or moderate in severity.

The most commonly reported AEs in the overall study population were injection site events, with 183 events reported by 29 subjects (73%). Injection site AEs included erythema (63%), pain (63%), induration (28%), swelling (20%), hemorrhage (10%), and pruritus (10%). All injection site events resolved spontaneously or with minor intervention (eg, application of ice packs).

Other AEs that were reported in ≥5% of subjects and more frequently reported in lademirsen (SAR339375)−treated subjects than placebo-treated subjects were abdominal pain (3 subjects [8%]), abdominal pain lower (2 [5%]), and back pain (2 [5%]).

There were no clinically important trends observed related to clinical laboratory, vital sign, electrocardiogram (ECG), or physical examination assessments.

PK results showed dose-dependent increases in plasma C_{max} (maximum concentration) and AUC (area under the concentration-time curve) consistent with the findings from nonclinical studies.

1.1.4.2 Study RG012-05

A Phase 1 study evaluated the safety, tolerability, and PK of multiple SC doses of lademirsen (SAR339375) in healthy adult subjects (males and females between 18 and 55 years of age). In the double-blind, multiple ascending dose study, 8 subjects in each of 3 sequential dose cohorts were randomized in a 3:1 ratio to receive 5 once-weekly fixed doses of either lademirsen (SAR339375) or matching placebo, with lademirsen (SAR339375) dose escalation from 55 mg (Cohort 1) to 110 mg (Cohort 2) to 220 mg (Cohort 3) dependent on review of the safety and PK data in each cohort by a Safety Evaluation Committee (SEC). The SEC had approved escalation to the weekly 110 mg fixed dose (corresponding to approximately 1.5 mg/kg in a 73 kg subject) and to the weekly 220 mg fixed dose (corresponding to approximately 3.0 mg/kg in a 73 kg subject). A single AE of asymptomatic thrombocytopenia with a platelet count nadir of 92 000/microL that resolved spontaneously over 10 weeks was observed in the 220 mg cohort. The remaining 5 subjects in the 220 mg cohort also experienced a mild reduction in platelet count; however, these did not drop below the lower limit of normal (LLN) and resolved following discontinuation of study drug.

1.1.4.3 Study PDY16327

PDY16327 was a Phase 1, open-label study to evaluate the safety, pharmacodynamics, and pharmacokinetics of subcutaneous lademirsen (SAR339375) for injection in subjects with Alport syndrome. The primary objective was to assess the safety and tolerability of lademirsen (SAR339375) in patients with Alport syndrome, and to assess the effect of lademirsen (SAR339375) on endogenous renal miR-21.

A total of 4 patients entered Part A of the study, in which 2 patients were allocated to each cohort:

- Part A Cohort 1, in which patients received 4 doses of lademirsen ([SAR339375] 1.5 mg/kg Q2W) and were assessed over 8 weeks.
- Part A Cohort 2, in which patients received a single 1.5 mg/kg dose of lademirsen (SAR339375) and were assessed over 4 weeks.

All 4 patients finished Part A and proceeded to Part B, in which all received lademirsen (SAR339375) 1.5 mg/kg Q2W for up to 48 weeks. All patients completed the study as planned. Of the 4 subjects included in PDY16327, 3 were female; all of patients were white, with a mean age of 45.3 years and a mean weight of 71.2 kg.

Lademirsen (SAR339375) was generally well tolerated with the exception of ISRs, which occurred in all 4 patients who participated. All AEs were of mild/moderate severity. There were no deaths, SAEs, or subject discontinuations due to AEs reported. All TEAEs in Part A resolved. In Part B, erythema at the injection site and injection site discoloration were considered not resolved for one patient; all other TEAEs related or possibly related to lademirsen (SAR339375) had resolved. AESIs of elevated liver enzymes were reported by 3 patients, but these events were not considered to be clinically significant and resolved by the end of the study. Two of the 4 patients developed positive ADA titers; neither patient experienced any AEs suggestive of systemic hypersensitivity reactions. Platelet counts were within the normal range for all patients during the study.

Available pharmacodynamics data for miR-21 and other biomarkers were limited and variable, and the number of patients was low, precluding any definitive conclusions.

1.2 RATIONALE

1.2.1 Justification of target

Dysregulation of miR-21 has been demonstrated to contribute to disease progression in multiple animal disease models of renal damage and fibrosis, including models of Alport syndrome. Optimal lademirsen (SAR339375) concentrations and dose administration schedules have been explored extensively in nonclinical rodent models of Alport syndrome. The nonclinical studies have demonstrated that lademirsen (SAR339375) effectively neutralizes miR-21 and decreases renal fibrosis. Thus, miR-21 is considered an excellent therapeutic target, and inhibition of miR-21 using lademirsen (SAR339375) may be effective for treating the renal fibrosis associated with Alport syndrome.

1.2.2 Justification of study design

In the double-blind, placebo-controlled treatment period of this study, subjects will be randomized in a 2:1 ratio to receive either lademirsen (SAR339375) 110 mg or placebo QW for 48 weeks. The purpose of the double-blind, placebo-controlled treatment period is to test the hypothesis that lademirsen (SAR339375) reduces the decline in renal function in subjects with Alport syndrome. A double-blind, placebo-controlled study design is the most rigorous way to test this hypothesis. Upon completion of the double-blind, placebo-controlled treatment period, subjects will be rolled into the open-label treatment period of this study, in which subjects will receive up to 48 weeks of lademirsen (SAR339375) QW treatment. The rationale for the length of both the double-blind, placebo-controlled period and the open-label extension is that, because Alport syndrome is a chronic, progressive disease, it is anticipated that long-term treatment with lademirsen (SAR339375) will be necessary for subjects to derive efficacy benefits.

1.2.3 Justification of route and dose regimen

Lademirsen (SAR339375) is administered by SC injection because oligonucleotide therapeutics are not orally bioavailable.

The dose regimen in the initial protocol (RG012-03) was 1.5 mg/kg, Q2W. The dose regimen proposed in this protocol amendment (ACT16248) is a fixed 110 mg once weekly (Q1W) dose. The reason for this change in dose regimen is based on the observed SUM (SAR339375 + RG0005) kidney concentrations in patients (Study PDY16327) with a 1.5 mg Q2W dose regimen being lower than the target SUM kidney concentrations at which efficacy had been seen in the Col4a3 mutant mouse model for Alport Syndrome. The human kidney concentration data were not available at the time of RG012-03 protocol preparation and, thus, predicted concentrations based on monkey data were used for dose regimen selection at that time.

A dose regimen of 110 mg lademirsen (SAR339375) Q1W is supported by the following:

- Safety and tolerability data from the single ascending dose study (RG012-02) in healthy volunteers (single doses of 0.5 to 8 mg/kg, equivalent to 35 to 560 mg/70 kg), and from the multiple ascending dose study (RG012-05) in healthy volunteers (5 x Q1W doses of 55 110 and 220 mg, equivalent to approximately 0.8, 1.6, and 3.1 mg/kg).
- Safety margins (animal/human exposure ratios) of 3.9 to 5.2-fold between plasma AUC at the NOAEL doses in the nonclinical chronic toxicity studies (50 mg/kg/week in mice and 3 mg/kg/week in monkeys) and the plasma AUC observed in healthy volunteers after 5 doses of 110 mg Q1W (Study RG012-05).
- Observed kidney concentrations in patients (Study PDY16327) relative to the target kidney concentrations observed in Col4a3 mouse model at effective doses, and observed kidney concentrations in monkeys, the species used to extrapolate human kidney concentrations based on the assumption that mg/kg dose scaling applies between monkeys and humans (28).

Summaries of the nonclinical and clinical data which support the 110 mg Q1W dose regimen are presented below:

Nonclinical kidney SUM concentration data:

- In pharmacology studies in Col4a3 mutant mice, good pharmacological activity (reduction in the increase in BUN and extended survival in Col4a3 mouse models of Alport syndrome) was observed at the 25 to 50 mg/kg dose levels; these doses correspond to estimated kidney SUM concentrations of approximately 87 to 141 µg/g.
- Improved multiple endpoints in Col4a3 mice such as renal function (measured by BUN) as well as kidney fibrosis (measured by Col1a1 gene expression) were generally associated with 15-50 µg/g concentrations of SUM in kidney, whereas increased survival was generally associated with estimated kidney concentrations of 50-140 µg/g of SUM.
- Mean SUM kidney concentration in cynomolgus monkeys on Day 7 after the last (4^{th}) 1.5 mg/kg Q2W dose was 70.2 µg/g (range 55.0 to 103 µg/g).

Kidney SUM concentrations in Alport patients

- Observed SUM concentrations in human kidney biopsies at 1.5 mg/kg (corresponding to approximately 110 mg fixed dose) administered Q2W were:
  - Subject 36-001, Day 9 after last (4^{th}) dose = 47.8 µg/g (mean of 2 observations)
  - Subject 36-003, Day 8 after last (4^{th}) dose = 17.8 µg/g (mean of 2 observations)

Although the patient kidney concentration data are limited (n=2 patients with multiple dose data), the SUM concentrations observed in patients are lower than, or at the low end of, the target concentrations (~50-140 µg/g) predicted to demonstrate robust efficacy in terms of decrease in BUN and potential increase in survival rate. Since the kidney concentrations in the PDY16327 study were measured at approximately one week after the last Q2W dose (instead of 2 weeks to correspond to C_{trough}), trough concentrations following Q2W dosing are likely to be even lower than the Day 8 or 9 concentrations observed in the 2 subjects above. Thus, a dosing frequency of Q1W, instead of Q2W is proposed in order to increase kidney SUM concentrations and maximize the potential to see efficacy in this (ACT16248) study. A potential increase in kidney SUM concentrations of ~2-fold can be expected with Q1W dosing relative to Q2W regimen.

Pre-clinical Toxicology:

The NOAELs for chronic weekly SC administration of lademirsen (SAR339375) in mouse and monkey were 50 mg/kg and 3 mg/kg, respectively. The calculated exposure ratios for SAR339375 (SUM), based on comparison of actual mean plasma exposures in mouse (50 mg/kg QW), monkey (3 mg/kg QW), and human (110 mg/kg QW) are approximately 5X and 4X for mouse and monkey respectively.

In addition to the change in dosing frequency, a flat-fixed dose of 110 mg, instead of a mg/kg dose of 1.5 mg, is selected for this study based on reports of no readily apparent impact of total body weight changes on plasma clearance of oligonucleotides (8, 29) and given that this class of compounds is typically administered as a flat-fixed dose in humans (28).

1.3 RISKS AND BENEFITS

1.3.1 Potential and identified risks

Based on a comprehensive review of available data for the lademirsen clinical development program, thrombocytopenia and ISRs are considered as important identified risks; and nephrotoxicity based on non-clinical histologic findings in the glomerulus, hepatotoxicity, clinically meaningful immunogenicity, and embryo-fetal toxicity are considered as important potential risks.

For additional information on lademirsen (SAR339375) risks and benefits, refer to the Investigator's Brochure.

For study conduct in Germany, please see Section 10.5.1.1 for further details.

1.3.2 Potential benefits

Benefits of treatment with lademirsen (SAR339375) in subjects with Alport syndrome have not been studied. However, the efficacy of lademirsen (SAR339375), either as monotherapy or in combination with ramipril, the current standard of care for subjects with Alport syndrome, has been demonstrated in genetic mouse models of Alport syndrome, as outlined above and detailed in the Investigator's Brochure. Given the monitorable risks, the margin of safety, and demonstrated efficacy in preclinical models, it is reasonable to examine the safety and efficacy of lademirsen (SAR339375) in subjects with Alport syndrome. It is unknown at this time whether subjects with Alport syndrome will derive clinical benefit from treatment with lademirsen (SAR339375).

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To assess the efficacy of lademirsen (SAR339375) in reducing the decline in renal function.
- To assess the safety and tolerability of lademirsen (SAR339375) in subjects with Alport syndrome.

2.2 SECONDARY OBJECTIVES

- To assess plasma pharmacokinetic (PK) parameters. C_{max} will be assessed for the parent compound (lademirsen [SAR339375]), its active major metabolite (RG0005), and the sum of lademirsen (SAR339375) and RG0005 (SUM) following administration of lademirsen (SAR339375). C_{trough} will be assessed in terms of SUM only.
- To assess potential formation of anti-drug antibodies (ADAs) following administration of lademirsen (SAR339375).
- To assess the pharmacodynamic effect of lademirsen (SAR339375) on miR-21 and on changes in renal injury and function biomarkers.

2.3 EXPLORATORY OBJECTIVES

- To assess the effect of lademirsen (SAR339375) on urine and blood biomarkers in Alport Syndrome subjects.

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN

This will be a randomized, double-blind, placebo-controlled, multi-center, Phase 2 study conducted in approximately 45 subjects with Alport syndrome at multiple investigative sites. At the completion of 48 weeks of double-blind, placebo-controlled treatment, all subjects will enter the 48-week open-label extension period in which all subjects will receive active treatment with lademirsen (SAR339375).

Screening and Baseline Period

Subjects may screen for enrollment after participation in the OBS16374 ATHENA Natural History Study or directly in this study. To qualify for this study, subjects must have confirmed Alport syndrome and meet all eligibility criteria described in Section 3.2.

For subjects from the ATHENA study, genotype, demographics, prior/concomitant medications, medical history, and family history data from that study may be used to satisfy entry criteria in the current study.

Double-Blind, Placebo-Controlled Treatment Period

Eligible subjects will be randomized in a 2:1 ratio to receive QW SC doses of lademirsen (SAR339375) 110 mg or placebo for 48 weeks with stratification by screening eGFR (<60 mL/min/1.73 m^2 versus ≥60 mL/min/1.73 m^2). Once randomized, the subject should be treated within 3 calendar days maximum.

The Schedule of Events for the double-blind, placebo-controlled treatment period is provided in Table 1, and a detailed list of procedures for each study visit is provided see Section 5.2. Certain visits outlined in the Schedule of Events (see Table 1) may be performed at home or at an alternate location by trained, qualified study personnel, to which the Investigator has delegated responsibility. See Section 5.7 for more details.

Study drug injections will be administered by trained, qualified personnel on the Investigator site or, as deemed acceptable by the Investigator, at home or at an alternate location by a trained, qualified healthcare professional.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be maintained at a stable dose and regimen for the duration of the trial. All other concomitant medications should also be maintained at a stable dose and regimen during this period. Concomitant medications may be adjusted to maintain standard of care. Any changes to concomitant medications must be documented in the eCRF.

Open-Label Treatment Extension Period

Subjects who complete the 48-week double-blind, placebo-controlled treatment period will be rolled over into a 48-week open-label treatment extension period in which all subjects will receive QW active treatment with lademirsen (SAR339375).

The open-label treatment period allows all the subjects to benefit from exposure to lademirsen (SAR339375) after the randomized period of the treatment. In addition, this allows us to gain long-term safety and efficacy data in Alport subjects.

The Schedule of Events for the open-label extension period is provided in Table 2, and a detailed list of study procedures is provided in Section 5.3. The Week 48 visit of the double-blind, placebo-controlled treatment period will serve as the baseline visit of the open-label extension for those placebo subjects who treated in the open-label extension. Procedures for study visits in the 48-week open-label extension will be nearly identical to those for the 48-week double-blind, placebo-controlled treatment period.

Study drug injections will be administered by trained, qualified personnel on the Investigator site or, as deemed acceptable by the Investigator, at home or an alternate location by a trained, qualified healthcare professional or on self-administration.

Dose Reduction

Before administering each dose of study drug, the Investigator or delegate will review a subject's most recent safety data. A subject's platelet count will be obtained weekly before dose administration. Platelet counts may be measured from a central laboratory and can exceptionally be measured at a local laboratory. The most recent subject's platelet counts, but not older than 10 days will be reviewed by the Investigator/physician before drug administration.

Following the resolution of a Grade 2 AE or increase in aminotransferases (return to normal or ≤ Grade 1 for AE) that does not otherwise trigger a stopping rule (see Section 3.4), the Investigator in consultation with the Sponsor Medical Manager may reduce an individual subject's dose down to 110 mg Q2W. Dose reductions should be discussed with the Sponsor Medical Manager before implementation. Once a subject's dose has been reduced, it will not be increased.

Follow-up Period

Any subject who discontinues early should complete the procedures for an early termination (ET) visit, enumerated in the Schedules of Events tables.

Subjects who complete the open-label treatment extension period will enter the post-treatment follow-up period. During the follow-up period, visits will occur at Follow-up Weeks 2, 4, and 10. Follow-up weeks are numbered starting from the last scheduled study visit in the active treatment period (eg, Follow-up Week 2 will occur 2 weeks after Week 96 or after ET). The Schedule of

Events for the follow-up period is provided in both Table 1 and Table 2, and a detailed list of procedures for each visit in the follow-up period is provided in Section 5.5.

3.2 STUDY POPULATION

Approximately 45 adult subjects will be enrolled. Subjects must meet all of the inclusion and none of the exclusion criteria to be eligible for study entry.

3.2.1 Inclusion criteria

I 01. Male or female.

I 02. Confirmed diagnosis of Alport syndrome.

1. Clinical diagnosis (hematuria, family history, hearing loss, ocular change), AND
2. Genetic confirmation of Alport Syndrome in the subject or the family member, OR
3. Kidney biopsy showing glomerular basement membrane abnormalities (eg, significant thinning, thickening, irregularity or lucencies) consistent with Alport Syndrome.

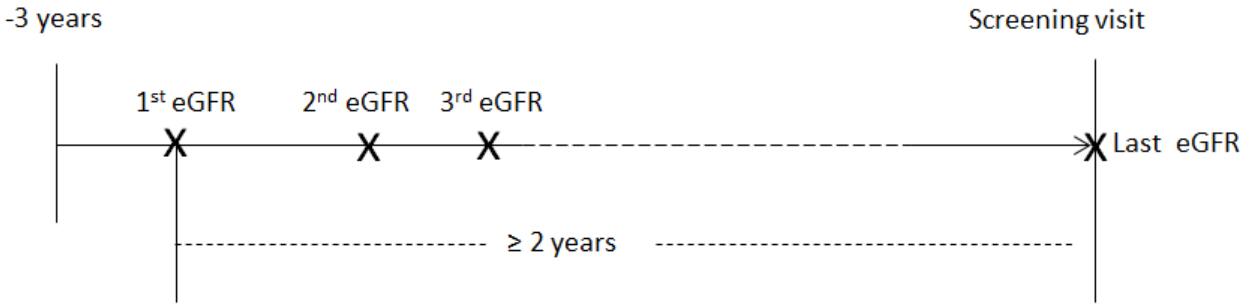
I 03. Age 18-55 years old.

I 04. eGFR >35 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2 (based on CKD-EPI) at screening (for study conducted in France, see Section 10.5.3).

I 05. **Renal Function Criteria (subjects must meet at least one of the following CRITERIA A or B or C):**

A) Prior eGFR Slope Criteria is defined as a decline in eGFR of ≥4 mL/min/1.73 m^2/year (eGFR slope ≤-4 mL/min/1.73 m^2/year) based on a linear regression slope analysis of ≥4 eGFR measurements within 3 years prior to the study and with a minimum of 2-year time span (the last, of the screening measurement, and first eGFR measurements should be separated by at least 2 years). eGFR should be calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (see Figure 1; for study conducted in France, see Section 10.5.3).

Figure 1 - Renal function criteria



B) Proteinuria: UPCR >2000 mg/g or UACR >1000 mg/g

C) eGFR (based on CKD-EPI): male 18-23 years old with eGFR <90 mL/min/1.73 m^2 (for study conducted in France, see Section 10.5.3).

I 06. ACE inhibitor and/or ARB, the dosing regimen should be stable for at least 30 days prior to screening.

I 07. Sexually active female subjects of childbearing potential and sexually mature male subjects must agree to practice true abstinence in line with their preferred and usual lifestyle or to use 2 acceptable effective methods of contraception for the entire duration of the study and for at least 10 weeks after last dose.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A) Male subjects

Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 10 weeks after the last dose of study intervention:

- Refrain from donating sperm

Plus either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

B) Female subjects

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

  OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4 during the intervention period and for at least 10 weeks after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during the study and for a period of six weeks. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine as required by local regulations) within 24 hours before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 10.4.
  - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

I 08. Negative drug screen for opiates, cocaine, heroin, phencyclidine, amphetamines (including ecstasy), barbiturates, benzodiazepines, and cannabinoids. At the Investigator's discretion, subjects prescribed benzodiazepines, cannabinoids, or opiates with positive results on a drug screen may be allowed.

I 09. Negative screening results for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIV) antibody.

- Hepatitis A virus (HAV) screening is not necessary, screenings required above is for identification of chronic diseases.

I 10. Screening hematology, clinical chemistries, coagulation, and urinalysis are not clinically significant, as assessed by the Investigator, and meet the following criteria:

A) Platelets, total white blood cell (WBC) count, and absolute neutrophil count within normal limits

B) Hemoglobin (Hb) ≥11 g/Dl

C) Total and direct bilirubin <1.5 x upper limit of normal (ULN), unless elevated bilirubin is associated with a known benign condition (eg, Gilbert's syndrome)

D) Alanine aminotransferase (ALT) <1.5 x ULN

E) Aspartate aminotransferase (AST) <1.5 x ULN

F) Alkaline phosphatase (ALP) <1.5 x ULN

G) Gamma-glutamyl transferase (GGT) <1.5 x ULN

Note: At the discretion of the Investigator, screening laboratory testing may be repeated once to confirm out-of-range (exclusionary) results.

I 11. Agree to report any new prescription medication, dose adjustment to existing medication, over-the-counter medication, or herbal supplement to the Investigator.

I 12. Able to understand all study procedures in the informed consent form (ICF) and willing to comply with all aspects of the protocol.

3.2.2 Exclusion criteria

Subjects meeting any of the following criteria will be ineligible to participate in this study:

E 01. Causes of chronic kidney disease aside from Alport syndrome (including but not limited to other heritable disorders leading to chronic kidney disease, diabetic nephropathy, hypertensive nephropathy, lupus nephritis, IgA nephropathy).

E 02. ESRD as evidenced by ongoing dialysis therapy or history of renal transplantation.

E 03. Any clinically significant illness within 30 days before screening or surgical or medical condition (other than Alport syndrome) that could interfere with the subject's study compliance; confound the study results; impact subject safety; or significantly alter the distribution, metabolism, or excretion of drugs, including but not limited to the following:

- Significant or unstable cardiac disease (unstable angina, myocardial infarction within the last 6 months, symptomatic coronary artery disease, congestive heart failure [New York Heart Association ≥ Grade 3], prolonged QT syndrome [torsade de pointes], significant arrhythmia, and/or any other clinically significant ECG abnormalities)
- Uncontrolled seizure disorder (eg, seizure in the last 12 months)
- Chronic infection (eg, tuberculosis)
- Metabolic disease (eg, diabetes mellitus)
- Evidence of urinary obstruction or difficulty in voiding at screening
- History of hypocomplementemia (low complement levels or activity)
- Maintenance medication known to cause QT prolongation

E 04. Weight >110 kg.

E 05. Any history of active malignancy within the last 1 year (history of localized basal cell or squamous cell carcinoma and cervical carcinoma in situ that has been excised/appropriately treated or a fully excised malignant lesion with a low probability of recurrence will not be considered exclusionary).

E 06. History or presence of alcoholism or drug abuse within 2 years before screening or other concurrent social conditions that would potentially interfere with the subject's study compliance, at the discretion of the Investigator.

E 07. Mental impairment or history of or current significant psychiatric disease that may impair ability to provide informed consent or impact compliance with study procedures.

E 08. Participation in a recent investigational study and receipt of an investigational drug or investigational use of a licensed drug within 30 days or 5 half-lives, whichever is longer, prior to screening.

E 09. Prior treatment with Bardoxolone within 90 days prior to screening.

E 10. History or presence of hypersensitivity or idiosyncratic, allergic, or other clinically significant reaction to the study drug (including placebo), inactive ingredients, or related compounds (eg, other oligonucleotide products).

E 11. Any other condition or circumstance that may make the subject unlikely to complete the study or comply with study procedures and requirements, or may pose a risk to the subject's safety and well-being.

E 12. Subjects dependent on the Sponsor or Investigator or employees of the clinical study site or any other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 13. Subjects that are accommodated in an institution because of regulatory or legal order.

E 14. Prisoners or subjects who are legally institutionalized.

3.3 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

For individuals who do not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure reason may not be expected within a reasonable time frame, the screen failure will be performed. The subject may be rescreened; if their clinical condition

changes, subject numbers will not be reused and a new subject number will be assigned. All the screening procedures will be repeated and entered in the screening visit pages.

In case the subject is a temporary screen failure, there is no need to have subject re-consent (eg, new ICF signed) if the subject finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the subject to participate, the Investigator should ensure the willingness of the subject to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the subject's chart. All the tests out of protocol window should be repeated and entered to the additional pages.

3.3.1 Withdrawal, removal, and replacement of subjects

All subjects will be informed that they have the right to discontinue study drug or to withdraw from the study at any time, for any reason, without prejudice, and without having to justify their reasons or decisions. Additionally, the Investigator may discontinue a subject's study drug at any time if he/she considers that to be in the subject's best interest or if the Investigator determines that continuing study drug would result in a significant safety risk for the subject.

A discontinuation of study drug occurs when an enrolled subject ceases study drug, regardless of the circumstances, prior to completion of the study. However, every effort should be made to observe subjects who have been dosed until the scheduled end of the follow-up period, even if they prematurely discontinue study drug.

Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-subject contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

If subjects no longer wish to take the IMP, they will be encouraged to remain in the study. The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Subjects who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented. All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the subject's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In case of premature discontinuation of study drug, the Investigator should schedule an early termination visit to record AE data and to collect samples for laboratory evaluations. This visit should be documented in the appropriate eCRF. The Investigator will record the reason for the study drug discontinuation, provide or arrange for appropriate follow-up for such subjects, and document the course of the subject's condition. In addition, the Investigator will report the subject's study drug discontinuation or study withdrawal to the Sponsor immediately.

Valid reasons for a subject to discontinue the study drug or to withdraw from this clinical study include but are not limited to:

- Withdrawal of informed consent

- Subject's decision to discontinue study drug
- Reaching the treatment stopping rules. Please see Section 3.3.1.1 below
- Occurrence of AEs for which permanent discontinuation is considered necessary by the Investigator
- Investigator's decision (eg, if in the Investigator's opinion it is not in the best medical interest of the subject to continue participation in the study)
- Any protocol deviation that may result in a significant risk to the subject's safety or protocol deviations that will interfere with the efficacy endpoints of this study
- Lost to follow-up (the subject stopped coming for visits, and study personnel are unable to contact the subject)

3.3.1.1 Individual treatment stopping criteria

Any Grade 2 AE (except for renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis) not resolved prior to the administering the next dose and deemed by the Investigator to be at least "possibly related" to study drug would result in a pausing of dosing (eg, dose not given) until the AE improves to ≤ Grade 1. Injection site reactions will be graded according to Table 6. Any Grade 2 (except erythema/redness) or Grade 3 ISRs which had not resolved or reached Grade 1 ("Mild", eg, limited tenderness, and/or induration, except erythema/redness) prior to the next dose, would result in a pausing of dosing. The continuation of dosing and dose level would be decided upon review between the Investigator and the Genzyme Corporation Study Medical Manager. For further details in dose reduction, see Section 4.5.

Occurrence of any Grade 3 (Severe) or higher AE (except for ISRs and renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis) will result in the cessation of dosing of the subject, unless it can be shown that the event was unrelated to participation in the clinical trial. The DMC will review the circumstances of the AE with the Sponsor and unblind the subject, as appropriate, to evaluate potential relatedness to study drug and will make a recommendation regarding the further dosing of the subject to the Sponsor. After deliberations, DMC will provide guidance to the Sponsor who will implement recommendations and communicate to the site.

With regard to AEs, study drug should be discontinued for subjects who experience any of the following:

- Grade 3 thrombocytopenia (platelet count from <50 000 to 25 000/microL) will trigger cessation of dosing for the subject.
- ALT or AST >5 × ULN, or ALT or AST >3 × ULN in association with total bilirubin >2 × ULN.
- An unintended weight loss of ≥20% from baseline.

- ≥50% decline for eGFR from the last measurement or confirmed ESRD (eGFR ≤15 mL/min/1.73 m^2 or dialysis or renal transplantation is needed).

In case of worsening of eGFR (that do not reach stopping criteria) or UPCR, the Investigator or the Sponsor could repeat the test before the next scheduled one as often as medically needed. The Sponsor needs to be consulted before a decision to discontinue the patient, unless it is a case of emergency.

3.3.1.2 Follow-up for drug discontinuation/subject withdrawal from the study

If a subject discontinues or is discontinued from study drug, the Investigator should take the following actions:

- Record discontinuation reason within the eCRF
- Complete the early termination visit (see Section 5.3)

If a subject is discontinued from study drug due to an AE, the Investigator will arrange follow-up with the subject as appropriate until the event has been resolved or stabilized. Every effort will be made to follow up with subjects who discontinue study drug because of serious AEs (SAEs) considered related to the study drug unless they withdraw informed consent.

If a subject fails to attend scheduled assessments, the Investigator must document the reasons and the circumstances as completely and accurately as possible.

For subjects who are lost to follow-up (eg, subjects whose status is unclear because they fail to appear for the study visits without stating an intention to withdraw), the Investigator should document in the source documents any steps taken to contact the subject (eg, dates of telephone calls, emails, registered letters).

Subjects who withdraw informed consent will not have further information or data collected from them, with the exception of follow-up information about AEs ongoing at the time of withdrawal.

3.4 DISCONTINUATION OF THE STUDY

The Sponsor may terminate the study at any time for any reason. In the event the study is terminated, the Institutional Review Board (IRB)/Ethics Committee (EC) and Competent Authority will be notified of the decision.

Study Suspension and Stopping Criteria

The occurrence of two similar Grade 3 (or higher) AEs (except for ISRs and renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis), or any death or two unexpected SAEs considered at least possibly related to participation in the clinical trial, or any TEAE that in the opinion of the Sponsor is of potential clinical significance for subjects safety will result in the recommendation to suspend all dosing and stop recruitment, then will trigger an ad hoc meeting with the DMC who will be asked to

consider the appropriateness of study conduct continuation unchanged, early study termination or modification.

Upon suspension of dosing, a full, unblinded review of the AEs will be performed by the DMC to evaluate the AEs and potential relationship to exposure to the study drug. Following the full, unblinded safety review, one of three outcomes is possible:

1. The study may be terminated.
2. The study design may be amended. For example, the dose of study drug may be reduced for all subjects (to 110 mg SC every other week (the pre-specified dose reduction for a Grade 2 AE), the dose regimen may be changed to reduce the dosing frequency, or inclusion/exclusion criteria may be modified (eg, baseline platelet count or other relevant laboratory or clinical parameter).
3. Stopping criteria are at the discretion of the DMC, the study may continue as originally planned, based on clear evidence that the stopping criteria have not been met and measures are in place to ensure subject safety.

4 TREATMENT PROCEDURES

4.1 INVESTIGATIONAL PRODUCTS

The investigational products may be supplied at the site or from the Investigator/site to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

4.1.1 Identity of investigational products

Lademirsen (SAR339375) for SC administration is supplied as 110 mg/mL solution in 5 mL glass vial. Each vial will contain a withdrawable volume of 2 mL.

Placebo matching lademirsen (SAR339375) for SC administration is supplied as sodium chloride and riboflavin (colorant) solution in 5 mL glass vial. Each vial will contain a withdrawable volume of 2 mL.

4.1.2 Packaging and labeling, handling and accountability

Lademirsen (SAR339375) and placebo will be supplied in a single use glass vial packed in a kit box. Each kit box will be labeled as required per country requirements.

All drug supplies will be provided by the Sponsor, and the logistics of supply will be managed by the Sponsor or an appropriate designee.

Investigators or other authorized persons (eg, pharmacists) are responsible for receiving and storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies and procedures.

The Investigator or designee, care giver for home injection, must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Study intervention shipment and storage for subjects who will have home injections are provided in the Pharmacy Manual.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance.

Under no circumstances will the Investigator supply IMP to a third party (except for direct to patient (DTP) shipment, for which a courier company has been approved by the Sponsor), allow

the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

A separate Pharmacy Manual will be provided detailing instructions for preparation, handling storage and accountability.

4.2 TREATMENT ASSIGNMENT

Once all the screening data become available, the Investigator will perform the final evaluation of the subject's eligibility. If a subject is not eligible, the reason will be recorded. Treatment assignment and randomization will be performed using a centralized treatment allocation system/IRT. The IRT (centralized treatment allocation system) generates the patient randomization list and allocates the treatment number and the corresponding treatment kits to the subjects accordingly.

Before randomizing a patient, the Investigator or designee will have to contact the centralized treatment allocation system/IRT.

For the double-blind, placebo-controlled treatment period, approximately 45 eligible subjects will be centrally randomized in a 2:1 ratio to lademirsen (SAR339375) 110 mg or placebo SC QW for 48 weeks, with stratification by screening eGFR (<60 mL/min/1.73 m^2 versus ≥60 mL/min/1.73 m^2).

For the open-label extension, all subjects will receive lademirsen (SAR339375) 110 mg SC QW for up to 48 weeks. Subjects who require dose reduction to 110 mg Q2W during the blinded period of the study will receive the same dose in the open-label period of the study.

4.3 TREATMENT ADMINISTRATION

A subject's platelet count will be obtained weekly before dose administration. Platelet counts may be measured from a central laboratory and can exceptionally be measured from a local laboratory. The most recent subject's platelet counts, but not older than 10 days will be reviewed by the Investigator/physician before drug administration.

Qualified and trained personnel will prepare the study drug on the day of administration and SC injection and administer all study drug injections. The study drug should be administered as a bolus in the anterior lower abdominal wall. The time of dosing and the region of the abdomen used should be recorded for doses administered. A separate document will provide additional details on the preparation and administration of study drug.

4.4 HOME INJECTION

Home injection may be possible where permitted by national and local regulations.

Subjects must meet the eligibility requirements outlined below. Subject's underlying comorbidities and ability to adhere to the requirements of the study need to be taken into account when evaluating subjects for eligibility to receive home injection. Any identified risk of noncompliance to monitoring of study requirements or potential for loss to follow up should lead to this subject not being eligible for home injection.

Home injection might begin at Week 1 for subjects agreed by the Investigator and meet the required criteria.

The following criteria must be documented in the subject's medical record:

- The Investigator must agree in writing that home injection is appropriate for the subject.
- The subject must be willing and able to comply with home injection procedures.
- The subject must have no ongoing (not yet recovered) SAEs that, in the opinion of the Investigator, may affect the subject's ability to tolerate the injection.
- Home injection infrastructure, resources, and procedures must be established and available according to applicable regional and local regulations.
- Subject has not experienced a severe AE or SAE considered related to lademirsen (SAR339375).
- Subject experiencing a severe AE or an SAE moderate or severe ISR while being injected at home will return to the study site for their following injection and will continue to receive injections at the study site until no such events are present for at least after 2 injections.
- In the event of manufacturing scale change, the subject will be required to receive the first injection at the site. All criteria for return to home injection will apply.

The subject must agree to report to the site staff (by email or by phone) all events that occurred between 2 injections prior to the next planned injection.

Prior to beginning home injections, training will be provided to the healthcare professional according to the protocol dosing requirements and pharmacy manual. Any new healthcare professional must be trained prior to resuming home injection.

During the 48 weeks double – blind randomized period, for subjects who are eligible and agree for home injection, the drug injections will be performed by a trained healthcare professional. Prior to each home visit, the Investigator or delegate will review a subject's most recent platelets count (not older than 10 days) then will contact the healthcare professional to confirm administration and the dose of the study drug.

- Before each injection: the healthcare professional will collect and will review safety assessments (AEs, with specific assessments about petechiae, gingival bleeding, bruising, and any new concomitant medications) with the Investigator or delegate to confirm or to change the study drug dosing. The requested blood sampling and other assessments (per Table 1) will be done.

- After each injection: the healthcare professional will confirm administration of the study drug to the site staff and will monitor the subject's injection site for 15 minutes. The site staff will contact the subjects the day following each injection to collect any safety events including ISR.

During the last 6 months (from Week 24) of the double-blind period, the subject will be trained on self-administration and handling of the study drug in preparation for the open-label extension period. The patient will be observed in self-administration technique during the training period.

During the open-label extension period, it is expected that the subjects will practice self-administration unless the Investigator or delegate deems that the subject is unable to do so or self-administration is not suitable by the subject. In the latter case, the drug injection will be done at home or at the site by qualified and trained personnel.

For subject who will practice self-administration during the open-label extension period:

- Before each injection: the requested blood sampling will be drawn by an assigned healthcare professional. The Investigator or delegate will contact the subject at the planned day of injection and will review and collect safety assessments (AEs, with answers to specific assessments about petechiae, gingival bleeding, bruising, and any new concomitant medications). The Investigator or delegate will confirm or change administration of the lademirsen (SAR339375) dose based on the most recent platelets count (not older than 10 days) and the reported AEs. **The injection will only be done after obtaining confirmation from the Investigator and after blood sampling.**
- After each injection: the subject will complete the "home dosing diary", including reporting of ISRs, and send a copy to the site via e-mail or fax. The original will be provided to the site during the next site visit. The site staff will contact the subject the day following the injection to monitor and collect safety events, including ISRs, and will schedule with the subject the next injection. Any ISRs will be assessed and graded by the Investigator or delegate.

For subjects who do not wish to perform self-injection, the home injection procedure will be the same as for double-blind period.

4.5 DOSE REDUCTION

Before administering each dose of study drug, the Investigator or delegate will review a subject's most recent safety data. A subject's platelet count will be obtained weekly before dose administration. Platelet counts will be measured from a central laboratory and can exceptionally be measured from a local laboratory. The most recent subject's platelet counts, but not older than 10 days, will be reviewed by the Investigator/physician before drug administration. Following the resolution of a Grade 2 AE or increase in aminotransferases (return to normal or ≤ Grade 1 for AE) that does not otherwise trigger a stopping rule (see Section 3.4), the Investigator in consultation with the Sponsor Medical Manager may reduce an individual subject's dose to 110 mg Q2W. Dose reductions should be discussed with the Sponsor Medical Manger before implementation.

Grade 2 thrombocytopenia (platelet count from <100 000 to 50 000/microL) will result in suspension of dosing pending a return of platelet count to > LLN and review by the Investigator and the Sponsor Medical Manager. If dosing is to resume, it will be reduced to 110 mg Q2W.

For actions related to laboratory abnormalities that are indicative of potential hepatotoxicity, any subject experiencing a moderate (Grade 2) alkaline phosphatase, or bilirubin elevation will have a dose suspension and related laboratory test should be done weekly until the value(s) return to the normal range. For actions related to elevation of aminotransferases, please refer to Section 10.3.2. If dosing is to resume, it will be reduced to 110 mg Q2W.

Injection site reactions will be graded according to Table 6. Any Grade 2 (except erythema/redness) or Grade 3 ISR must have resolved or reached Grade 1 ("Mild", eg, limited tenderness, and/or induration, except erythema/redness) prior to the next dose or subsequent dosing will be suspended. Consideration of resumed dosing at dose 110 mg Q2W will be based on review of the AE and time course to resolution in consultation with the Sponsor Medical Manager.

Once a subject's dose has been reduced, it will not be increased.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.6.

4.6 RANDOMIZATION CODE BREAKING DURING THE STUDY

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the subject. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a subject's treatment assignment unless this could delay emergency treatment for the subject.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. The code-breaking can also be performed by contacting the "24-hour alert system". A patient card, including the relevant "24-hour alert system" telephone number will be provided to every patient who will participate in the study.

If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The Investigator should document the date, time of day and reason for code breaking in the source documentation and case report form.

Subject will only be withdrawn from IMP administration when the code break call is made at the site level. That means if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the subject will be withdrawn from the treatment. Please refer to Section 3.3.1 of the protocol for details on handling of patient treatment discontinuation.

4.7 TREATMENT COMPLIANCE

Appointed team members will be identified at each center who will be responsible for the receipt, handling, and accountability of the study drug. Records of the study drug used, dosages administered, and intervals between visits will be kept during the study. Further details are provided in the Pharmacy Manual and relevant monitoring plan.

4.8 PRIOR AND CONCOMITANT MEDICATIONS

Prior medications/therapy (eg, given within 30 days before signing the ICF) and ongoing medications/therapy will be recorded on the eCRF Prior/Concomitant Medications Page. If additional concomitant medication becomes necessary during the study treatment period, this must also be documented and appropriately listed on the eCRF Prior/Concomitant Medications Page.

Subjects must agree to the following restrictions regarding concomitant medications during the study:

- To inform the site of any new prescription medication or dose adjustment to existing medication.
- To inform the site of any over-the-counter medication or herbal supplement.
- Not to participate in any other investigational drug trial.

Concomitant medications should be maintained at a stable dose and regimen during the study. Investigators should take particular care to avoid changing medications that affect blood pressure or renal function, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), statins, diuretics, and calcium channel blockers. Concomitant medications may be adjusted to maintain standard of care. Any change in concomitant medications after signing the ICF must be recorded in the eCRF, with the type of medication, dose, duration, and indication.

Vaccination for coronavirus disease 2019 (COVID-19) will not have an impact on subject enrollment or study drug treatment. No wash-out period is required between vaccination and initiation of study drug. Nevertheless, it is preferred that the COVID-19 vaccination and the study drug injection are separated by at least 48 hours to allow an adequate evaluation of potential AEs.

4.9 DIETARY GUIDANCE

Investigators should encourage subjects to maintain a consistent renal diet throughout the study, as significant changes may affect key outcome measures. In particular, subjects should be counseled to avoid atypically high protein meals in the days prior to visits that include serum chemistry and urinalysis assessments.

5 STUDY PROCEDURES

The timing of the procedures and assessments to be performed is outlined in Table 1 for screening and the double-blind, placebo-controlled treatment period and in Table 2 for the open-label treatment period and study follow-up. Additional details of the study procedures are given in Section 6. Rescreening of subjects is permitted with consultation of the Study Medical Manager.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.6.

5.1 SCREENING

The following assessments, procedures, and data collection will be performed during screening prior to drug administration:

- Obtain written informed consent before performing any study-related procedure
- Demographics data collection (age, gender, ethnicity)
  - For study conducted in France, see Section 10.5.3.
- Medical history
- Family history relevant to Alport syndrome and renal disease
- Type IV collagen alpha chain gene 1 (COL4A3/4/5*)* genotyping
- Prior medications/therapy (given within 30 days prior to signing the ICF)
- Concomitant medications (eg, any medication taken after signing the ICF)
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate) and body weight
- Complete physical examination and height measurement
- 12-lead ECG
- Drug and alcohol screen
- HbsAG, HCV antibody, and HIV-1/2 antibody screen
- 24-hour urine sample
- Urinalysis
- CBC with differential
- Serum chemistry (including creatinine and Cystatin C for calculation of eGFR per the CKD-EPI; see Section 10.5.3 for study conducted in France)
- Lipid panel
- High-sensitivity C-reactive protein (hs-CRP)
- Coagulation panel

- Blood pregnancy
- AE assessment beginning after the ICF is signed

5.2 DOUBLE-BLIND, PLACEBO-CONTROLLED TREATMENT PERIOD

Eligible subjects will be randomized in a 2:1 ratio to receive QW subcutaneous (SC) doses of lademirsen (SAR339375) 110 mg or placebo for 48 weeks. Once randomized, the subject should be treated within 3 calendar days maximum. Details of the procedure for randomization will be provided in a separate document.

The Schedule of Events for the double-blind, placebo-controlled treatment period is provided in Table 1. Study drug injections will be administered by study personnel during scheduled study site visits or (as deemed acceptable by the Investigator) at home visits. Certain visits outlined in the Schedule of Events (see Table 1) may be performed at an alternate location by trained, qualified study personnel, to which the Investigator has delegated responsibility.

The following assessments, procedures, and data collection will be performed prior to drug administration, if not otherwise specified, at the study visits during the double-blind, placebo-controlled treatment period:

Day 1 - Baseline/Dosing Site Visit

Tests that are common between screening and baseline visits will not have to be repeated at baseline if done within 7 days prior to first dosing.

- Complete physical examination
- 12-lead ECG
- Urinalysis
- Coagulation panel
- Lipid panel
- hs-CRP

The following tests should be performed on baseline visit prior to the first injection:

- Concomitant medications
- Hearing assessment
- Biomarkers from blood and urine samples (for study conduct in China, see Section 10.5.2.2)
- Blood sampling for PK (4 hours pre-dose and 4 hours post dose)
- Blood sampling for complement (C3, C3a, C4, and Bb) at 0.5 hours pre-dose; 0.5 hours and 4 hours post-dose

- Blood sampling for markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG)
- Plasma/serum for storage to support exploratory objective on biomarker (for study conduct in China, see Section 10.5.2.3)
- Vital signs (0.5 to 1 hours pre- and 4 hours post-dose) and body weight
- 24-hour urine sample
- CBC with differential
- Serum chemistry
- ADA
- Injection of study drug
- Assessment of AEs including ISRs (Minimum of 2 hours post-injection observation period)
- miR-21
- Urine Pregnancy
- Assignment to treatment group

Weeks: 1, 2 and 3 (±2 days) - *Option for Alternative Location Visit

- Concomitant medications
- CBC with differential
- Serum chemistry at Week 2 only
- Assessment of AEs including ISRs
- Injection of study drug
- ADA

Week 4 (±2 days) - Site Visit

- Concomitant medications
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate) and body weight
- Urinalysis
- Spot UPCR
- CBC with differential
- Coagulation panel
- Serum chemistry
- Lipid panel

- hs-CRP
- Urine pregnancy
- PK (up to 4 hours before dose administration)
- ADA
- Assessment of AEs including ISRs
- Injection of study drug

Weeks: 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27, 29, 30, 31, 33, 34, 35, 37, 38, 39, 41, 42, 43, 45, 46 and 47 (all ±2 days) - *Option for Alternative Location Visit

- Concomitant medications
- CBC with differential
- Assessment of AEs including ISRs
- Injection of study drug

Weeks: 8, 16, 20, 28, 32, 40, 44 (all ±2 days) - *Option for Alternative Location Visit

- Concomitant medications
- CBC with differential
- Coagulation panel
- Serum chemistry
- Urine pregnancy
- Spot UPCR
- Assessment of AEs including ISRs
- Injection of study drug

Weeks: 12, 24, 36, 48 (all ±2 days) - * Site visits

- Concomitant medications
- Complete physical examination (Week 24 and Week 48); limited physical examination (Week 12 and Week 36)
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate) and body weight. At Week 48, vital signs will be done at 0.5 to 1 hour pre- and 4 hour post-dose)
- 12-lead ECG
- 24-hour urine sample
- Urinalysis

- CBC with differential
- Coagulation panel
- Serum chemistry
- Lipid panel
- hs-CRP
- Urine pregnancy
- Blood pregnancy (on Week 48 only)
- Hearing assessment (on Week 48 only)
- ADA
- Biomarkers from blood and urine samples (for study conduct in China, see Section 10.5.2.2)
- Blood sampling for PK (up to 4 hours before dose administration and 4 hours post-dose at W24 and W48)
- Blood sampling for complement (C3, C3a, C4, and Bb) at 0.5 hour pre-dose
- Blood sampling for markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG)
- Plasma/serum for storage (for study conduct in China, see Section 10.5.2.3)
- miR-21
- Injection of study drug
- Assessment of AEs including ISRs

5.3 OPEN-LABEL EXTENSION TREATMENT PERIOD

Subjects who complete the 48-week double-blind, placebo-controlled treatment period will be rolled over into the 48-week open-label extension period in which all subjects will receive active treatment with lademirsen (SAR339375) 110 mg QW. Subjects who complete the double-blind, placebo-controlled treatment period but who will not continue with the open-label extension will enter directly into the post-treatment follow-up period (see Section 5.5).

The open-label treatment period allows all the subjects to benefit from exposure to lademirsen (SAR339375) after the randomized period of the treatment. In addition, this allows us to gain long-term safety and efficacy data in Alport subjects. Procedures for study visits in the 48-week open-label extension will be nearly identical to those for the 48-week double-blind, placebo-controlled treatment period.

The following assessments, procedures, and data collection will be performed prior to dose administration, if not specify, at the study visits during the open-label extension treatment period:

Week 48 (±2 days) - Site Visit

The Week 48 visit of the double-blind, placebo-controlled treatment period will serve as the baseline visit of the open-label extension. Subjects continuing on to the open-label extension will receive their first open-label dose of lademirsen (SAR339375) at this visit. In addition to the procedures specified for this visit in Section 5.2, vital signs will be taken both pre- and post-dose and AEs including information related to ISRs will be assessed for at least 2 hours after injection at Week 48.

Weeks: 49, 50, 51, 53, 54, 55, 57, 58, 59, 61, 62, 63, 65, 66, 67, 69, 70, 71, 73, 74, 75, 77, 78, 79, 81, 82, 83, 85, 86, 87, 89, 90, 91, 93, 94 and 95 (±2 days) - *Option for Alternative Location Visit

- CBC with differential
- Assessment of AEs including ISRs
- Injection of study drug

Week 52 (±2 days) - Site Visit

- Concomitant medications
- Vital signs and body weight
- Urinalysis
- Spot UPCR
- CBC with differential
- Coagulation panel
- Serum chemistry
- Lipid panel
- hs-CRP
- Urine pregnancy
- Assessment of AEs including ISRs
- Injection of study drug

Weeks: 56, 64, 68, 76, 80, 88, 92 (all ±2 days) - *Option for Alternative Location Visit

- Concomitant medications
- CBC with differential
- Urine pregnancy
- Spot UPCR
- Serum chemistry

- Coagulation panel
- Assessment of AEs including ISRs
- Injection of study drug

Weeks: 60, 72, 84, and 96 (all ±2 days) - Site Visits

- Concomitant medications
- Vital signs and body weight
- Limited physical exam (symptom-directed, at Weeks 60 and 84) or complete physical exam (at Weeks 72 and 96)
- Hearing Assessment at Week 96
- 12-lead ECG
- 24-hour urine sample
- Urinalysis
- CBC with differential
- Coagulation panel
- Urine pregnancy
- Serum chemistry
- Lipid panel
- hs-CRP
- Blood sample for PK (pre-dose)
- Blood sample for complement (C3, C3a, C4 and Bb) (pre-dose)
- Blood sampling for markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG)
- ADA
- Biomarkers from blood and urine samples (see Section 10.5.2.2 for study conduct in China)
- miR-21
- Assessment of AEs including ISRs
- Injection of study drug (not Week 96)

5.4 EARLY TERMINATION

Any subject who discontinues before completing either active treatment period (double-blind placebo or open-label extension periods) should be encouraged to return to the study site to complete the following end-of-study procedures. With the exception of CBC, serum and urine chemistry, and coagulation panel, the specified laboratory assessments do not need to be completed if they were completed as part of a study visit within the 4 previous weeks.

- Concomitant medications
- Vital signs and body weight
- Complete physical exam
- Hearing Assessment
- 12-lead ECG
- Assessment of AEs including ISRs
- 24-hour urine sample
- Urinalysis
- CBC with differential
- Serum chemistry
- Lipid panel
- hs-CRP
- Coagulation panel
- Blood sample for PK and complement (C3, C3a, C4, and Bb)
- Blood sampling for markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG)
- ADAs
- Biomarkers from blood and urine samples (for study conduct in China, see Section 10.5.2.2)
- miR-21, plasma/serum storage (for study conduct in China, see Section 10.5.2.3), record adverse events
- Urine pregnancy

5.5 FOLLOW-UP PERIOD

Subjects who complete the open-label treatment extension period or subjects who discontinue early and have completed the early termination visit will enter the post-treatment follow-up period, which will be the same for all subjects. Follow-up weeks are numbered starting from the

last scheduled study visit in the active treatment period (eg, Follow-up Week 2 will occur 2 weeks after Week 96 or after ET).

Follow-up Weeks 2 and 4 (both ±3 days) - *Option for Alternative Location Visit

- Concomitant medications
- Collection of information related to potential AEs including ISRs
- CBC with differential

Follow-up Week 10 (±3 days) - Site Visit

- Concomitant medications
- Vital signs and body weight
- Complete physical exam
- Collection of information related to potential AEs including ISRs
- Complement (C3, C3a, C4, and Bb)
- Blood sampling for markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG)
- miR-21
- Urinalysis
- CBC with differential
- Serum chemistry
- Lipid panel
- hs-CRP
- Coagulation panel
- ADAs

5.6 UNSCHEDULED VISITS

Unscheduled visits are those visits that occur beyond regularly scheduled visits and are performed in order to assess a previously noted AE (especially if the AE is considered by the Investigator to be possibly related to the use of study drug), abnormal/alarming laboratory values, and/or clinical findings. In such cases, the Investigator may at his/her discretion arrange for a subject to have an unscheduled visit. The subject will be contacted to arrange an unscheduled visit to assess the noticed abnormalities. **Only focused assessments (guided by the reason for the visit) are foreseen for these visits**, and there will be no need to collect very extensive additional laboratory or other safety and efficacy data.

The unscheduled visits could be done at alternative location (including at home), and at the Investigator's discretion, for the assessment of AEs related to abnormal/alarming laboratory values.

The Unscheduled Visit Page in the eCRF must be completed (Table 1, Table 2).

5.7 ALTERNATE LOCATION VISIT

Subjects will be seen at the Investigational site, or at an Alternate Location including subject's home by trained, qualified personnel to whom the Investigator has delegated responsibility. All staff performing activities at an Alternate Location will be appropriately trained in the protocol, study drug administration, study assessments and procedures to be performed. They will be documented in the delegation of duties log. The purpose of this flexibility, where available, is to offer subjects the option of having their visits performed at a more convenient location (including the subject's home), due to the frequency of study visits and length of study, and the potential for subjects to live a significant distance from their main Investigational site.

5.8 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last subject in the trial globally.

6 BACKGROUND, SAFETY, EFFICACY, PHARMACODYNAMIC, AND PHARMACOKINETIC ASSESSMENTS

The timing of procedures and assessments to be performed is provided in Table 1 (for screening and the double-blind, placebo-controlled treatment period), Table 2 (for the open-label treatment period), and Section 5.

6.1 MEDICAL HISTORY AND FAMILY HISTORY

A subject's significant prior (eg, occurring before signing the ICF) and ongoing illnesses, surgeries, and smoking history should be documented on the eCRF Medical History Page. Medical history relevant to Alport syndrome will include past lab tests related to disease progression and should be documented on the appropriate eCRF page. Family history relevant to Alport syndrome and renal disease should be documented on the eCRF Family History Page. Medical history and family history data collected in the ATHENA study may be used for this study. Additional illnesses present from the time when the ICF is signed until the completion of the last follow-up visit are to be documented as AEs on the eCRF Adverse Event Page.

6.2 SAFETY ASSESSMENTS

Safety assessments will consist of monitoring and recording all AEs, including SAEs, physical examination, vital sign assessment, ECG recording, clinical laboratory results (hematology, serum chemistry, lipids, coagulation, complement, urinalysis), and regular monitoring of ISRs.

6.2.1 Adverse events

An AE is any undesirable sign, symptom, or medical condition occurring after signing the ICF. Information about all AEs, regardless of seriousness or relationship to study treatment, whether volunteered by the subject, discovered by questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the AE eCRF page and followed as appropriate.

Medical conditions present prior to study entry will be documented in the Medical History eCRF. However, medical conditions occurring after signing the ICF are to be recorded as AEs. Treatment-emergent adverse events (TEAEs) are defined as AEs with onset after the first dose of study drug or existing AEs that worsened after the first dose of study drug until the last administration of study medication plus 10 weeks follow up.

The Investigator (or delegate) is obliged to interview subjects at each visit and clarify/discuss any abnormality that may indicate a potential AE.

Subjects should be encouraged to report AEs that occur between scheduled visits to the Investigator or between home injections to the nurse.

AEs will be recorded from the time of signing the ICF until the end of the safety follow-up. If any AE is ongoing at the time of subject withdrawal, the subject will be asked to return for clinic visits or to respond to follow-up by telephone (if the AE is considered not related or unlikely related to study drug) until resolution or stabilization of this AE.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to study treatment, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study treatment. When AEs occur on the day of study drug administration, the approximate time of day should be provided.

Any AE that occurs during the study must be monitored and followed up until one or more of the following criteria have been met:

- It has resolved to ≤ Grade 1 or baseline level
- Pathological laboratory findings have returned to normal
- Steady state has been achieved

A subset of AEs will be closely monitored (ie, events identified as AESIs; see Section 6.2.2 and Table 3).

It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

As far as possible, each AE will also be described by:

- Duration (start and end dates)
- Severity grade
- Relationship to the study drug
- Action(s) taken and, as relevant, the outcome

6.2.2 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 1 [Section 10.1]).

- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).

- Symptomatic overdose (serious or non-serious) with IMP:
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as increase of at least 30% above the intended dose at each administration or any two doses separated by <5 days.
- Other specific AESIs subject to close monitoring:
  - All Grade ≥2 events listed in Table 3, except for eGFR
  - Grade ≥3 events of eGFR

6.2.3 Adverse events grading

Table 3 - Grading system for the definition of AESIs

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life threatening event (Grade 4)
Platelets	125 000 to 100 000 cells/µL	<100 000 to 50 000 cells/µL	<50 000 to 25 000 cells/µL	<25 000 cells/µL
ALT or AST[a]	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Direct Bilirubin	NA	NA	> ULN with signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (eg, signs and symptoms of liver failure)
Total Bilirubin	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN
Alkaline phosphatase	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
eGFR	NA	10 to <30% decrease from participant's baseline	30 to <50% decrease from participant's baseline	≥50% decrease from participant's baseline or dialysis needed

ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; NA: not applicable; ULN: upper limit of normal

Grading criteria are based on the DAIDS grading system (30). All deaths related to an AE are to be classified as Grade 5.

a For management of elevated aminotransferases, please refer to Section 10.3.2.

For events not defined in Table 3, the following guidelines are to be used to classify adverse events (see Table 4).

Table 4 - Classification of adverse events by severity

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life threatening (Grade 4)	Grade 5
Clinical AE NOT identified in Table 3	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death	Death related to AE

AE: adverse event
Grading criteria are based on the DAIDS grading system (30).

If there is an increase in severity of an AE, it will be recorded as a single event. The worst grade of severity for the AE should be recorded in the source data and eCRF.

An AE that is assessed as severe (having a "severe" or Grade 3 classification) should not be confused with an SAE. "Severe" is a category in rating the intensity of an event. An event is defined as "serious" when it meets one of the pre-defined outcomes described in Section 6.2.5.

The Investigator will assess any causal relationship of an AE to study drug not related to treatment or related to treatment.

6.2.4 Adverse event outcome

If the same AE occurs several times in the same subject, and the previous AE has "recovered/resolved" or "recovering/resolving" as an outcome, then the subsequent AE must be documented and assessed as a new AE each time unless the event is considered to be a continuation of the previously reported event rather than reoccurrence of the event.

Outcome of the AE will be recorded as defined below in Table 5.

Table 5 - Adverse event outcome

Not recovered/not resolved - One of the possible results of an AE outcome that indicates that the event has not improved or recuperated.
Recovered/resolved - One of the possible results of an AE outcome that indicates that the event has improved or recuperated. The subject recovered from the AE. Record the AE stop date.
Recovering/resolving - One of the possible results of an AE outcome that indicates that the event is improving. No AE stop date should be recorded when an AE is recovering/resolving.
Recovered/resolved with sequelae - One of the possible results of an AE outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated.
Unknown - There is an inability to access the subject or the subject's records to determine the outcome (eg, subject withdraws consent or is lost to follow-up). No AE stop date should be recorded.
Fatal - The AE directly caused death. Record the date of death as the AE stop date.

6.2.5 Serious adverse events

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it meets one or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in subject hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event

Important medical events that may not be immediately life-threatening or result in death or hospitalization are considered SAEs, based upon appropriate medical judgment, if they are thought to jeopardize the subject or require intervention to prevent one of the other outcomes listed in the definition above. Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Information about all SAEs will be collected and recorded on the Serious Adverse Event Report Form and reported to the Sponsor within 24 hours of learning of its occurrence.

Events **not** to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment that was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of SAE given above and **not** resulting in hospital admission

Any SAE occurring after signing the ICF to the end of a patient's study participation must be reported to the Sponsor. SAEs occurring after study participation have to be reported only if considered related to study drug as per Investigator judgment.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study treatment.

Instructions about completing initial and follow-up SAE Report Forms and sending them to the Sponsor/CRO are given in Section 9.1.1.

6.2.6 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AESIs (as defined in Section 6.2.2), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined Section 3.3.1). Further information on follow-up procedures is provided in Appendix 1 (Section 10.1).

6.2.7 Procedures in case of pregnancy

COLLECTION OF PREGNANCY INFORMATION:

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive lademirsen (SAR339375).
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) are always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in

Section 10.1 of the protocol. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

6.2.8 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified by the reference safety information (lademirsen [SAR339375] Investigator's Brochure).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the [Investigator's Brochure/IDFU/package insert or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

6.2.9 Guidelines for reporting product complaints (lademirsen [SAR339375])

Any defect in the lademirsen (SAR339375) must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

- Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

6.2.10 Physical examination/body system assessments

Complete or limited physical examinations or body system assessments will be performed by qualified study personnel (eg, physician, nurse practitioner, nurse). Height should be measured at screening. Limited examinations will be symptom-directed. Body system assessments will

evaluate general appearance, HEENT (head, ears, eyes, nose, throat), the cardiovascular system, the respiratory system, the abdomen, the musculoskeletal system, and the skin. Any confirmed clinically significant examination findings occurring after signing the ICF are to be recorded as AEs.

6.2.11 Vital signs and body weight

Vital signs (systolic and diastolic blood pressure measurements, pulse rate, body temperature, and respiratory rate) and body weight will be evaluated at each on site visit. Moreover, on Day 1 of the double-blind, placebo-controlled treatment period and at Week 48 if the subject is continuing into the open-label treatment extension period, vital signs should be assessed both 0.5 to 1 hour pre- and 4 hours post-dose.

Where feasible, vital signs should be measured before blood is drawn and after the subject has been sitting comfortably for 5 minutes with the blood pressure cuff in place on the nondominant arm. Blood pressure, and pulse rate measurements will be taken first and may be done manually or by automated recorder. Temperature will be obtained. Respiratory rate will be determined by observation for at least 30 seconds.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure and heart rate measurements will be repeated at the Investigator's discretion. Any confirmed clinically significant vital sign measurements occurring before signing the ICF are to be designated as medical history. Any confirmed clinically significant vital sign measurements occurring after signing the ICF are to be recorded as AEs.

6.2.12 Electrocardiogram assessment

A standard 12-lead ECG will include a general diagnostic impression as well as measurement of the heart rate, PR interval, QRS duration, QT interval, and the Fridericia-corrected QT interval (QTcF). ECGs will be centrally read for results.

Any ECG measurement determined by the Investigator to be clinically significant (occurring after signing the ICF) will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will be closely monitored until their resolution.

6.2.13 Hearing assessment

Hearing will be assessed during the Treatment Period and Extension Period using a pure tone audiometry (air only) test at defined frequencies at baseline, Week 48 and 96.

6.2.14 Laboratory assessments

All analyses must be done with the minimally required blood amount, and the number of needle insertions should be minimized during the blood collection.

All hematology (including CBC with differential), serum chemistry, serology parameters (HBsAg, HCV antibody, HIV-1/2 antibody), *COL4A3/4/5* genotyping, and urine analyses will be done centrally. Samples for PK analysis will be sent to the contract research organization (CRO). Samples for ADA analysis will be sent to the CRO.

Laboratory management details, including preparation, labeling, and storage of aliquots, will be described in a separate document.

Clinical laboratory results, not including PK, pharmacodynamics, and biomarker results (except for BUN, UPCR, UACR, creatinine and Cystatin C), will be sent back to the Investigator after completion of analyses.

All laboratory reports must be reviewed, signed, and dated by the Investigator or delegated co-Investigator. A legible copy of all reports must be filed in a subject medical record (source document) for that visit and the exact data must be recorded in the eCRF.

Hematology

CBC with differential will comprise the following parameters: hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), and platelet count.

Serum chemistry

Serum chemistry will comprise the following parameters: total protein, glucose (in fasting condition as per site habit), Cystatin C, creatinine for calculation of eGFR per the CKD-EPI creatinine equation (for study conducted in France, see Section 10.5.3), uric acid, lactate dehydrogenase, sodium, potassium, chloride, bicarbonate, calcium, iron, phosphate, BUN, and hs-CRP. A hepatic function panel will also be evaluated as part of serum chemistry.

Hepatic function panel

The hepatic function panel will comprise the following parameters: albumin, total bilirubin, direct bilirubin, ALT, AST, ALP, and GGT.

Lipid panel

The lipid panel will comprise the following parameters: total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Coagulation panel

The coagulation panel will comprise the following parameters: prothrombin time, aPTT, international normalized ratio (INR), and fibrinogen.

Serology parameters

All subjects will be tested for HBsAg, HCV antibody, and HIV-1/2 antibodies at screening visit.

Genotype

All subjects will be tested for COL4A3/4/5 genotype at screening visit.

Drug and alcohol screen

The drug and alcohol screen will include measurement of opiates, cocaine, heroin, phencyclidine, amphetamines (including ecstasy), barbiturates, benzodiazepines, cannabinoids, and alcohol.

Urine analysis

Urinalysis reports will include the following: color, appearance, specific gravity, pH, total protein, glucose, ketones, leukocyte esterase, nitrate, bilirubin, urobilinogen, urine sediment, microalbuminuria, creatinine, hematuria, and microscopy.

The 24-hour urine assessment will provide accurate measures of creatinine clearance, fractional excretion of sodium, total protein, and total albumin, in addition to standard urinalysis.

Anti-drug antibodies

Anti-drug antibodies (IgG) will be evaluated with a direct-binding ELISA method.

Complement

Complement C3, C3a, C4, and Bb will be measured on Day 1 in samples obtained 0.5 hour pre-dose and 0.5 and 4 hours post-dose and pre-dose for other visits as specified in Tables 1 and 2.

Abnormal Laboratory Results

Any abnormal laboratory test result (after signing the ICF) considered by the Investigator to be clinically significant will be recorded as an AE. Clinically significant laboratory values include those that require an intervention. Clinically significant laboratory values will be graded by severity as outlined in Table 4. Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

6.2.15 Monitoring of platelet count

Because of the potential for thrombocytopenia associated with the administration of an oligonucleotide drug, a subject's platelet count will be obtained weekly before dose administration. Platelet counts may be measured from a central laboratory and can exceptionally be measured from a local laboratory. The most recent subject's platelet counts, but, not older than 10 days, will be reviewed by the Investigator/physician before each drug administration.

6.2.16 Injection site reactions

Qualified study personnel (eg, physician, nurse practitioner, nurse) will assess the injection site and surrounding area. Injection site reactions will be rated according to the Food and Drug

Administration (FDA) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (31) as summarized in Table 6. Any reaction meeting the criteria for an AE (Section 6.1) should also be recorded as an AE.

For self-administrations during the open-label period, ISRs will be reported as described in Section 4.4.

Table 6 - Injection site grading (local reaction)

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Erythema/Redness*	2.5 - 5 cm	5.1 - 10 cm	>10 cm
Induration/Swelling**	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	>10 cm or prevents daily activity

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.2.17 Safety oversight

An independent Data Monitoring Committee (DMC) will be comprised of individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC members are independent of the project/study teams and are not involved in the study conduct. The primary responsibilities of the DMC are to review and evaluate the study data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to project/study team as detailed in the DMC charter.

The DMC will review data every six months and on an ad hoc basis as necessary throughout the study. The DMC will conduct a review of the relevant safety data outputs, PK, and will closely monitor AESIs (eg, platelet counts, eGFR).

The DMC may be consulted whenever the Investigator considers that worsening of eGFR and UPCR values are medically relevant.

The DMC will also review data at a planned interim analysis (IA), as described in Section 7.2.7.

The roles and responsibilities of the DMC, as well as, the DMC meeting timelines will be described in detail in a separate charter.

6.3 EFFICACY ASSESSMENTS

6.3.1 Estimated GFR

Estimated GFR will be calculated using the CKD-EPI creatinine equation (32).

eGFR = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males.

For study conducted in France, see Section 10.5.3.

6.4 PHARMACODYNAMIC ASSESSMENTS AND BIOMARKERS

Pharmacodynamics will be assessed by measurement of the following:

- Circulating miR-21.

Renal injury and function biomarkers:

- In blood only: BUN
- In urine only: protein/creatinine ratio, albumin/creatinine ratio, and EGF
- In both blood and urine: creatinine, Cystatin C, NGAL, and TGF-β

The UPCR will be performed every 4 weeks (using first morning void urine), either using spot urine or 24h-h urine collection at D1, W12, W24, W36, W48, W60, W72, W84, W96). In case of worsening of UPCR, the Investigator could repeat the UPCR before the next scheduled test.

Exploratory biomarkers to be evaluated may include but are not necessarily limited to the following:

- In blood only: microRNAs (miRs) other than miR-21
- In urine only: KIM-1 and calbindin-D28k
- In both blood and urine: β-2 microglobulin and CTGF

For study conduct in China, see Section 10.5.2.2 for pharmacodynamic assessments and biomarkers.

6.5 PHARMACOKINETIC ASSESSMENTS

Plasma PK samples will be collected 4 hours post-dose on Day 1, Week 24, and Week 48 of the Treatment Period, for determination of maximum plasma concentrations (approximate C_{max}) of lademirsen (SAR339375), RG0005, and SUM. In addition, pre-dose plasma PK samples will be collected (up to 4 hours before dose administration) on Day 1 and Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 for determination of minimum plasma concentrations (C_{trough}) of SUM (see Table 1). No PK samples will be withdrawn on Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 if injection is not

administered. In case visit is performed without injection administered, only pre-dose PK sample will be withdrawn. Time and date of PK sampling, as well as the date of the last prior administration of study drug should be recorded in the eCRF.

A manual for blood sampling, collection, processing, and shipment will be provided.

6.6 DISPOSITION OF SAMPLES AFTER STUDY COMPLETION

Collected blood and urine samples (except PK and ADA samples) may be stored and used in the future for the discovery, analysis, verification and/or validation of other biomarkers or tests for renal disease. The samples will be kept for a prolonged period of time (eg, up to 5 years). Each sample will be identified by its barcode number and will not directly identify the subject on the label. Consent from the subject to store the samples will be requested, and subjects may elect to opt out of prolonged sample storage at any time by indicating so in the ICF. PK samples will be disposed of following completion of CSR. ADA samples may be disposed of following completion of CSR or may be kept for additional ADA characterization and/or method development, if warranted based on the ADA data obtained in this study.

For study conduct in China, see Section 10.5.2.3.

7 STATISTICAL ANALYSIS

7.1 ENDPOINTS

7.1.1 Efficacy endpoints

- Annualized change in estimated glomerular filtration rate (eGFR) from baseline during the placebo-controlled treatment period
- Absolute and percentage change in eGFR values from baseline at Week 24 and 48
- Number and proportion of subjects who reach ESRD as defined by an eGFR ≤15 mL/min/1.73 m^2 or initiation of hemodialysis or renal transplantation during the placebo-controlled treatment period
- Absolute and percent change in eGFR values from baseline at Week 96
- Proportion of subjects with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% reduction at Week 24, 48 and 96

7.1.2 Safety endpoints

- Incidence and severity of treatment-emergent AEs and serious adverse events (SAEs)
- Observed values and changes from baseline in clinical laboratory parameters (eg, hematology, chemistry, complement, and urinalysis)
- Observed values and changes from baseline in vital signs
- Observed changes from baseline in 12-lead ECG
- Observed changes from baseline in physical examinations
- Incidence and titer of ADAs
- Association of AEs with ADAs

7.1.3 Pharmacodynamic endpoints

- Changes in circulating miR-21 at Weeks 24, 48, and 96
- Change in renal injury and function biomarkers from baseline at Weeks 24, 48, and 96:
  - In blood only: BUN;
  - In urine only: protein/creatinine ratio, albumin/creatinine ratio, and EGF;
  - In both blood and urine: creatinine, Cystatin C, TGF-β, and NGAL.

7.1.4 Exploratory endpoints

- Changes in exploratory biomarkers, which may include but are not necessarily limited to:
  - In blood only: microRNAs (miRs) other than miR-21

- In both blood and urine: β-2 microglobulin and CTGF
- In urine only: KIM-1 and calbindin-D28k

- Please see Section 10.5.2.1.2 for study conduct in China.

7.1.5 Pharmacokinetic endpoint

- Plasma concentrations of lademirsen (SAR339375), RG0005, and SUM in C_{max} samples and SUM only in C_{trough} samples.

7.2 STATISTICAL METHODS AND ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the subject populations to be included in the analyses. This section is a summary of the planned primary and secondary analyses.

7.2.1 Determination of sample size

An approximate 45 total subjects will be randomized in 2:1 ratio to lademirsen (SAR339375) versus placebo. The sample size will provide approximately 75% power to detect a reduced rate of decline of 5 mL/min/1.73 m^2/year (~50% reduction) in eGFR annualized rate under lademirsen (SAR339375) treatment, in comparison to placebo.

Power calculations were based on simulations. The following model parameters were obtained from preliminary analysis of the ATHENA Natural History Study (OBS16374) data:

- Average linear decline in eGFR of 10 mL/min/1.73 m^2/year in placebo arm
- Standard deviation (SD) for the residual error of eGFR of [redacted] mL/min/1.73 m^2 and SD for random effect of slope to be [redacted] mL/min/1.73 m^2/year
- Mean and SD for intercept to be [redacted] mL/min/1.73 m^2 and [redacted] mL/min/1.73 m^2, respectively

In addition, power calculations were based on a success criterion defined in Section 7.2.5 and a 10% dropout rate was assumed.

7.2.2 Analysis populations

The **Intent-to-Treat (ITT) Population** will consist of all randomized subjects analyzed according to the treatment group allocated by randomization. The ITT Population will be the primary efficacy analysis population.

The **Safety Population** will consist of all subjects who receive at least one dose or partial of a dose of the IMP, analyzed according to the treatment actually received.

The **PK Population** will consist of all subjects who receive at least one dose of the IMP and have at least one post-dose PK sample to determine plasma concentrations of lademirsen (SAR339375).

7.2.3 Demographic and baseline characteristics

Demographics will be presented using descriptive statistics (eg, mean, standard deviation, median, and range for continuous variables; number and percentage of subjects for categorical variables). No hypothesis tests will be performed on demographic and baseline characteristics.

7.2.4 Safety analysis

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the Safety Population. The baseline value is defined generally as the last available value before randomization. The treatment-emergent adverse event (TEAE) period is defined as the time between the first administration of study medication to the last administration of study medication plus 10 weeks follow up.

Adverse events will be presented by System Organ Class (SOC) and Preferred Term (PT) for each treatment group, the number (n) and percentage (%) of subjects experiencing an AE. The numbers and percentages of subjects with at least one TEAE, treatment-emergent SAE, TEAE leading to death, and TEAE leading to permanent treatment discontinuation will be tabulated by treatment group. In addition, TEAEs will be described according to maxim intensity and relation to the study drug.

- The following deaths summaries will be generated
  Death in nonrandomized subjects or randomized and not treated subjects
- Treatment-emergent AE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of subjects sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT
- AESI will be summarized by treatment group

Results and change from baseline for the laboratory parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of subjects, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The following definitions will be applied to laboratory parameters.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests.

- PCSA criteria will determine which subjects had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such subjects will be the numerator for the on-treatment PCSA percentage.

The proportion of subjects who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided. Vital signs, ECG and physical examinations will be summarized using descriptive statistics.

7.2.5 Efficacy analysis

Estimated GFR will be calculated using the CKD-EPI creatinine equation as described by (32). For French subjects, see Section 10.5.3.

Annualized rate of change in eGFR during the placebo-controlled treatment period will be compared between lademirsen (SAR339375) and placebo using a linear mixed effect model. ATHENA Natural History Study (OBS16374) data will be used as prior information supplementing the placebo arm, using a Bayesian approach.

The model will include eGFR measurements from baseline to Week 48 as response variables, and it will include fix effects of treatment (lademirsen [SAR339375] or placebo), screening eGFR stratification factor, time, and treatment-by-time interaction. In addition, it will include random intercept and random slope for time to account for the between subject variability. Time will be treated as continuous variable based on actual eGFR assessment date relative to the randomization date.

A prior distribution for the slope of the placebo group was determined based on the annualized rate of change in eGFR observed in a subgroup of subjects from ATHENA Natural History Study, who are considered as rapid progressors meeting renal function criteria similar to I 05 in Section 3.2.1. The prior distribution assumes a normal distribution for the slope of eGFR in the placebo group, with a mean of -10 and standard deviation of 2.22. Non-informative priors will be used for other parameters in the model. Efficacy of lademirsen (SAR339375) will be based on the posterior probability that the slope of the lademirsen (SAR339375) group is greater than the slope of the placebo group. A posterior probability of at least 95% will be considered significant.

The primary estimand will be the difference in mean slope of eGFR estimated from baseline to Week 48 in ITT population, regardless of whether or not subjects completed the study period of 48 weeks.

Change and percent change from baseline in eGFR at Week 24 and 48 will be analyzed using mixed effects model with repeated measures (MMRM), based on eGFR measurements up to Week 48.

The number and proportion of subjects who reach ESRD or initiation of hemodialysis or renal transplantation will be summarized by treatment group. The proportion will be estimated based on

total subjects in ITT population, as well as the Kaplan-Meier estimate taking consideration of lost to follow-up during the study.

Efficacy endpoints that include data from the open-label extension period will be summarized using descriptive statistics.

Exploratory analyses will be described in the statistical analysis plan finalized before database lock.

7.2.6 Other analyses

PK, pharmacodynamic, and exploratory biomarker analyses (see Section 10.5.2.2 for study conduct in China) will be described in the statistical analysis plan finalized before database lock. Measured plasma concentrations (observed PK parameters C_{max} and C_{trough}) for lademirsen (SAR339375), RG0005, and SUM (as applicable) will be summarized using descriptive statistics (eg, mean, standard deviation (SD), median, min-max, and coefficient of variation [%CV].

The incidence and titer of ADA will be provided by treatment groups. Association between ADA status and safety may be explored.

[redacted]

8 DATA MANAGEMENT

8.1 DATA HANDLING

Data will be collected by means of eCRFs. The eCRF must be kept current to reflect subject status during the course of the study. A subject identification number will be used to identify the subject. Completion instructions will be provided.

The study will use an Internet-Based Remote Data Entry System or electronic data capture (EDC) system to collect the clinical trial data at the investigational sites. The system complies with 21 Code of Federal Regulations (CFR) Part 11 and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP). Queries are generally sent to the investigational site using an electronic data query system that provides an automatic audit trail of the corrections made by designated Investigator staff. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

Source documents are to be retained to enable a reconstruction and evaluation of the trial. No original observations will be entered directly into the computerized system without source documentation. Laboratory data will be processed centrally.

Access to the EDC is controlled with user ID and password and can only be granted to appropriately trained users. Different types of users have different privileges assigned in the EDC system. A user access list is maintained throughout the study.

The Investigator will receive subject data for archiving at the investigational site following database lock.

8.2 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator and institutions involved in this study will agree to allow study monitors from the Sponsor or its designee(s) direct access to all source data, CRFs, and documents, including a subject's complete medical record if necessary. Access must also be granted to authorized auditors, IRB/IEC reviewers, and all applicable regulatory bodies as necessary.

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

8.3 PROTECTION OF PERSONAL DATA

The completion of the study involves the collection and processing of personal data. All processing of personal data at the clinic and by the Sponsor must be carried out in accordance with national legislation concerning the protection of personal data.

The Investigator must ensure that the subject's privacy is maintained. On the CRF or other documents submitted to the Sponsor, subjects will be identified by a subject identification number only. Documents that are not submitted to the Sponsor (eg, signed ICFs) should be kept in a strictly confidential file by the Investigator.

As part of the required content of the ICF, subjects will be informed that their records may be reviewed by the Sponsor or its designee and by regulatory agencies. Should access to medical records require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

8.4 CODING DICTIONARIES

Concomitant medications entered into the database will be coded using the most current World Health Organization Drug Dictionary, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

8.5 DATABASE MANAGEMENT AND QUALITY CONTROL

Data queries will be reviewed by site and by data type to highlight any data issues that may be addressed through additional training or enhancements to the data validation programs.

A formal quality control review will also be conducted prior to database lock.

Any required changes to the database design and programming will be managed through a detailed change control process.

9 STUDY MANAGEMENT/PROCEDURES AND INSTRUCTIONS

9.1 SAFETY-RELATED PROCEDURES

9.1.1 Rapid notification on serious adverse events

All AEs that meet any seriousness criteria and AESI must be reported within 24 hours of awareness of the AE.

SAEs and complementary report forms will be reported via eCRF; any additional information will be reported to the contact address on the Sponsor Contact List.

The photocopy of all examinations carried out and the dates on which these examinations were performed should be reported to the representative of the monitoring team (refer to the Sponsor Contact List). Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

Do not delay reporting SAEs. Investigators should not wait to receive additional information to fully document the event before reporting the SAE. The SAE report should provide the known information at the time of awareness that an SAE has occurred. A follow-up report should be sent when additional details are known.

All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, subject status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to further document within the week (7 days) following initial notification any SAE that is fatal or life threatening.

A back-up plan is used (using paper flow) when the eCRF system does not work.

9.1.2 Dosing deviations

Over- or under-dosing are considered protocol deviations. The Investigator must notify Genzyme Corporation within 24 hours of any occurrence of overdose with study drug by telephone and by faxing/emailing a completed Protocol Deviation Form.

Symptomatic overdose (serious or non-serious) with IMP: In case of accidental or intentional overdose with the study treatment, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.

Overdose is defined as increase of at least 30% above the intended dose at each administration or any two doses separated by <5 days.

9.2 REGULATORY ISSUES, ETHICS, AND GOOD CLINICAL PRACTICE

9.2.1 Regulatory guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki in the version of 1996 and the applicable amendments, and/or all relevant federal regulations, as set forth in Parts 50, 54, 56 of Title 21 of the CFR, in compliance with GCP guidelines, and as per all applicable local regulatory guidelines and Directive of the European Parliament, guidelines set out in Volume 10 of the publication "The rules governing medicinal products in the European Union", and other applicable European Medicines Agency regulations.

9.2.2 Ethical review

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

9.2.3 Informed consent

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative (defined as an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial) and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.6.

9.2.4 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki in the version of 1996 and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

9.2.5 Sponsor obligation

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

The Sponsor or its designee (eg, contract research organization [CRO]) will provide protocol training to the site study personnel, as appropriate. Clinical monitors will conduct site visits, as

needed, to ensure the site procedures are being carried out in accordance with the protocol and GCP. Throughout the study period, the clinical monitor will be available to address any issues that may arise. This availability includes access by phone, fax, and e-mail.

Injury in subjects possibly arising from participating in this trial is covered by the liability insurance of the Investigator or Sponsor. This insurance provides coverage for damage to the subjects through injury or death caused by the trial.

The Investigator, the clinical site pharmacist, or other personnel allowed to store and dispense lademirsen (SAR339375) will be responsible for ensuring that the lademirsen (SAR339375) used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All lademirsen (SAR339375) shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of lademirsen (SAR339375) issued and returned is maintained.

Any quality issue noticed with the receipt or use of lademirsen (SAR339375) provided by the Sponsor (deficiency in condition, packaging, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor, who will initiate a complaint procedure (see Section 9.2.7).

A potential defect in the quality of lademirsen (SAR339375) provided by the Sponsor may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall lademirsen (SAR339375) and eliminate potential hazards.

Under no circumstances will the Investigator supply lademirsen (SAR339375) provided by the Sponsor to a third party, allow the lademirsen (SAR339375) provided by the Sponsor to be used other than as directed by this clinical trial protocol, or dispose of lademirsen (SAR339375) provided by the Sponsor in any other manner.

9.2.6 Principal Investigator

The Principal Investigator has the overall responsibility for the conduct and compliance of this clinical trial according to this protocol and GCP.

Investigators and other key personnel shall provide curriculum vitae or equivalent that will confirm their suitability for the clinical study. All Investigators and key personnel should be listed together with their responsibilities in the study on a signature and delegation log.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

9.2.7 Guidelines for reporting product complaints (lademirsen [SAR339375])

Any defect in the lademirsen (SAR339375) must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

9.3 ADMINISTRATIVE PROCEDURES

9.3.1 Protocol amendment and protocol deviations

Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IECs and Regulatory Authorities for information only. The Sponsor (or designee) will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

Protocol Deviations

Should protocol deviations that affect a subject's safety occur, the Sponsor must be informed as soon as possible. Protocol deviations will be included in the Clinical Study Report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

9.3.2 Monitoring procedures

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Before the study start, during the initiation visit, a Sponsor representative will review the protocol and the eCRF with the Investigator(s) and their staff.

During the study, monitoring visits will be made at appropriate times. Clinical monitors will monitor the site regularly to check the completeness of subject records, the accuracy of entries on the eCRF, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the clinical monitor during these visits.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables will be checked. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

9.3.3 Study documentation, confidentiality, and records retention

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.3.4 Data quality control and quality assurance

9.3.4.1 Data handling

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

9.3.5 Audits and inspections

Periodically, the Sponsor or its authorized representatives audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. A regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor, or its designee, immediately if contacted by a regulatory agency, an IEC or an IRB about an inspection.

9.3.6 Financing and insurance

Prior to the commencement of the study, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

9.3.7 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.3.8 Dissemination of clinical study data

The Sponsor shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include www.clinicaltrials.gov, www.clinicaltrialregister.eu, and www.sanofi.com, as well as some national registries.

In addition, results from clinical trials in subjects are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property.

For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to www.clinicalstudydatarequest.com.

Individual subject data and supporting clinical documents are available for request at www.clinicalstudydatarequest.com. While making information available we continue to protect the privacy of subjects in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: www.clinicalstudydatarequest.com.

9.3.9 Data protection

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the Global Data Protection Regulation (GDPR).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subject race will be collected in this study to calculate eGFR (for study conducted in France, see Section 10.5.3). Subject ethnicity will also be collected in this study, where permitted by local regulations, as a requirement for some regulatory agencies (eg, in the African American population for the FDA in the US, or Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

9.3.10 Data quality assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.3.11 Source documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

9.3.12 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio,
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines,
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator,
  - Total number of subjects included earlier than expected.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

- An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (eg, not related to progression of underlying disease):
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

A) Results in death

B) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

C) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

E) Is a congenital anomaly/birth defect

F) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. **However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to the Sponsor's representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found on the Sponsor Contact List.

SAE reporting via paper CRF (if eCRF is not available)

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the Sponsor Contact List.

10.2 APPENDIX 2: CLINICAL LABORATORY

The tests detailed in Table 7 will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results and normal ranges must be entered into the CRF.

- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 3.2.1 and Section 3.2.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 - Protocol required safety laboratory assessments

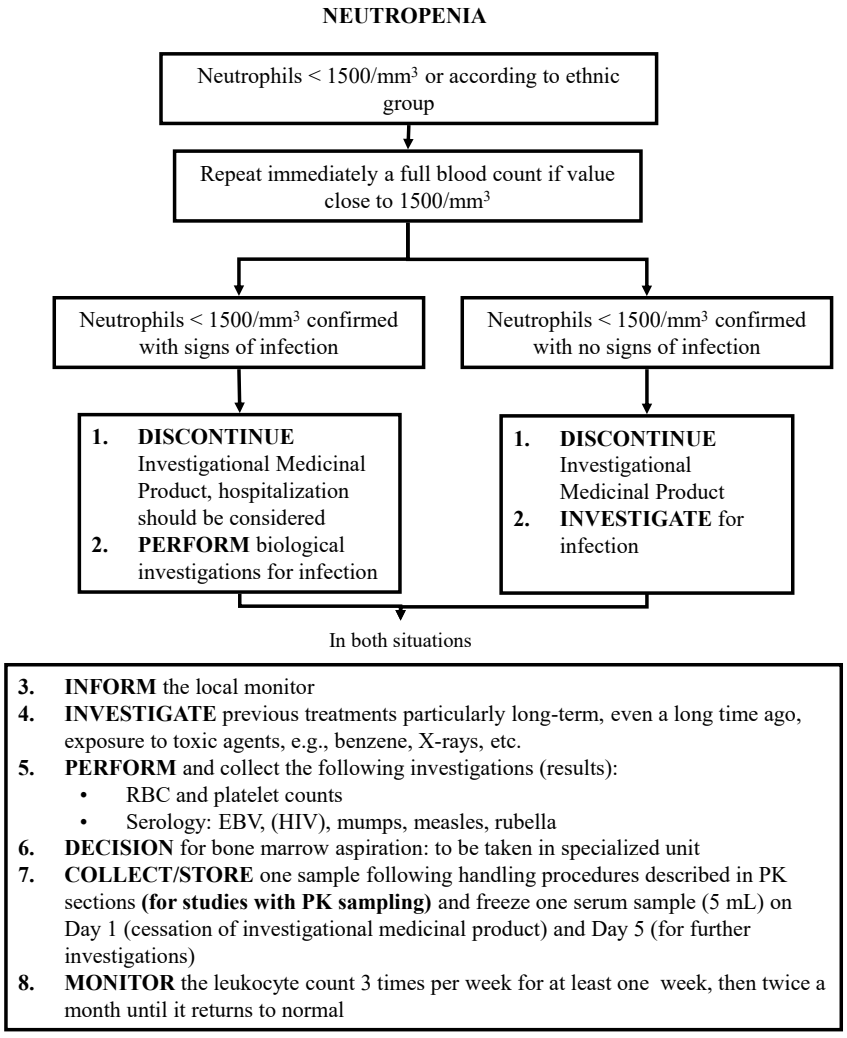
Laboratory assessments	Parameters
Hematology	To include hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with 5-part differential count, and total red blood cell count.
Clinical chemistry	To include creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total and direct bilirubin, ALT, AST, alkaline phosphatase, GGT, lactate dehydrogenase, sodium, potassium, chloride, bicarbonate, calcium, iron, phosphate, total cholesterol, triglycerides, HDL, LDL, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and fibrinogen.
Routine urinalysis	To include specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen, and bilirubin. If specific gravity, PH, glucose, ketones, nitrate, leukocyte esterase, urobilinogen, and bilirubin parameters on the dipstick are abnormal, the investigation will be done by the Investigator as per local practice.
Other tests	Clinical laboratory testing at Screening Visit 1 will include hepatitis screen covering HBs Ag, hepatitis B surface antibody (HBs Ab), HBc Ab, hepatitis C virus antibodies (HCV Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (negative) and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the Investigator believes the subject is a false positive, or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the Investigator believes the subject is a false positive. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 APPENDIX 3: SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

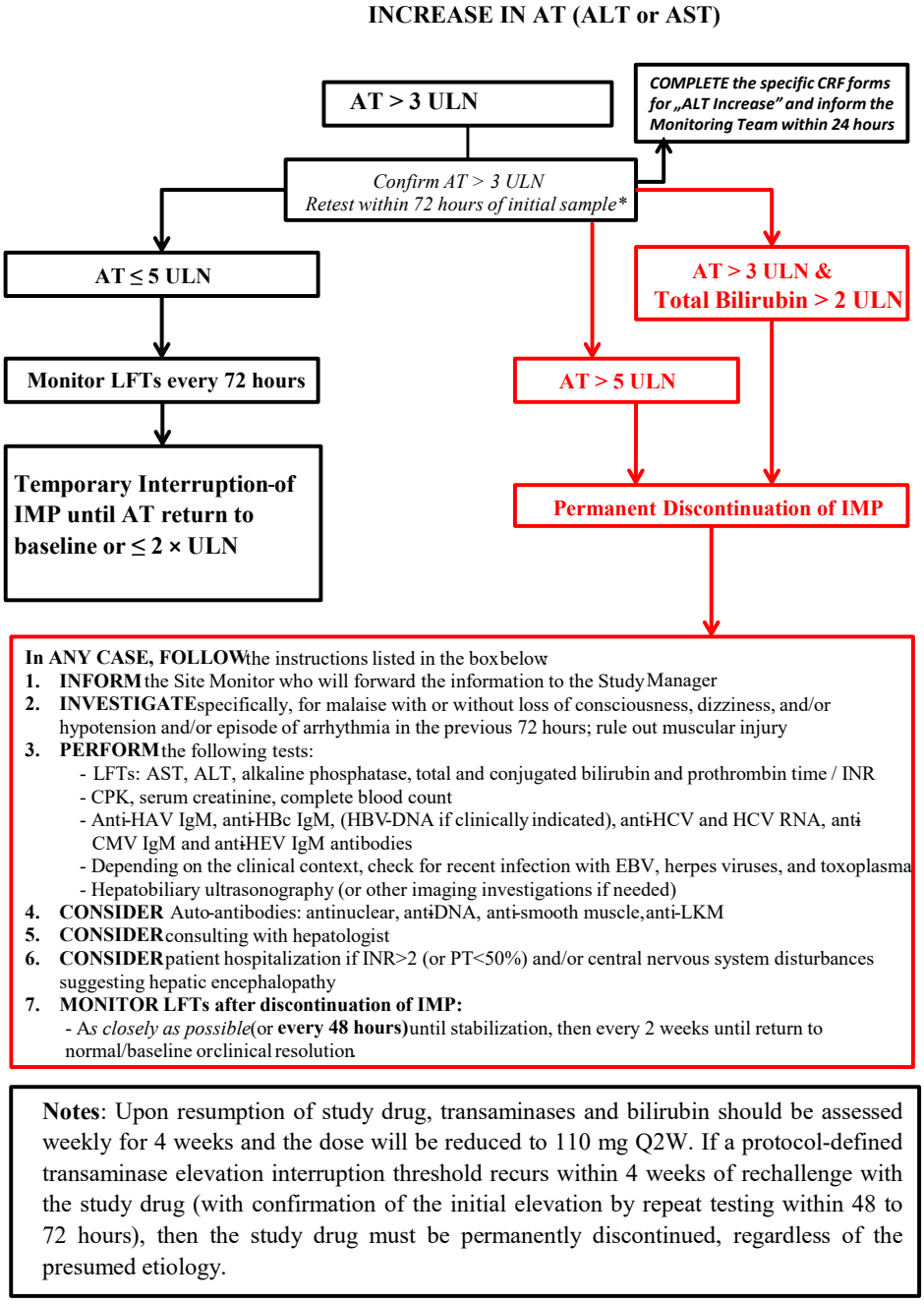
10.3.1 Neutropenia



Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.1 is met.

10.3.2 Abnormal liver function



"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 10.1 for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

COLLECTION OF PREGNANCY INFORMATION:

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive lademirsen (SAR339375).
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within [24 hours] of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) are always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 10.1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: COUNTRY-SPECIFIC REQUIREMENTS

10.5.1 Germany

10.5.1.1 Additional details regarding potential risks associated with study participation

More detailed information about the potential risks associated with study participation are provided below. Additional details about the known and expected benefits and risks associated with lademirsen (SAR339375), and the reasonably expected adverse events of lademirsen (SAR339375), may be found in the Investigator's Brochure.

As stated in Section 1.3.1, potential side effects of lademirsen (SAR339375) fall into three broad categories: 1) class effects, 2) nonclinical toxicology findings, and 3) clinical data with lademirsen (SAR339375). Side effects observed with other oligonucleotide drugs include reductions in complement and platelet counts and abnormalities in liver function tests. Nonclinical toxicity studies have identified reduced albumin, hemoglobin, other red blood cell (RBC) parameters, and platelets; activation of the alternative complement pathway; prolongation of activated partial thromboplastin time (aPTT), and weight loss as side effects. In the RG012-05 Phase 1 multiple ascending dose study a Grade 1 thrombocytopenia AE occurred in a single subject which spontaneously resolved while the subject continued to receive lademirsen (SAR339375). Injection site reactions observed in both the single ascending dose and multiple ascending studies were generally mild and infrequently moderate and did not lead to discontinuation of study drug.

10.5.1.1.1 Immune system effects

Chronic administration of lademirsen (SAR339375) was associated with dose-related pro-inflammatory effects in both mice and monkeys, as expected for this drug class. Findings included 1) decreased platelet counts (as discussed in IB Section 7.1.3), 2) increased serum globulin concentrations, 3) changes in lymphoid organ weight, 4) infiltration of histiocytes/mononuclear cells/lymphocytes into tissues, and/or 5) lymphoid tissues changes such as hematopoiesis, white pulp development in spleen, germinal center hyperplasia, decreased cellularity in spleen and lymph nodes, sinus plasmacytosis in lymph nodes, and/or decreased cortical cellularity in thymus.

However, oligonucleotide-related complement activation is considered to be species specific and not translatable to humans. The likelihood of complement activation by lademirsen (SAR339375) and/or its active N-1 metabolite (RG0005) in clinical trials is low because the plasma SUM (SAR339375 + RG0005) C_{max} at 110 mg QW (Study RG012-05) was 2.27 µg/mL, which is substantially lower than the plasma concentrations (≥~26 µg/mL) required for complement activation in monkeys. Furthermore, humans are less sensitive to oligonucleotide-related complement activation than monkeys (Shen et al, 2014; listed in Section 10.5.1.1.5).

10.5.1.1.2 Injection site effects

Lademirsen (SAR339375)-related injection site observations seen in a few 100 and 300 mg/kg/week male mice included hair loss and/or skin scab/crust of the back, neck, shoulder,

or injection (dose) site. In monkeys in the 13- and 39-week studies, lademirsen (SAR339375)-related changes at the injection site were observed in a few 30 and 100 mg/kg/week animals (discoloration, erythema, scab/crust, and lump/swollen) and typically occurred after the first dose and/or were transient. Microscopically in the 39-week study, epidermal hyperplasia, fibroplasia, mononuclear/mixed cell infiltrates, and SC hemorrhage were observed at injection sites in test article-treatment monkeys.

In addition to the nonclinical findings, mild ISRs occurred commonly with lademirsen (SAR339375) in clinical studies; 43% and 46% of subjects in the healthy volunteer studies RG012-02 and RG012-05, respectively, experienced mild ISRs. Moderate ISRs occurred in 30% and 21% of subjects in RG012-02 and RG012-05 studies, respectively. In the PDY16327 (RG012-06) study, conducted in patients with Alport syndrome, all patients reported mild and/or moderate ISRs during the study. No severe ISRs have been reported in the clinical studies.

10.5.1.1.3 Anti-drug antibody effects

Anti-drug antibodies were evaluated in the 39-week monkey study. In all lademirsen (SAR339375)-treatment groups (ie, 3 to 100 mg/kg/week), confirmed positive ADA responses were observed with the time of onset in animals ranging from 2-9 months after the start of treatment. ADAs were also present in the recovery phase. ADA responses generally resulted in highly elevated (several-fold) plasma trough concentrations but had no meaningful impact on plasma C_{max} and AUC values for lademirsen (SAR339375), RG0005, and SUM, except in animals with titers of 12 800 or higher. In these animals (titers ≥12 800) several-fold increases in C_{max} and AUC were also observed, in addition to increases in C_{trough}. Although ADAs correlated with increases in serum IgG, IgM, and gamma globulin concentrations, microscopic examination did not indicate any changes indicative of antibody-mediated effects. However, high ADA titers (>100 000) were observed in five of the eight monkeys with glomerulopathy; the causal relationship is unclear, particularly since IHC staining suggests a mechanism mediated by complement activation rather than by immune complex deposition.

The results of ADA testing in healthy volunteers (study RG012-05) show a low incidence of confirmed antibody responses to lademirsen (SAR339375) treatment that are transient. In patients with Alport syndrome (study PDY16327), 2 of 4 subjects developed low titers of ADAs (but without associated AEs suggestive of systemic hypersensitivity reactions). Due to the limited number of subjects in the PDY16327 study, a potential association between ADAs and ISR could not be established. ADAs have also been reported in clinical trials with other oligonucleotides. As the presence of high titers of ADAs was associated with changes in the overall exposure of lademirsen (SAR339375) and glomerulopathy in the chronic monkey toxicity study, monitoring of ADA is warranted and is planned for ACT16248.

It is not known whether the ADA observed in 2 of 4 subjects in study PDY16327 were neutralizing antibodies (NAb) or not. However, it is known from literature data that oligonucleotide therapeutics distribute rapidly to intracellular sites of action. Thus, even if an immune response occurred proximal to the site of action, the majority of the targeted drug is likely to be inaccessible to the ADA. Because of this, it is unlikely that the ADA would be able to

bind to enough of the drug to have a clinically relevant neutralizing effect (Stebbins et al, 2019; listed in Section 10.5.1.1.5).

10.5.1.1.4 Drug accumulation effects

Oligonucleotides generally accumulate in liver and kidneys; thus there is a theoretical risk of liver and/or kidney toxicity following repeated administration of oligonucleotide therapeutics. Concentrations of lademirsen (SAR339375), RG0005, and SUM (SAR339375 + RG0005) were measured in mouse liver and kidney (24 h post-dose) following the first and last doses in a 26-week mouse toxicity study (RG012.Tox.004). Accumulation of SUM in mouse liver and kidney at doses of 50 to 300 mg/kg ranged from 3.5 to 5.0-fold (liver) and 1.8 to 2.9-fold (kidney).

10.5.1.1.5 References supporting the additional details regarding potential risks

Shen L, Frazer-Abel A, Reynolds PR, Giclas PC, Chappell A, Pangburn MK, et al. Mechanistic understanding for the greater sensitivity of monkeys to antisense oligonucleotide-mediated complement activation compared with humans. J Pharmacol Exp Ther. 2014;351(3):709-17.

Stebbins CC, Petrillo M, Stevenson LF. Immunogenicity for antisense oligonucleotides: a risk-based assessment. Bioanalysis. 2019 Nov;11(21):1913-6.

10.5.2 China

10.5.2.1 Study objectives and endpoints

10.5.2.1.1 Exploratory objectives

There are no exploratory objectives for Chinese subjects.

The content of this section supersedes the content of Section 2.3 for study conduct in China.

10.5.2.1.2 Pharmacodynamic and exploratory endpoints

No exploratory endpoints will be evaluated for Chinese subjects.

The content of this section supersedes the content of Section 7.1.3 for study conduct in China.

10.5.2.2 Pharmacodynamic assessments and biomarkers

No exploratory biomarkers will be evaluated for Chinese subjects. The following assessments will not be evaluated for Chinese subjects: β2-microglobulin, calbindin-D28k, CTGF, microRNAs (other than miR-21, as listed above), and KIM-1.

The content of this section supersedes the content of Section 6.4 for study conduct in China.

10.5.2.3 Sample storage and disposition of samples after study completion

Plasma/serum samples for storage to support exploratory objectives (listed in Table 1, Section 5.2, and Section 5.4) will not be collected for Chinese subjects.

All residual mandatory samples from Chinese subjects have to be destroyed upon CSR completion, at the latest.

The content of this section supersedes the content of Section 6.6 for study conduct in China.

10.5.3 France

Race will not be collected and will not be used in the eGFR calculation for French subjects. For these subjects, the eGFR will be calculated using the new CKD-EPI creatinine equation (2021) which does not have a race variable (33):

eGFR = $142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female], where Scr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, and min indicates the minimum of Scr/κ and 1 and max indicates the maximum of Scr/κ and 1.

10.6 APPENDIX 6: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency; this agreement must be provided in writing by the Sponsor and will be kept in the Investigator file.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, screening and enrollment may be temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

10.6.1 Informed consent

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs), and the verbal information given to the patient should be documented in the subject's medical record.

10.6.2 Study procedures

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

1. New screenings during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor's agreement is obtained. Rescreening will be permitted when the situation normalizes and only if allowed by local competent authorities and after Sponsor's agreement is obtained.
2. If onsite visits or alternative location (out of subject's home) are not possible, all visits from week 1 (including those planned to be done onsite) will be performed at home by a trained healthcare professional and if allowed by local competent authorities for:
   - Treatment administration
   - Blood sampling for safety (at least hematology, hepatic function panel, coagulation panel) and efficacy assessment (at least serum creatinine for eGFR calculation), and pregnancy test (if applicable)
   - Measuring vital signs
   - Monitoring of ISR, AEs and SAEs

The use of a local laboratory may be allowed for safety follow up in case the central lab cannot be used.

The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment. All data collected remotely will be properly documented in the subject's medical record and the study CRF.

For all assessments which will not be performed remotely, the assessment windows will be extended until subjects may access the site.

If onsite visit and home visit are not possible, a temporary treatment discontinuation may be considered. The Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment.

Contingencies implemented due to emergency will be documented in the subject's medical record.

10.6.3 Temporary discontinuation

A temporary treatment discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency.

Reinitiation of study drug can only occur once the Investigator has determined, according to his/her best judgement, that the study drug did not contribute to the occurrence of the epidemic event (eg, COVID-19).

For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

10.6.4 Statistical analysis

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.7 APPENDIX 7: ABBREVIATIONS

%:	percentage
ACE:	angiotensin-converting enzyme
ACR:	albumin to creatinine ratio
ADAs:	anti-drug antibodies
ADAS:	autosomal dominant Alport syndrome
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANA:	anti-nuclear antibody
aPTT:	activated partial thromboplastin time
ARAS:	autosomal recessive Alport syndrome
ARB:	angiotensin II receptor blocker
AST:	aspartate aminotransferase
AUC:	area under the concentration-time curve
BUN:	blood urea nitrogen
CBC:	complete blood count
CFR:	Code of Federal Regulations
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
COL1A1:	Type I collagen alpha chain gene 1
COL3A1:	Type III collagen alpha chain gene 1
COL4A3/4/5:	Type IV collagen alpha chain gene 1
CONSORT:	Consolidated Standards of Reporting Trials
COVID-19:	coronavirus disease 2019
CRO:	contract research organization
CSR:	clinical study report
CTGF:	connective tissue growth factor
CV:	coefficient of variation
DMC:	Data Monitoring Committee
DTP:	direct to patient
ECG:	electrocardiogram
eCRF:	electronic case report form
EDC:	electronic data capture
EGF:	epidermal growth factor
eGFR:	estimated glomerular filtration rate
ESRD:	end-stage renal disease
ET:	early termination
FDA:	Food and Drug Administration
FSH:	follicle stimulating hormone
GCP:	Good Clinical Practice
GDPR:	Global Data Protection Regulation
GFR:	glomerular filtration rate

GGT:	gamma-glutamyl transferase
GLP:	Good Laboratory Practice
HAV:	hepatitis A virus
HBs Ab:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HCV:	hepatitis C virus
HDL:	high-density lipoprotein
HEENT:	head, ears, eyes, nose, throat
HIPAA:	Health Insurance Portability and Accountability Act
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
hs-CRP:	high-sensitivity C-reactive protein
IA:	interim analysis
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP:	investigational medicinal product
IND:	investigational new drug
INR:	international normalized ratio
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
ISR:	injection site reaction
ITT:	intent-to-treat
KIM-1:	kidney injury molecule-1
LDL:	low-density lipoprotein
LLN:	lower limit of normal
MedDRA:	Medical Dictionary for Regulatory Activities
miR:	microRNA
MMRM:	mixed effects model with repeated measures
n:	number
NGAL:	neutrophil gelatinase-associated lipocalin
NHP:	non-human primates
NOAEL:	no-observed-adverse-effect levels
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetic
PPARα:	peroxisome proliferator-activated receptor alpha
PT:	preferred term
Q2W:	every two weeks
QTcF:	Fridericia-corrected QT interval
QW:	every week
RBC:	red blood cell
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous(ly)

SD:	standard deviation
SEC:	Safety Evaluation Committee
SOC:	System Organ Class
SUM:	SAR339375 + RG0005
TEAE:	treatment-emergent adverse event
TGF-β:	transforming growth factor-β
TK:	toxicokinetic
UACR:	urine albumin-to-creatinine
ULN:	upper limit of normal
UPCR:	urine protein-to-creatinine ratio
UUO:	unilateral ureteral obstruction
WBC:	white blood cell
WOCBP:	woman of childbearing potential
XLAS:	X-linked Alport syndrome

10.8 APPENDIX 8: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the names and addresses of the monitoring team's representative.

10.8.1 Amended protocol 11 (10 August 2021)

This amended protocol (amendment 11) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to clarify the action to be taken with study drug dosing for adverse events and injection site reactions, to revise the stopping criteria for study drug dosing, and to revise the definition of adverse events of special interest.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis / Individual Treatment Stopping Criteria AND 3.3.1.1 Individual Treatment Stopping Criteria	The phrase "except for renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis" was added in parenthesis in the first paragraph.	To clarify the action to be taken with study drug dosing for Grade 2 adverse events associated with renal function parameters and considered by the Investigator to be at least possibly related to study drug.

Section # and Name	Description of Change	Brief Rationale
	The following sentence was added to the first paragraph regarding the grading of injection site reactions and the action to be taken for study drug dosing: "Injection site reactions (ISRs) will be graded according to Table 6. Any Grade 2 (except erythema/redness) or Grade 3 ISRs which had not resolved or reached Grade 1 ("Mild", eg, limited tenderness, and/or induration, except erythema/redness) prior to the next dose, would result in a pausing of dosing."	For alignment with the update in Section 4.5.
	The event "eGFR" was added to the parenthesis in the first sentence of the second paragraph.	For clarification.
	In the list of adverse events for which study drug should be discontinued, the third bullet regarding unintended weight loss was revised to increase the threshold for change to ≥20% from baseline. In addition, the fourth bullet regarding estimated glomerular filtration rate and its decline was revised to include a decline of ≥50% from the last measurement, and not from baseline, or confirmed end-stage renal disease.	To reflect that 1) estimated glomerular filtration rate decrease is the expected progression of the underlying disease (as a reminder, change in estimated glomerular filtration rate is the primary efficacy endpoint of this study), and 2) mild or moderate weight loss is an expected manifestation of the underlying disease.
Protocol Synopsis / Study Suspension and Stopping Criteria AND 3.4 Discontinuation of the Study	The phrase "except for ISRs and renal function parameters related to the underlying disease process including eGFR, creatinine, BUN, and urinalysis" was added in parenthesis to the first paragraph.	To align with the revised guidance for study drug dosing with regard to injection site reactions or adverse events associated with renal function parameters.
Protocol Synopsis / Table 1	Schedule of events revised to include 1 day post injection follow-up assessments to be performed on a weekly basis.	For clarification.
	Serum chemistry, lipid panel, and high-sensitivity C-reactive protein assessments included for unscheduled visits.	For consistency with the assessments to be performed at unscheduled visits during the open-label treatment extension period and follow-up period.
Protocol Synopsis / Table 2	Schedule of events revised to (1) remove blood sampling for pharmacokinetic (pre-dose) assessments at unscheduled visits, and (2) include 1 day post injection follow-up assessments to be performed on a weekly basis from Week 48 to Week 96 (corresponding footnote [cc] added to describe purpose/scope of follow-up assessment).	Pharmacokinetic sampling at unscheduled visits removed for consistency with the assessments to be performed during the double-blind, placebo-controlled treatment period. Post injection follow-up assessments added for clarification.

Section # and Name	Description of Change	Brief Rationale
	Blood sampling for complement removed from unscheduled visits.	For consistency with the assessments to be performed at unscheduled visits during the double-blind, placebo-controlled treatment period.
Protocol Synopsis / Table 1 AND Protocol Synopsis / Table 2	Footnote "q" in Table 1 and footnote "i" in Table 2 describing urinalysis parameters revised to the following "Urinalysis: assessment of colour and appearance, and dipstick test for specific gravity, erythrocytes, pH, protein, glucose, ketones, leukocyte esterase, nitrate, bilirubin, and urobilinogen will be done locally. Microscopic examination of urine sediment, microalbuminuria, urine creatinine, and urine protein will be a laboratory test."	To clarify which urinalysis parameters will be performed locally (and with a dipstick test) and which will be performed by central laboratory.
1.3.1 Potential Risks	Section 1.3.1 title and content revised to describe both identified and potential risks associated with lademirsen (in accordance with this change, Section 1.3 title revised to "Risks and Benefits").	For alignment with the language in the current Investigator's Brochure.
4.5 Dose Reduction	The fourth paragraph was revised to the following "Any Grade 2 (except erythema/redness) or Grade 3 ISRs which had not resolved or reached Grade 1 ("Mild", eg, limited tenderness, and/or induration, except erythema/redness) prior to the next dose, would result in a pausing of dosing."	To clarify the grading of injection site reactions and the action to be taken with study drug dosing for Grade 2 and Grade 3 injection site reactions.
4.6 Randomization Code Breaking During the Study	The first paragraph was revised to the following "If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a subject's treatment assignment unless this could delay emergency treatment for the subject."	To align with standardized template language.
	Minor revisions were made to the third paragraph as follows "If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence."	
	Second sentence of final paragraph revised to include "then the subject will be withdrawn from the treatment".	For clarification.

Section # and Name	Description of Change	Brief Rationale
4.8 Prior and Concomitant Medications	Statement regarding coronavirus disease 2019 vaccination added: "Vaccination for coronavirus disease 2019 (COVID-19) will not have an impact on subject enrollment or study drug treatment. No wash-out period is required between vaccination and initiation of study drug. Nevertheless, it is preferred that the COVID-19 vaccination and the study drug injection are separated by at least 48 hours to allow an adequate evaluation of potential AEs."	To clarify that coronavirus disease 2019 vaccination is not deemed to impact study conduct.
6.2.1 Adverse Events	Phrase "Grade ≥2" removed from description of adverse events of special interest in parenthesis.	For alignment with revised definition of adverse events of special interest added in Sections 6.2.2 and 6.2.3.
6.2.2 Adverse Event of Special Interest	For other specific adverse events of special interest to be closely monitored, text updated to include all Grade ≥2 events listed in Table 3 (except for estimated glomerular filtration rate) and Grade ≥3 events of estimated glomerular filtration rate.	To reflect that adverse events of special interest subject to close monitoring have been revised to include all Grade ≥2 events (as per Table 3), except for estimated glomerular filtration rate, and Grade ≥3 events of estimated glomerular filtration rate. Estimated glomerular filtration rate decrease is the expected progression of the underlying disease (as a reminder, change in estimated glomerular filtration rate is the primary efficacy endpoint of this study).
6.2.3 Adverse Events Grading	Table 3 revised as follows: Unintentional weight loss parameter removed Footnote a: deleted Footnote b: renumbered to footnote a.	Weight loss observed in animal studies occurred with a substantially higher dose of lademirsen than that used in the current study. Significant unintentional weight loss has not been observed in any clinical studies to date.
6.2.4 Adverse Event Outcome	Description of adverse event outcomes revised from "recovered" and "recovering", to "recovered/resolved" and "recovering/resolving".	For alignment with the adverse event outcome definitions presented in Table 5.
6.2.7 Procedures in Case of Pregnancy AND 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	For female subjects who become pregnant, the phrase "occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age" was added to the description of spontaneous abortion.	To clarify the definition of spontaneous abortion and to add/define the term stillbirth.
6.2.14 Laboratory Assessments	The statement "except for BUN, UPCR, UACR, creatinine and Cystatin C" was added in parenthesis to the fourth paragraph.	For clarification.

Section # and Name	Description of Change	Brief Rationale
7.2.5 Efficacy Analysis	Third paragraph revised to include screening eGFR as a stratification factor in the linear mixed effect modelling of annualized rate of change in eGFR during the placebo-controlled treatment period.	To reflect the stratification factors included, as standard, in this statistical model.
	Sentence stating "However, those data collected after the study drug discontinuation or the initiation of non-study treatment (eg, renal transplantation) will not be included." deleted from fifth paragraph.	For alignment with Regulatory Agency guidance for reporting primary estimands.
7.2.7 Interim Analysis	The numerical value assigned as the pre-specified threshold for declaring study futility at the interim analysis was removed ("eg, 30%" was removed from the first sentence of the fourth paragraph).	This information will be specified in the statistical analysis plan.
9.1.1 Rapid Notification on Serious Adverse Events	Study procedures revised to state that 1) any serious adverse events or adverse events of special interest must be reported within 24 hours of awareness of the adverse event, and 2) to specify the location of the study team contact list.	For clarification.
9.3.2 Monitoring Procedures	Text revised to remove references to site visits and on-site monitoring.	Procedures revised to permit remote monitoring of study sites.
9.3.9 Data Protection	New paragraph added: "Subject race will be collected in this study to calculate eGFR. Subject ethnicity will also be collected in this study, where permitted by local regulations, as a requirement for some regulatory agencies (eg, in the African American population for the FDA in the US, or Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)."	To specify that subject race and ethnicity will be collected during the study, and to clarify the rationale for collecting these data.
10.1 Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Procedures revised to specify the location of the study team contact list for reporting serious adverse event (either via electronic data collection tool or via paper CRF).	For clarification.
10.5.2.3 Sample Storage and Disposition of Samples after Study Completion	Procedures for storing samples from Chinese subjects revised to the following "All residual mandatory samples from Chinese subjects have to be destroyed upon CSR completion, at the latest."	To clarify that samples from Chinese subjects must be destroyed by the time of clinical study report completion.
10.8.1 Amended Protocol 10 (22 January 2021)	New section created to contain the prior amendment's history, and subsequent sections renumbered accordingly. Minor formatting updates applied.	To conform with the usual process for amendment history.

In addition, minor editorial, stylistic, and/or grammatical changes were made throughout this document.

10.8.2 Amended protocol 10 (22 January 2021)

This amended protocol (amendment 10) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

To implement updated guidance for management of liver function abnormalities, and other clarifications, following Regulatory Agency feedback.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes	The section is updated to reflect Amended Protocol 10.	This action is taken to conform with the usual Sanofi process for amended protocols.
Protocol Synopsis / Study Design and Methodology	The language regarding the participation of subjects in the open-label treatment extension period was revised by replacing "all subjects will have the opportunity to enter the 48-week open-label extension period" with "all subjects will enter the 48-week open-label extension period".	Clarification due to Regulatory Agency feedback since the open-label treatment extension period is a required part of the study.
Protocol Synopsis / Double-Blind, Placebo-Controlled Treatment Period	The second paragraph regarding home injections was reworded to match the language of Section 3.1 (Overall Study Design/Double-Blind, Placebo-Controlled Treatment Period).	Clarification for consistent presentation between sections.
Protocol Synopsis / Open-Label Treatment Extension Period	As above, the text in the first paragraph "will be eligible to roll over into" was replaced by "will be rolled over into".	Clarification due to Regulatory Agency feedback since the open-label treatment extension period is a required part of the study.
	The second paragraph in the prior version of the protocol regarding subjects who complete the double-blind treatment period but who will not enter the open-label treatment extension period was removed. In addition, the last paragraph in the prior version regarding those who did not complete the double-blind period and early terminate was deleted.	For clarification and simplification regarding when patients proceed to the follow-up period.
Protocol Synopsis / Follow-up Period	In the second paragraph: the phrase "or subjects who discontinue early and have completed the early termination visit" was added. In addition, "Week 48" and "of the double-blind part" were removed from the parentheses.	For clarification regarding the procedure for advancing to the follow-up period.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis / Dose Reduction	The phrase "or increase in aminotransferases" was added in the first sentence of the second paragraph	In accordance with the new guidance for management of elevated aminotransferases (Section 10.3.2) and the update in Section 4.5.
Protocol Synopsis / Individual Treatment Stopping Criteria And 3.3.1.1 Individual treatment stopping criteria	In the list of situations in which study drug should be discontinued, the second bullet regarding liver function abnormality was revised to include specific thresholds for ALT, AST, and total bilirubin.	Added for further clarification in accordance with the new guidance in Section 10.3.2, per Regulatory Agency request.
Protocol Synopsis / Pharmacokinetic Assessment	The words "lademirsen (SAR339375), RG0005, and" were added to the first sentence describing which C_{max} concentrations will be determined.	For consistency with Section 6.5 and other sections of the protocol.
Protocol Synopsis / Table 1	In footnotes b & e, the language regarding subjects being "eligible" and "choosing" to roll over to the open-label treatment extension period was revised to say that the subjects "will be rolled" and "will enter" into the open-label treatment extension period, respectively.	Clarification due to Regulatory Agency feedback since the open-label treatment extension period is a required part of the study.
	In footnote d: the second sentence was simplified to say for subjects who "discontinue early …", and the timing of follow-up week 2 was clarified.	For clarification.
Protocol Synopsis / Tables 1 and 2	The last sentence regarding the timeframe of the ET visit was added to footnotes c of Table 1 and b of Table 2.	For clarification.
	Footnotes t of Table 1 (double-blind period schedule of events) and k of Table 2 (open-label treatment extension period schedule of events) were updated with a sentence containing a link to Section 10.3.2.	For guidance in the event of elevated aminotransferases.
Protocol Synopsis / Table 2	The tick marks for the hearing assessment and exploratory biomarkers at USV in the schedule of events were removed.	These assessments at USV should have been removed in the prior amendment (consistent with Table 1); this action represents a correction of the schedule of events table only.
	"ET visit" was added in footnote c.	For clarification on the timing of follow-up Week 2.
1.2.2 Justification of study design And 3.1 Overall Study Design And 5.3 Open-Label Extension Treatment Period	Similar changes to those made in the Protocol Synopsis/ Study design and Methodology and Protocol synopsis/ Open-label treatment extension period sections were made regarding the language for participation of subjects in the open-label treatment extension period.	Clarification due to Regulatory Agency feedback since the open-label treatment extension period is a required part of the study.

Section # and Name	Description of Change	Brief Rationale
3.1 Overall Study Design	Under the subsection "Double-Blind, Placebo-Controlled Treatment Period": the phrase "or at an alternate location" was added to the third paragraph.	Clarification for consistency with the Protocol Synopsis.
	Under the subsection "Open-Label Treatment Extension Period": The third paragraph in the prior version of the protocol (regarding subjects who did not complete the double-blind treatment period) was removed.	For clarification and simplification regarding when patients proceed to the follow-up period.
	Under the subsection "Open-Label Treatment Extension Period": The phrase "or an alternate location" was added.	Clarification.
	Under the subsection "Dose Reduction": the phrase "or increase in aminotransferases" was added in the first sentence of the second paragraph	In accordance with the new guidance for management of elevated aminotransferases (Section 10.3.2) and the update in Section 4.5.
	Under the subsection "Dose Reduction": the words "Medical Manager" were added in the first paragraph.	For clarification and consistency with Section 4.5.
	Under the "Follow-up Period" subsection: "Week 48" was removed from the last paragraph.	For clarification since the open-label treatment extension period is a required part of the study.
4.5 Dose reduction	The text "or increase in aminotransferases" was added to the following sentence in the first paragraph: "The most recent subject's platelet counts, but not older than 10 days, will be reviewed by the Investigator/physician before drug administration. Following the resolution of a Grade 2 AE (return to normal or ≤ Grade 1 for AE) that does not otherwise trigger a stopping rule (see Section 3.4), …". In addition, the word "transaminase" was removed from the first sentence of the third paragraph, and a sentence with link to Section 10.3.2 was added in the third paragraph for further information about aminotransferases.	In accordance with the new guidance for management of elevated aminotransferases (Section 10.3.2).
	The abbreviation "AE" was removed from the second sentence in the paragraph beginning "Injection Site Reactions (ISRs)…".	Minor clarification that the paragraph is about ISRs, and not other adverse events.
5.4 Early termination	The clarification "(double-blind placebo or open-label extension periods)" was added to the first sentence.	Clarification of the treatment period.

Section # and Name	Description of Change	Brief Rationale
5.5 Follow-up period	The first sentence was revised to refer to subjects "who discontinue early and have completed the early termination visit" instead of referring to subjects who complete the double-blind period but who do not continue to the open-label period. In addition, "Week 48" and "of the double-blind part" were removed from the parenthesis in the first paragraph.	For clarification regarding the procedure for advancing to the follow-up period.
6.2.2 Adverse event of special interest And 9.1.2 Dosing deviations	The definition of overdose was updated: the timeframe between two doses was revised from ≤5 days to <5 days.	Clarification for consistency with the allowed visit window (5-9 days).
6.2.3 Adverse events grading	Footnote b was added to Table 3.	For guidance in the event of elevated aminotransferases.
6.2.8 Regulatory reporting requirements for SAEs	The section was retitled from "Sponsor obligation" in the prior version, and all prior content except the 3rd bullet in the current version were removed. The rest of the content was added for the current version.	The deleted information is duplicated in Section 9.2.5 and/or did not align to current Sanofi standard wording.
9.2.5 Sponsor obligation	The first two paragraphs (including sub-bullets) were removed.	The deleted information was duplicated in Section 6.2.8, which was updated as described above.
10.3 Appendix 3: Safety: Suggested Actions and Follow-up Assessments	In the sentence following the neutropenia decision tree, the link to Section "10.3" (in Amended Protocol 09) was revised to Section "10.1".	Typographical error in prior version.
	Headers 10.3.1 (Neutropenia) and 10.3.2 (Abnormal liver function) were created.	To organize the content of this appendix.
	In Section 10.3.2 (abnormal liver function), safety guidance was added for the identification, management and follow-up of treatment-emergent abnormal liver function tests.	Due to Regulatory Agency request.
Section 10.8.1 Amended protocol 09 (11 September 2020)	New section is created to contain the prior amendment's history, and subsequent sections are renumbered accordingly. Minor formatting updates are applied.	This action is taken to conform with the usual process for amendment history.

In addition, minor editorial, stylistic, and/or grammatical changes were made throughout this document.

10.8.3 Amended protocol 09 (11 September 2020)

This amended protocol (amendment 09) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to align the protocol globally with country specific requirements applicable to all country participants, to clarify the process of home injection and of subject drug delivery and to provide contingency measurements for regional or national emergency context.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout document	Updated protocol numbering, dates, and headers.	This action is taken to conform with the usual Sanofi process for amended protocols, in accordance with Amended Protocol 09.
	The term “RG456070” is replaced with “SAR339375”.	To align with the change in the product code due to change in Sponsor (Regulus Therapeutics to Sanofi).
Title, title page, and throughout the protocol	Added “Lademirsen” to the Investigational Medicinal Product row and to the occurrences of “SAR339375” throughout the protocol.	Lademirsen is the INN for this compound.
Protocol Amendment Summary of Changes	The section is updated to reflect Amended Protocol 09.	This action is taken to conform with the usual Sanofi process for amended protocols.
Protocol Synopsis - Study Objectives; Section 2.2 Secondary Objectives; and Section 2.3 Exploratory Objectives	The secondary objective related to pharmacodynamic effects is applied globally, and the China-specific reference is removed.	These changes are in line with the changes in the classification of the endpoints (see below for details) and align objectives globally.
	The exploratory objective of renal function assessment is removed.	
Protocol Synopsis - Study Endpoints; and Section 7.1.1 Efficacy endpoints	The endpoints “absolute and percent change in eGFR from baseline at Week 96, and proportion of subjects with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% reduction at Week 24, 48, and 96” are moved from exploratory endpoints to efficacy endpoints and this classification is applied globally.	These changes are in line with the changes in the classification of the endpoints, and regroup these two relevant clinical endpoints with the other efficacy endpoints.
	The reference to the China-specific efficacy endpoints is removed.	These changes are made to align endpoints globally.
Protocol Synopsis - Study Endpoints; and Section 7.1.2 Safety endpoints	The words “treatment-emergent” are added to the first safety endpoint.	These changes are made to better define the AEs to be analyzed.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis - Study Endpoints; Section 7.1.3 Pharmacodynamic endpoints; and Section 7.1.4 Exploratory endpoints	The "Exploratory endpoints: Efficacy, Pharmacodynamic and Biomarker Endpoints" section is split into two separate sections, "Pharmacodynamic Endpoints" and "Exploratory endpoints" (corresponding to the same changes in Sections 7.1.3 and 7.1.4, respectively), in addition to the movement of two endpoints (absolute and percent change in eGFR and reduction in eGFR) to efficacy endpoints. Other changes are made with respect to the endpoints in the initial section, which include: revision of the list of renal biomarkers (KIM-1 and β2-microglobulin removed; EGF and TGF-β added); addition of β2-microglobulin and KIM-1 as exploratory endpoints; removal of EGF and TGF-β from the exploratory endpoints list; and the exploratory "microRNAs" is qualified with "other than miR-21".	These changes are in line with the changes in the classification of endpoints, and align endpoints globally.
Protocol Synopsis - Follow-up Period and Study Duration	The last visit during the follow-up period is revised to occur at Week 10 instead of Week 6, and the link to the UK-specific section is consequently removed. In addition, in the Study Duration section, the link to the Germany-specific section regarding the end of study clarification is removed. Accordingly, the planned length of participation in the study for each subject was revised to say up to approximately "110" weeks.	For the purpose of harmonization, the duration of follow-up and end of study specifications are applied globally.
Protocol Synopsis - Individual Treatment Stopping Criteria; and Section 3.3.1.1 Individual Treatment Stopping Criteria	The sentence "With regard to AEs of interest, study drug…" is revised to "With regard to AEs, study drug…".	For clarification.
Protocol Synopsis - Analysis Populations; and Section 7.2.2 Analysis Populations	The definition of PK Population is revised in Section 7.2.2 and is added to the Protocol Synopsis: the specification "analyzed according to the treatment actually received" is removed, and the sample is clarified as "post-dose".	Only samples from patients who received drug are analyzed, so this specification is not needed. "Post-dose" is added to clarify the timing post-baseline. The definition is missing in the Protocol Synopsis in the prior version.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis - Table 1 (Schedule of events for screening and double-blind, placebo-controlled treatment period and follow-up period)	The visit days at Follow-up Weeks 2, 4, and 10 are revised from Days 14, 28, and 70 to Days 15, 29, and 71 respectively.	For consistency in calculation of study days.
	The last follow-up visit is revised from Week 6 (Day 42) to Week 10 (Day 71), and the UK-specific links and notations in the Table and footnotes contained in the prior version of the protocol are removed.	For the purpose of harmonization, the duration of the post-treatment follow-up period is applied globally.
	The hearing assessment, complement, miR-21, and exploratory biomarkers assessments are removed from the USV.	The aim of the unscheduled visit is to follow up for safety such as abnormal values for parameters (eg, laboratory tests, vital signs) which have an impact on the drug injection continuation; these assessments are not relevant in this regard.
	Footnote n is revised to state that vital signs are collected prior to drug administration throughout the study (except as specified in the footnote).	For clarification.
	Footnote r is clarified to indicate that the full hematology panel is performed at each visit during the follow-up period.	This change is made to align with the updated follow-up visit schedule.
	"urea" is removed from footnote t (regarding serum chemistry).	This assessment is a duplicate with blood urea nitrogen.
	Footnote aa: KIM-1, β2-microglobulin and creatinine are removed, Cystatin C is specified as "urine Cystatin C", and TGF-β and EGF are added.	To align with updates in endpoints. Creatinine removed because it is already among the serum chemistry test.
	Footnote bb: KIM-1 and β2-microglobulin are added, and TGF-β and EGF are removed.	To align with updates in endpoints.
	Footnote jj from the prior version (regarding UK-specificities) is removed.	The duration of the post-treatment follow-up period is applied globally.
	The alternate location option is selected for unscheduled visits (USV). Footnotes jj and kk are added regarding USVs.	To allow flexibility of the visit at alternate location and for clarification.
Protocol Synopsis - Table 1 (Schedule of events for screening and double-blind, placebo-controlled treatment period and follow-up period); and Section 5.2 Double-blind, placebo-controlled treatment period	The ADA assessment is added to the assessment schedule for Weeks 1, 2, and 3.	To better understand the timeframe for potential ADA development.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis - Table 2 (Schedule of events for open-label treatment extension period and follow-up period)	The footnote on the "ET" header is corrected from "a" to "b".	Typographical error in the prior edition.
	The visit days at Follow-up Weeks 2, 4, and 10 are revised from Days 14, 28, and 70 to Days 15, 29, and 71 respectively.	For consistency in calculation of study days.
	The last follow-up visit is revised from Week 6 (Day 42) to Week 10 (Day 71), and the UK-specific links and notations in the Table and footnotes contained in the prior version of the protocol are removed.	For the purpose of harmonization, the duration of the post-treatment follow-up period is applied globally.
	"urea" is removed from footnote k (regarding serum chemistry).	This assessment is a duplicate with blood urea nitrogen.
	Footnote r: KIM-1, creatinine, and β2-microglobulin are removed, Cystatin C is specified as "urine Cystatin C", and TGF-β and EGF are added.	To align with updates in endpoints. Creatinine is removed because it is already among the serum chemistry test.
	Footnote s: KIM-1 and β2-microglobulin are added, and TGF-β and EGF are removed.	To align with updates in endpoints.
	Footnote u: the second bullet is clarified to indicate that the drug administration should follow blood sampling.	To provide precision on the time of drug administration.
	Footnote w is clarified to indicate that the full hematology panel is performed at each visit during the follow-up period.	This change is made to align with the updated follow-up visit schedule.
	Footnote aa from the prior version (regarding UK-specificities) is removed.	The duration of the post-treatment follow-up period is applied globally.
	An alternate location option is selected for unscheduled visits (USV). Footnotes aa and bb are added regarding USVs.	To allow flexibility of the visit at alternate location and for clarification.
Section 1.1.2 Lademirsen (SAR339375)	The INN lademirsen is added to the title of this section.	To align with the change in the product code related to the Sponsor (Sanofi), and to introduce lademirsen as the INN recently assigned to this compound.
	The first sentence is revised to introduce lademirsen as the INN for SAR339375.	
Section 1.1.4.3 Study PDY16327	The section is added.	To reflect current clinical experience, as the PDY16327 study has completed.
Section 1.2.3 Justification of route and dose regimen	The first bullet under the nonclinical kidney SUM concentration data is revised.	To reflect nonclinical pharmacology data.
Section 3.1 Overall Study Design	In the first paragraph of the "Open-Label Treatment Extension Period" section, the words "will continue" are removed from the second sentence.	To correct contradictory language in this paragraph and for consistency with the Protocol Synopsis.
	In the "Follow-up Period" section: the last visit during the follow-up period is revised to occur at week follow-up Week 10, and the link to the UK-specific section is removed.	For the purpose of harmonization, the duration of the post-treatment follow-up period is applied globally.
Section 3.2.1 Inclusion criteria and Section 3.2.2 Exclusion criteria	Aligned numbering to protocol synopsis.	Corrected typographical errors in numbering in prior version.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Investigational Products	The sentence regarding supply by courier is added.	To provide flexibility regarding provision of supplies to study participants.
Section 4.4 Home injection	The statement regarding the reporting of all events between 2 injections (after the list of documentation criteria) is added.	To ensure that patients who will have home injection(s) will report all adverse events.
	The statement "Prior to beginning home injections…" is revised and the subsequent sentence is added.	To clarify the training requirement for healthcare professionals.
	The details of home injections during both the double-blind and open label periods are expanded.	To provide clarifications regarding the home injection.
	Clarifications are made to the paragraph "During the last 6 months…".	For clarification.
Section 4.5 Dose reduction, Section 5 Study Procedures, Section 7.2.7 Interim analysis, and Section 9.2.3 Informed consent	The sentence regarding emergency declarations is added.	To anticipate actions in case of national or regional emergency.
Section 5 Study Procedures	The link to the German-specific section is removed.	For the purpose of harmonization, the he end of study definition is applied globally (Section 5.8 is created).
Section 5.2 Double-Blind, Placebo-Controlled Treatment Period	For Day 1: concomitant medications reporting is moved from the list of tests not to be repeated at baseline if done within 7 days prior to first dosing to the list of tests to be done at the baseline visit prior to the first injection.	To collect concomitant treatment medications at each visit.
Section 5.5 Follow-up Period	The last visit during the follow-up period is revised to occur at Week 10 (from Week 6), and the link to the UK-specific section is removed	For the purpose of harmonization, the duration of the post-treatment follow-up period is applied globally.
Section 5.6 Unscheduled Visits	The statement "The unscheduled visits could be done at alternative location (including at home), and at the Investigator's discretion, for assessment of AEs related to abnormal/alarming laboratory values." is added.	To provide flexibility regarding the unscheduled visits.
Section 5.8 End of Study Definition	This section is created.	To provide the definition of the end of study.
Section 6.1 Medical History and Family History	The timeframe for documenting additional illnesses for a patient (last sentence) is updated from the end of study to the completion of the last follow-up visit.	To clarify the timeframe of all additional illnesses to be as AEs.
	The clarification for Germany is removed from the last sentence.	The end of study definition is applied globally (not only in Germany) in this amended protocol.
Section 6.2.1 Adverse events	The statement "until the last administration of study medication plus 10 weeks follow up" is added to the definition of TEAEs in the second paragraph.	To provide clarification on the definition of TEAEs.
	The statement that a subset of AEs (Grade ≥2 AESIs) will be closely monitored is added.	For clarification.

Section # and Name	Description of Change	Brief Rationale
Section 6.2.2 Adverse event of special interest	This section is created, and subsequent sections are renumbered accordingly.	To provide definitions and clarifications regarding AESIs.
Section 6.2.3 Adverse events grading	The section header is added. Subsequent sections are renumbered accordingly.	For clarification.
	Tables 3 and 4 (located in Section 6.2.1 of the prior protocol version) are modified to more closely align with the DAIDS criteria. The DAIDS criteria reference is added to Section 11, accordingly.	For clarification.
Section 6.2.4 Adverse event outcome	The section header is added. Subsequent sections are renumbered accordingly. Minor revisions are made to the text to align with Table 5 (located in Section 6.2.1 of the prior protocol version).	For clarification and alignment with terminology in Table 5.
Section 6.2.5 Serious adverse events	The paragraph regarding SAEs occurring after signing the ICF to the end of the study is revised to any SAE occurring after the ICF signing "to the end of a patient's study participation", and the link to the German-specific end of study definition is removed.	For clarification.
	The paragraph regarding Investigator responsibility for AEs and SAEs is added.	For clarification.
Section 6.2.6 Follow-up of AEs and SAEs	This section is created, and subsequent sections are renumbered accordingly.	To provide clarity for the AE/SAE follow-up procedure.
Section 6.2.14 Laboratory assessments	"urea" is removed from the list of serum chemistry.	This assessment is a duplicate with blood urea nitrogen.
	"IgG" is added to the description of ADAs.	For clarification.
Section 6.2.16 Injection site reactions	The sentence preceding Table 6 was added regarding ISR reporting for self-administrations.	For clarification.
Section 6.2.17 Safety oversight	The second paragraph is revised to say "and will closely monitor AESIs" and platelet counts and eGFR are added as examples.	For clarification.
Section 6.4 Pharmacodynamic assessments and biomarkers	Circulating miR-21 is added as a pharmacodynamics assessment.	For clarification.
	The list of renal injury and function biomarkers is revised (KIM-1 and β2-microglobulin are removed; EGF and TGF-β are added). In the list of exploratory biomarkers, β2-microglobulin and KIM-1 are added, and TGF-β and EGF are removed. The exploratory "microRNAs" is clarified as microRNAs "other than miR-21".	These changes are made to align assessments globally.
Section 7.1.5 Pharmacokinetic endpoints	This section (7.1.4 in the prior version) was renumbered to 7.1.5.	The preceding section was split into two (7.1.3 and 7.1.4) as described above.
Section 7.2.4 Safety analysis	The first paragraph is updated to indicate "plus 10 weeks" and to remove the link to UK-specifications for follow-up.	For the purpose of harmonization, the duration of the post-treatment follow-up period is applied globally.

Section # and Name	Description of Change	Brief Rationale
Section 10.2 Appendix 2: Clinical Laboratory	Neutrophil and eosinophil counts are removed from Table 7 because they are not study biomarkers.	For consistency with other sections of the protocol.
	The clinical chemistry parameters in Table 7 are revised to align with the coagulation panel, serum chemistry, and lipid panel assessments specified in the Schedule of Activities (Tables 1 & 2).	For clarification.
Section 10.5 Appendix 5: Country-specific Requirements	The section for the United Kingdom (10.5.1 in Amended Protocol 08) is removed, and subsequent sections are renumbered accordingly.	For the purpose of harmonization, the duration of the post-treatment follow-up period is applied globally.
Section 10.5.1 Germany	The section for the end of study definition (10.5.2.1 End of study definition in Amended Protocol 08) is removed, and subsequent sections are renumbered accordingly.	The end of study definition is applied globally (Section 5.8 is created).
Section 10.5.2 China	The section for the secondary objectives (10.5.3.1.1 Secondary objectives in Amended Protocol 08) and efficacy endpoints (10.5.3.1.3 Efficacy endpoints) are removed, and subsequent sections are renumbered accordingly.	The secondary objectives and efficacy endpoints are aligned globally.
Section 10.5.2.1.2 Pharmacodynamic and exploratory endpoints	China-specific pharmacodynamic endpoints are removed.	The pharmacodynamic endpoints are aligned globally.
Section 10.5.2.2 Pharmacodynamic assessments and biomarkers	China-specific pharmacodynamic assessments are removed.	The pharmacodynamic assessments are aligned globally.
Section 10.6 Appendix 6: Contingency measures for a regional or national emergency that is declared by a governmental agency	The entire section is added, and subsequent sections are renumbered accordingly.	To describe actions to be set up in case of a regional or national emergency.
Section 10.8.1 Amended protocol 08 (18 March 2020)	New section is created to contain the prior amendment's history, and subsequent sections are renumbered accordingly. Minor formatting updates are applied.	This action is taken to conform with the usual process for amendment history.
Section 11 References	Reference 30 (DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events) is added in accordance with the revisions in Section 6.2.3, and subsequent references were renumbered accordingly.	For clarification.

In addition, minor editorial, stylistic, and/or grammatical changes were made throughout this document.

10.8.4 Amended protocol 08 (18 March 2020)

This amended protocol (amendment 08) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to align with the requirements of the Human Genetics Resources Administration of China (HGRAC).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout document	Updated protocol numbering, dates, and headers.	This action was taken to conform with the usual Sanofi process for amended protocols, in accordance with Amended Protocol 08.
Protocol Amendment Summary of Changes	The section was updated to reflect Amended Protocol 08.	This action was taken to conform with the usual Sanofi process for amended protocols.
Protocol Synopsis (Study Objectives and Study Endpoints subsections), 2.2 Secondary Objectives, 2.3 Exploratory Objectives, 7.1.1 Efficacy endpoints, 7.1.3 Exploratory endpoints: efficacy, pharmacodynamic and biomarker endpoints	Links to the Section 10.5.3.1 subsections were added.	These links were added because the subsection was created in accordance with country-specific requirements.
Protocol Synopsis (Tables 1 & 2), 5.2 Double-Blind, Placebo-Controlled Treatment Period, 5.3 Open-Label Extension Treatment Period, 5.4 Early Termination, 6.4 Pharmacodynamic Assessments and Biomarkers	Links to Section 10.5.3.2 were added to Table 1 footnotes aa and bb, Table 2 footnotes r and s, the relevant visits of Sections 5.2 and 5.3, and Sections 5.4 and 6.4.	These links were added because the subsection was created in accordance with country-specific requirements.
Section 7.2.6 Other analyses	A link to Section 10.5.3.2 was added.	This link was added because the subsection was created in accordance with country-specific requirements.
Protocol Synopsis (Disposition of Samples after Study Completion subsection), Table 1, 5.2 Double-Blind, Placebo-Controlled Treatment Period, 5.4 Early Termination, 6.6 Disposition of Samples After Study Completion	Links to 10.5.3.3 were added.	These links were added because the subsection was created in accordance with country-specific requirements.
10.5 Appendix 5: Country-specific requirements	Subsection 10.5.3 and subsections were created for study conduct in China.	This change is due to HGRAC requirements: modifications in study objectives/endpoints and sample storage/disposition with consideration of the Chinese country-specific requirements for Chinese patients.
Section 10.7.1 Amended protocol 07 (20 February 2020)	New section was created to contain the prior amendment's history, and subsequent sections were renumbered accordingly. Minor formatting updates were applied.	This action was taken to conform with the usual process for amendment history.

Please note that no other changes were made throughout this document.

10.8.5 Amended protocol 07 (20 February 2020)

This amended protocol (amendment 07) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of this amendment is to respond to requests from the German health authority.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout document	Updated protocol numbering, dates, and headers.	This action was taken to conform with the usual Sanofi process for amended protocols, in accordance with Amended Protocol 07.
Protocol Amendment Summary of Changes	The section was updated to reflect Amended Protocol 07.	This action was taken to conform with the usual Sanofi process for amended protocols.
Protocol Synopsis (Study Duration)	A link to Section 10.5.2.1 was added.	To provide the clarification relating to the end of study requested by the German health authority.
1.3.1 Potential risks	A link to Section 10.5.2.2 was added.	To more clearly present the risks associated with participation in ACT16248, in accordance with the regulatory agency request.
5 Study Procedures, 6.1 Medical History and Family History, and 6.2.2 Serious adverse events	A link to Section 10.5.2.1 was added.	To provide the clarification relating to the end of study requested by the German health authority.
10.5 Appendix 5: Country-specific requirements	Subsection 10.5.2 and subsections were created for Germany.	This change is due to regulatory requests: to more clearly define the end of the study, and to more clearly present the potential risks associated with participation in ACT16248.
Section 10.7.1 Amended protocol 06 (15 January 2020)	New section was created to contain the prior amendment's history, and subsequent sections were renumbered accordingly. Minor formatting updates were applied.	This action was taken to conform with the usual process for amendment history.

Please note that no other changes were made throughout this document.

10.8.6 Amended protocol 06 (15 January 2020)

This amended protocol (amendment 06) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The duration of follow-up was updated to 10 weeks for patients in the United Kingdom due to regulatory agency request.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Updated to reflect Amended Clinical Trial Protocol 06.	This action was taken to conform with the usual Sanofi process for amended protocols.
Throughout document	Headers were updated.	This change is in accordance with Amended Protocol 06.
Protocol Synopsis (Follow-Up Period section)	A reference to Section 10.5.1 was added to the second paragraph.	This change is due to regulatory request.
Protocol Synopsis (Study Duration)	References to Section 10.5.1 were added.	This change is due to regulatory request.
Protocol Synopsis (Tables 1 and 2)	In the “Follow-up” column, “10 (UK)” and “70 (UK)” were added to Week 6 and Study Day 42, respectively, with a clarification in footnotes jj and aa (newly added to Tables 1 and 2, respectively) to refer to Section 10.5.1 for UK specifications.	This change is due to regulatory request.
	For footnotes o and r in Table 1 and footnotes g, p, and w in Table 2, clarifications were added to refer to Section 10.5.1 for UK specifications.	Clarifications were added in accordance with the regulatory request.
3.1 Overall Study Design (Follow-up Period subsection)	A reference to Section 10.5.1 was added to the second paragraph.	This change is due to regulatory request.
5.5 Follow-up Period	A reference to Section 10.5.1 was added to the “Follow-up Week 6” subheading.	This change is due to regulatory request.
7.2.4 Safety analysis	A reference to Section 10.5.1 was added to the first paragraph.	This change is due to regulatory request.
10.5 Country-specific requirements	Subsection 10.5.1 was created for the United Kingdom, and the duration of follow-up specific to the UK was described.	This change is due to regulatory request.
Section 10.7.1 Amended protocol 05 (07 November 2019)	New section was created to contain the prior amendment’s history, and subsequent sections were renumbered accordingly. Minor formatting updates were applied.	This action was taken to conform with the usual process for amendment history.

Please note that no other changes were made throughout this document.

10.8.7 Amended protocol 05 (07 November 2019)

This amended protocol (amendment 05) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

A new EudraCT number was issued for this study, as the prior number had reflected study completion.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	The EudraCT number was updated.	A new EudraCT number was issued for this study.
Section 10.7.1 Amended protocol 04 (01 August 2019)	New section was created to contain the prior amendment's history, and subsequent sections were renumbered accordingly.	This action was taken to conform with the usual process for amendment history.

Please note that no other changes were made throughout this document.

10.8.8 Amended protocol 04 (01 August 2019)

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Changes were made to the protocol to implement several updates listed in the following table.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Title was updated to reflect Amended Clinical Trial Protocol 04.	The change was made to reflect the update of the amended clinical trial protocol.
Title Page	Protocol Date was changed to reflect 01-Aug-2019.	The change was made to reflect the updated date of approval of the document.
Protocol Amendment Summary of Changes	The document history was updated to include the Amended Clinical Trial Protocol 04 with date, and version of 01 August 2019, version 2.	The change was made to reflect the update of the amended clinical trial protocol, approval date, and version.
	Overall rational for the amendment was updated.	This change was made to provide an updated overall rational for amended clinical trial protocol 04.

Section # and Name	Description of Change	Brief Rationale
Protocol amendment summary of changes table	This section was updated to reflect the changes to amended clinical trial protocol 04.	This change was made to provide update on summary of changes to amended clinical trial protocol 04.
Protocol Synopsis	Secondary objective was clarified to describe terms C_{max} and C_{trough}.	This change was made to further develop the pharmacokinetic endpoint evaluated. Assay that can measure both parent and metabolite (used for C_{max}) is not sensitive enough to detect very low concentrations (C_{trough}). The assay used to measure low concentrations is very sensitive but cannot distinguish between parent and metabolite.
	Added time point during the placebo-controlled treatment period under the first bullet of efficacy endpoints.	This change was made to provide clarification of the time point for this endpoint.
	Clarification of pharmacokinetic endpoint: Plasma concentrations of RG456070, RG0005, and SUM in C_{max} samples and SUM only in C_{trough} samples was provided.	This change was made to further develop the pharmacokinetic endpoint evaluated.
	eGFR was removed from the exceptions of the occurrence of any Grade 3 or higher AE from Individual Stopping Criteria.	This change was made to include eGFR Grade 3 (eGFR <15) as a stopping criteria.
	Text was modified with regard to AEs of interest to include discontinuation of subjects who experience ≥50% decline for eGFR from baseline.	This change was made to include the decline eGFR as a stopping criteria.
	Text was modified to include any TEAE that in the opinion of the sponsor is of potential clinical significance for subject's safety.	The text was modified to include occurrence of events suggesting significant safety concern as stopping criteria.
	Added "adult" to description of the study population.	This change was made to clarify the study population.
	Pharmacokinetic assessment: Removal of post baseline visit with PK sampling. Addition of statement that no PK samples will be withdrawn if injection is not administered on Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96.	Changes were made to clarify PK sampling if injection is not administered.
	Removed duplicated sentence under pharmacokinetic analysis.	This change was made to correct duplication of information in this section.

Section # and Name	Description of Change	Brief Rationale
Table 1 Schedule of events for screening and double-blind, placebo-controlled treatment period and follow-up period	Urine Pregnancy added testing on ET	Urine pregnancy testing is necessary at ET to ensure that patient will not be pregnant during the study intervention and at the end of study intervention.
	Assessment of markers of inflammation: quantitative immunoglobulins (γ-globulin, IgG, IgM) was added with same schedule of assessment as complement, on W0, W12, W24, W36, W48, on ET and at Follow up W6.	Changes were made to monitor markers of inflammation to be consistent with the investigator brochure.
	IRT contact was added for W0, W4, W8, W12, W16, W20, W24, W28, W32, W36, W40, W44, and W48.	This item was added to specify IRT contact timepoints.
	Footnote “m” included collection on a weekly basis for changes to the medications taken after signing ICF.	Changes were made to clarify the timepoint of conmed collection.
	Footnote ”p” removed urinalysis.	The language “Urinalysis” was removed to differentiate “Urinalysis” to 24 H urine panel (albumin, creatinine, sodium, total protein). As sampling is done in same visit.
	Footnote “q” added urinalysis, which tests will be done by dipstick test, and that microscopy urine analysis will be a laboratory test.	The language “Urinalysis” was added to specify the testing being performed. Clarification of the test to be used for urinalysis was also provided.
	Footnote “r” added the following statement “during treatment period and bi - weekly during follow up period”.	This change was made to clarify the timepoint during the treatment period and follow up period.
	Footnote “t” removed (SPEP) testing stating that If subject experienced low protein <1 g the investigation will be done by the investigator as per local practice.	This change removes complexity for the conduct of the study.
	Footnote “t” modified text to add: In case of worsening of eGFR, the investigator could repeat the eGFR before the next scheduled test.	Text was modified to provide Medical Monitors have heightened vigilance and the flexibility to increase frequency of monitoring based on key outcome measures (ie, eGFR, proteinuria).
	Footnote “x” included 4 hours post-dose PK sampling. Removal of Post baseline visits with PK sampling and addition that no PK samples will be withdrawn if injection is not administered on W4, W12, W24, W36, and W48.	Changes were made to clarify PK sampling if injection is not administered.
	Spot urine protein-to-creatinine ratio (UPCR) testing was added at W4, W8, W16, W20, W28, W32, W40, and W44.	Changes were made to closely follow up the renal function.
	Footnote “aa” was modified to remove Urine protein/Creatinine ratio. And added text to describe when urine protein/creatinine ration will be performed.	Changes were made to clarify frequency of urine protein-to-creatinine ratio.

Section # and Name	Description of Change	Brief Rationale
Table 2 Schedule of events for open-label treatment extension period and follow- up period	Assessment of markers of inflammation: quantitative immunoglobulins (γ-globulin, IgG, IgM) was added with same schedule of assessment as complement, on Weeks 48, W52, W60, W72, W84, W96 on ET and at Follow up W6	Changes were made to monitor markers of inflammation to be consistent with the investigator brochure.
	IRT contact was added for W52, W56, W60, W64, W68, W72, W76, W80, W84, W88, W92, and W96.	Changes were made to specify IRT contact timepoints.
	Spot UPCR testing was added to W48, W52, W56, W64, W68, W76, W80, W88, W92.	Changes were made to closely follow up the renal function.
	Additional testing criteria for W48 for post dose PK was added.	Changes were made to keep consistency of the study protocol throughout the document.
	Footnote “h” removed urinalysis.	The language “Urinalysis” was removed to differentiate “Urinalysis” to 24 H urine panel (albumin, creatinine, sodium, total protein). As sampling is done in same visit.
	Footnote “i” added urinalysis, which tests will be done by dipstick test, and that microscopy urine analysis will be a laboratory test	The language “Urinalysis” was added to specify the testing being performed. Clarification of the test to be used for urinalysis was also provided.
	Footnote “r” was modified to remove Urine protein/Creatinine ratio. And added text to describe when urine protein/creatinine ration will be performed.	Changes were made to clarify frequency of urine protein-to-creatinine ratio.
	Footnote “x” added that no PK samples will be withdrawn if injection was not administered on W60, W72, W84, and W96.	Changes were made to clarify PK sampling if injection is not administered.
1.1.3 Nonclinical experience	Clarification of the microscopic findings were observations were provided.	Changes were made to this section to clarify where observations of microscopic findings occurred.
	Change of the no-observed-adverse-effect levels (NOAELs) for monkey studies was made.	Changes were made to correct the NOAELs for monkeys.

Section # and Name	Description of Change	Brief Rationale
1.2.3 Justification of route and dose regimen	Nonclinical and Clinical data observed and target, and Pre-Clinical toxicology was edited to reflect reason for therapy study design. Pre-clinical toxicology was changed to update the NOAELs for monkeys and the calculated exposure ratios for RG456070; and the following paragraph was removed: Mean plasma exposure (AUC) at the chronic study NOAELs were 70.3 ug*hr/mL for mouse and 172.7 ug*hr/mL for monkey. Plasma exposure in clinical study RG012-05 MAD (110 mg QW x 5) was 24.4 ug*hr/mL. Plasma exposure ratios calculated based on the nonclinical data are 6X for mouse and 15X for monkey.	Information has been arranged in a more logical order than previously recorded. Data which could not be verified, or that have no reports, have been deleted. References to modeling and predicted data have been deleted. No modeling data are used in the revised justification for 110 Q1W dose. Information in “pre-clinical toxicology” has been updated to be consistent with the new version of the investigator brochure. These changes are part of the update of the “pre-clinical toxicology”.
2.2 Secondary Objectives	Secondary objective was clarified to describe terms C_{max} and C_{trough}.	This change was made to further develop the pharmacokinetic endpoint evaluated. Assay that can measure both parent and metabolite (used for C_{max}) is not sensitive enough to detect very low concentrations (C_{trough}). The assay used to measure low concentrations is very sensitive but cannot distinguish between parent and metabolite.
3.2 Study Population	Added “adult” to description of the study population.	This change was made to clarify the study population.
3.2.1 Inclusion Criteria	I07 changed the use of 2 acceptable effective methods of contraception from for at least 6 weeks after the last dose, to at least 10 weeks after the last dose in both female and male subjects.	Changes were made to be consistent with the latest version of the IB.
3.3 Screen Failures	Subjects may be rescreened if their clinical condition changes and a new subject number will be assigned. The same number previously used will not be assigned to the subject.	Changes were made to clarify rescreening of patients.
3.3.1.1 Individual treatment stopping criteria	eGFR was removed from the exceptions of the occurrence of any Grade 3 or higher AE from Individual Stopping Criteria. Text was modified with regard to AEs of interest to include discontinuation of subjects who experience ≥50% decline for eGFR from baseline.	This change was made to include eGFR Grade 3 (eGFR <15) as a stopping criteria. This change was made to include the decline for eGFR as stopping criteria.

Section # and Name	Description of Change	Brief Rationale
3.4 Discontinuation of Study	Text was modified to include any TEAE that in the opinion of the sponsor is of potential clinical significance for subject's safety.	The text was modified to include occurrence of events suggesting significant safety concern as stopping criteria.
4.2 Treatment Assignment	Treatment assignment and randomization will be performed using a centralized treatment allocation system/IRT. The IRT (centralized treatment allocation system) generates the patient randomization list and allocates the treatment number and the corresponding treatment kits to the patients accordingly. Before randomizing a patient, the Investigator or designee will have to contact the centralized treatment allocation system/IRT.	Changes were made to clarify method of treatment assignment.
4.6 Randomization Code Breaking During The Study	This entire section was added.	Changes were made to clarify the code breaking procedure and to adhere with Sanofi policy.
5.2 Double-Blind, Placebo-Controlled Treatment Period	Pre-dose and post dose blood sampling for PK was added.	Changes were made to keep consistency of the study protocol throughout the document.
	0.5 hours post-dose blood sampling was added for complement (C3, C3a, C4, and Bb).	Changes were made to keep consistency of the study protocol throughout the document.
	Blood sampling to assess markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG) was added for Day 1 Baseline/Dosing Site Visit, Weeks: 12, 24, 36, 48 (all ±2 days) * Site visits.	Changes were made to monitor markers of inflammation to be consistent with the investigator brochure.
	(all ±2 days) was added for Weeks: 12, 24, 36, 48.	Changes were made to clarify the visit windows.
	Hearing assessment (on Week 48 only) was added.	Changes were made to keep consistency of the study protocol throughout the document.
	Testing was added for Spot UPCR for Week 4 (±2 days) Site Visit, Weeks: 8, 16, 20, 28, 32, 40, 44 (all ±2 days) *Option for Alternative Location Visit.	Changes were made to closely follow up the renal function.
5.3 Open-Label Extension Treatment Period	Blood sampling to assess markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG) was added for Weeks: 60, 72, 84, and 96 (all ±2 days) Site Visits.	Changes were made to monitor markers of inflammation to be consistent with the investigator brochure.
	Testing was added for Spot UPCR for Week 52 (±2 days) Site Visit, and Weeks: 56, 64, 68, 76, 80, 88, 92 (all ±2 days) *Option for Alternative Location Visit.	Changes were made to closely follow up the renal function.

Section # and Name	Description of Change	Brief Rationale
5.4 Early Termination	Urine pregnancy test was added.	Urine pregnancy testing at ET to ensure that patient will not be pregnant during the study intervention and at the end of study intervention.
	Blood sampling to assess markers of inflammation (quantitative immunoglobulins: γ-globulin, IgM, IgG) was added.	Changes were made to monitor markers of inflammation to be consistent with the investigator brochure.
5.5 Follow-up Period	Blood sampling for markers of inflammation (γ-globulin, IgM, IgG) was added for Follow-up Week 6 (±3 days) Site Visit.	Changes were made to monitor markers of inflammation to be consistent with the investigator brochure.
6.2.1 Adverse events	Removal of following criteria for ending AE monitoring: It has been shown to be unrelated to the study drug.	Changes were made to align with standard Genzyme Corporation process.
6.2.6 Physical examination/body system assessments	Removal of statement referring to schedule of events.	Changes were made to align with the new design of the study.
6.2.13 Safety oversight	Text was modified to include that the DMC may be consulted at the discretion of whenever the investigator considers that worsening of eGFR and UPCR values are medically relevant.	Changes were made to allow investigators the consultation with the DMC in case of worsening of eGFR or UPCR is medically relevant.
6.4 Pharmacodynamic Assessments and Biomarkers	Text was modified to include that Urine protein/creatinine ratio (UPCR) will be performed every 4 weeks (using the first morning void urine) either using 24 hours spot urine sample or 24 hour urine collection (at D1, W12, W24, W36, W48, W60, W72, W84, W96). In case of worsening of UPCR, the investigator could repeat the UPCR before the next scheduled test.	Changes were made to clarify frequency of urine protein-to-creatinine ratio and to state possibility of investigator to repeat UPCR.
6.5 Pharmacokinetic Assessments	Removal of post baseline visit with PK sampling. Addition of statement that no PK samples will be withdrawn if injection is not administered on Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96.	Changes were made to clarify PK sampling if injection is not administered.
7.1.1 Efficacy endpoints	Added time point during the placebo-controlled treatment period under the first bullet of efficacy endpoints.	This change was made to provide clarification of the time point for this endpoint.
7.1.4 Pharmacokinetic endpoint	Clarification of Plasma concentrations of RG456070, RG0005, and SUM in C_{max} samples and SUM only in C_{trough} samples was provided.	This change was made to further develop the pharmacokinetic endpoint evaluated.

Section # and Name	Description of Change	Brief Rationale
7.2.4 Safety analysis	Clarification of the TEAE period as the time between the first administration of the study medication to the last administration of study medication plus 6 weeks follow up.	End of the TEAE period changed from end of study to last IMP plus 6 weeks follow up to be more precise.
7.2.5 Efficacy analysis	Clarification that the placebo group prior distribution assume a normal distribution for the slope of eGFR.	This change was made to state that the placebo group has this normal distribution.
	Changes to verbiage were made to clarify the description of the model for analyzed change in eGFR.	This change was made to increase clarity of the information described.
9.1.2 Dosing deviations	Clarification of the definition of an overdose was added.	Changes were made to clarify the definition of the overdose.
10.2 Appendix 2: Clinical Laboratory	Clinical chemistry and routine urinalysis parameters removed not applicable assessments.	Changes were made to remove complexity for the conduct of the study.
10.2. Appendix 2: Clinical Laboratory, Table 7 - Protocol required safety laboratory assessments	Routine urinalysis text for management of abnormal results has been modified.	Changes were made to this section to clarify management of dipstick abnormal results.

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.

10.8.9 Amended protocol 03 (23 April 2019)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Clinical development and the commercialization rights of RG-012 were granted from Regulus Therapeutics Inc. (Regulus) to Genzyme Corporation, which will be assuming responsibility of the current clinical program.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	The Regulus logo and reference to Regulus within the confidentiality statement were deleted.	These changes were made due to the transfer in the development of RG-012.
	The title was updated to reflect the change from dosing every other week to weekly dose administration. “Every Week in Patients with Alport Syndrome”.	The title was changed to reflect the change in study drug administration and the amendment.
	The title was updated to reflect “Subcutaneous” injection.	The title was changed to reflect the change in study design to indicate the injection route and the amendment.
	The sponsor was changed to reflect Genzyme Corporation.	The sponsor was changed to reflect the new owner of the product.
	The study number was changed to “ACT16248” from RG012-03.	This change was made due to the transfer in the development of RG012-03 from Regulus to Genzyme Corporation.
	Investigational Medicinal Product was changed to SAR339375.	This change was made due to the transfer in the development of RG-012.
	Study Name HERA was added to title page.	This addition was made to reflect the name of the study which was previously omitted.
	Sponsor address was changed to Genzyme Corporation 50 Binney Street Cambridge, Massachusetts 02142.	This change was made reflect the new sponsor’s address.
Sponsor Approval Page	Removed this page from amended protocol 03.	Not applicable with the Genzyme Corporation standard.
Investigator Protocol Agreement Page	Removed this page from amended protocol 03.	Not applicable with the Genzyme Corporation standard.
Protocol Amendment Summary of Changes	Section added to describe document history, overall rationale for amendment, and protocol amendment summary of changes table.	This section was inserted to better align with the Genzyme Corporation standard, following transfer in the development of RG-012.
Names and Addresses	A new field for the Monitoring Team’s Representative and contact information was added.	This change was made to align with the Genzyme Corporation standard.
List of Abbreviations and Acronyms	The list has been moved to Section 10.6 Appendix 6 and additional abbreviations have been added to the list. Abbreviations for ADUA, ANCOVA, CMH, DAP, EC, GMP, IUD, IUS, PP, and SOP have been removed from the list of abbreviations.	The changes were made to better align with the Genzyme Corporation standard, and to remove or add abbreviations that are relevant to other revisions made elsewhere in the amended protocol 03.
Throughout the entire protocol, including headers	“Regulus” has been changed to “the Sponsor” or “Genzyme Corporation,” as appropriate, and the Sponsor address and contact details have been updated.	This change was made due to the transfer in the development of RG-012.

Section # and Name	Description of Change	Brief Rationale
Throughout the entire protocol, including headers	The Regulus study drug code (RG012-03) has been updated to the Genzyme Corporation study code (ACT16248) throughout, as has the compound code (RG-012, updated to the Genzyme Corporation code SAR339375).	These changes were made due to the transfer in the development of RG-012.
Protocol Synopsis and throughout the entire protocol	The primary objective has been presented as two points.	These changes were made to provide clarification.
Protocol Synopsis and throughout the entire protocol	The secondary objective has been edited to include specific PK parameters (C_{max} and C_{trough}).	The secondary objective added PK parameters for clarification.
Protocol Synopsis and throughout the entire protocol	Safety endpoint "Association of ADAs with adverse events" has been added.	This change was made to further develop the safety endpoint evaluated.
Protocol Synopsis and throughout the entire protocol	Exploratory endpoints for difference in eGFR slope between the pretreatment period and treatment period were removed from the protocol.	This change was made as some of the subjects may not have eGFR slope available on pretreatment period.
Protocol Synopsis and throughout the entire protocol	Exploratory endpoint for absolute and percent change in eGFR values from baseline at Week 96 was added.	This change was made due to the unavailability of some subjects.
Protocol Synopsis and throughout the entire protocol	Exploratory endpoint for the proportion of subjects who are treatment responders based on a decline in eGFR was removed.	This change was made to further develop the efficacy endpoint evaluated.
Protocol Synopsis and Section 7.1.3	Exploratory endpoint for the proportion of subjects with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40%, reduction at Week 24, 48 and 96 was added.	This change was made to further develop the efficacy endpoint evaluated.
Protocol Synopsis and throughout the entire protocol	Exploratory endpoint to characterize the effect of SAR339375 changes in renal biomarkers (BUN), albumin/creatinine ratio, and cyctatin C was edited. This endpoint removed assessment of kidney injury molecule 1 [KIM 1], beta 2 microglobulin, and neutrophil gelatinase associated with lipocalin [NGAL].	This change was made to further develop the efficacy endpoint evaluated and remove complexity for the conduct of the study and subjects.
Protocol Synopsis and throughout the entire protocol	Exploratory endpoint for changes in exploratory biomarkers (which may include but are not necessarily limited to, in blood only: microRNAs (miR);in both blood and urine: transforming growth factor-β [TGF-β], and connective tissue growth factor [CTGF); in urine only: calbindin-D28k, epidermal growth factor [EGF]).	This change was made to further develop the efficacy endpoint evaluated and remove complexity for the conduct of the study and subjects.
Protocol Synopsis and throughout the entire protocol	Exploratory endpoint changes in podocyturia as measured by analysis of podocyte numbers and podocyte specific mRNAs in urine was removed.	This change was made to further develop the efficacy endpoint evaluated and remove complexity for the conduct of the study subjects.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and throughout the entire protocol	Exploratory endpoint change over time in quality of life (QoL) as measured using the Short Form 36 Health Survey (SF-36) was removed.	Removal of exploratory endpoints evaluating changes to biomarkers and measurement of quality of life (QoL) of subjects was considered. The assessment of the effect of SAR339375 on QoL would add complexity for the conduct of the study and subjects. In addition, there was no change in SF36 data in early CKD subjects from the ATHENA registry (OBS16374, formerly RG012-01), thus the analysis has been removed.
Protocol Synopsis and throughout the entire protocol	Pharmacokinetic endpoint plasma concentrations added (C_{max} and C_{trough}) and removed calculated PK parameters from this endpoint.	This change was made to further develop the pharmacokinetic endpoint evaluated.
Protocol Synopsis and throughout the entire protocol	Reference to OBS16374, formerly RG012-01, ATHENA Natural History Study has been made.	These changes were made due to the transfer in the development of RG-012.
Protocol Synopsis and throughout the entire protocol	The number of subjects was increased from 40 to 45.	This change was made to include recruitment of approximately 45 adult subjects both male and female preventing the exposure of children at this early stage of development of SAR339375.
Protocol Synopsis and throughout the entire protocol	Removal of the following criteria: a baseline urine protein/creatinine ratio ≥300 mg/g, and baseline eGFR progression criteria if aged 31-60.	The study is modified to update inclusion criteria to reflect the change in the targeted patient population.
Protocol Synopsis and throughout the entire protocol	Change the ratio of randomization from 1:1 to 2:1.	The change was made to update the dosing regimen to increase likelihood of showing a statistical difference in the study.
Protocol Synopsis and throughout the entire protocol	Change the dosing from Q2W to QW.	The change was made because the weekly administration of SAR339375 is more likely to result in target kidney concentration than Q2W administration that would provide maximum clinical benefit. This demonstrated efficacy was seen in a nonclinical model, whilst still maintaining an acceptable safety margin. The dosing frequency has been increased from Q2W to Q1W based on observed drug concentrations in human kidney samples. (Preliminary data from ongoing open label part of the kidney biopsy study PDY16327, formerly RG012-06) relative to predicted target kidney concentrations based on nonclinical kidney PK (mouse and non-human primates (NHP)) and efficacy (mouse). AE profile observed in the open label part of PDY16327 within 1 year treatment supports the increase in dose.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and throughout the entire protocol	Addition of criteria in the double-blind, placebo-controlled treatment period to include the statement that: Once randomized, the subject should be treated within 3 calendar days maximum.	The change was made to reflect the change in the study design.
Protocol Synopsis and throughout the entire protocol	Addition of language in the open-label treatment extension period that specifies subjects who do not complete the 48-week double-blind, placebo-controlled treatment period and "early terminate" will enter the follow-up period.	The change was made to reflect the change in the study design.
Protocol Synopsis and throughout the entire document	Addition of language in the follow-up period to include an example of when the follow up period will occur. “Or after ET of the double blind part”.	The change was made to provide clarity and define the follow-up period.
Protocol Synopsis and throughout the entire document	Safety Management language was removed and replaced with standard Genzyme Corporation language.	This section was changed to better align with the Genzyme Corporation standard, following transfer in the development of RG-012.
Protocol Synopsis and throughout the entire document	Safety Management language referencing the Safety Review Committee was replaced with Data Monitoring Committee.	The change was made to reflect the standard Genzyme Corporation language.
Protocol Synopsis and throughout the entire document	Dose Reduction language was changed to reflect a subject’s platelet count will be obtained weekly before dose administration. Platelet counts will be measured at a central laboratory and can exceptionally be measured at a local laboratory. The subject’s most recent platelet counts but not older than 10 days will be reviewed by the Investigator/physician before drug administration.	This change was made to determine the safety of SAR339375 and its effect on reducing platelet counts.
Protocol Synopsis and throughout the entire document	Individual Treatment Stopping Criteria changes to the reference from the Regulus Medical Monitor to the Genzyme Corporation Study Medical Manager (SMM) were made.	This change was made to reflect the standard Genzyme Corporation language.
Protocol Synopsis and throughout the entire document	Study Stopping Criteria was changed to Study Suspension and Stopping Criteria.	This change was made to incorporate suspension criteria previously omitted.
Protocol Synopsis and throughout the entire document	Study Suspension and Stopping Criteria was changed to Grade 3 (or higher) AEs, or any death or two SAEs considered at least possibly related to participation in the clinical trial, will result in the recommendation to suspend all dosing and stop recruitment, then will trigger an ad hoc meeting with the DMC who will be asked to consider the appropriateness of study conduct continuation study as unchanged, early study termination or modification.	The criteria have been modified to reflect the information that we have for the rate of occurrence of AEs and SAEs in the other trials.
Protocol Synopsis and throughout the entire document	Study drug dose was changed from 1.5 mg/kg every two weeks to 110 mg every week. Study drug dose reduction was changed from 0.75 mg/kg to 110 mg every other week.	This change was made to standardize the dosing regimen in the protocol.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and throughout the entire document	Study Stopping Criteria is at the discretion of the DMC was added to the Study Suspension and Stopping Criteria.	This change was made to reflect the standard Genzyme Corporation language.
Protocol Synopsis and throughout the entire document	Investigational Medicinal product removed reference to RG-012 and the RG456070 as the drug substance. Formulation information was also removed and replaced with information about how SAR339375 will be supplied. This product will be supplied as a 110 mg/mL solution in a 5 mL glass vial. Each vial will contain a withdrawable volume of 2 mL for single use of administration.	This change was made further specific the IMP in further detail.
Protocol Synopsis and throughout the entire document	Investigational Medicinal Product language regarding how the placebo will be supplied was removed and replaced with information stating that the placebo matching SAR339375 for SC administration will be supplied as sodium chloride and riboflavin (colorant) solution in 5 mL glass vial. Each vial will contain a withdrawable volume of 2 mL.	This change was made further specific the placebo in further detail.
Protocol Synopsis and throughout the entire document	Summary of Eligibility Requirements changes to Inclusion criteria included the removal of some criteria and the addition of other criteria. The study added females in the inclusion criteria. The study added the need for a confirmed clinical diagnosis of Alport syndrome, (hematuria, family history, hearing loss, ocular change) and genetic confirmation of Alport syndrome in the subject or the family member, or kidney biopsy showing glomerular basement membrane abnormalities consistent with Alport Syndrome. The study changed the age from the possibility to expand inclusion to 12-60 year olds to exclusively including 18-55 years old. The lower limit of the eGFR was changed from >40 to >35 mL/min/1.73 m^2 (based on CKD-EPI) at screening. The inclusion criteria also added Renal Function Criteria that subjects must meet one of the three criteria provided. Change to the stability of ACE or ARB treatment was included for at least 30 days prior to screening. Inclusion criteria to address sexually active females and women of childbearing potential were added. Contraceptive use by men or women was also added. Hepatitis A virus screening is not required was added.	The study is modified to update inclusion criteria to include recruitment of approximately 45 adult subjects both male and female preventing the exposure of children at this early stage of development of SAR339375. The updated inclusion criteria will allow for expansion of the study population and prohibit limitation to X-linked Alport Syndrome. In order to better identify rapid progressors, additional renal function inclusion criteria were added based on the baseline eGFR and proteinuria. These new criteria are based on the analysis of the ATHENA registry data. Inclusion criteria were also updated to include ACE/ARB treatment at stable dose for at least 30 days since ACE/ARB are the current standard of care. Inclusion criteria addressing contraceptive use for sexually active males, females, and women of childbearing potential were added to comply with Genzyme Corporation standards. Clarification of screening for chronic diseases was added.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and throughout the entire document	Summary of Eligibility Requirements changes to Exclusion criteria included the addition of language to the Exclusion Criteria 01 identifying causes of chronic kidney disease aside from Alport syndrome (including but not limited to "other heritable disorder leading to chronic kidney disease" was made. Bullet point for Exclusion Criteria 03 was also added: "Maintenance mediation known to cause QT prolongation" was made. The language of Exclusion Criteria 05 was modified to add "cervical carcinoma in situ".	These changes are for specification of the therapy study design.
Protocol Synopsis and throughout the entire document	Exclusion criteria 09 prior treatment with Bardoxolone within 90 days prior to screening was added.	These changes were made to prevent concomitant action between Bardoxolone and SAR339375.
Protocol Synopsis and throughout the entire document	Exclusion criteria 12, 13, and 14 have been added.	These changes are for specification of the therapy study design.
Protocol Synopsis, Section 4.2, and throughout the entire document	Treatment Assignment change to include language that states for open label extension period: "Subjects who require dose reduction will receive SAR339375 as per the same dose that they received in the blinded phase of the study" was added.	These changes are for specification of the therapy study design.
Protocol Synopsis, Section 6.5, and throughout the entire document	Pharmacokinetic Analysis was changed to indicate that Plasma samples will be collected 4 hours post-dose on Day 1, Week 24, and Week 48 of the treatment period for the determination of maximum plasma concentrations. In addition, pre-dose plasma PK samples will be collected (up to 4 hours before dose administration) on Day 1 and through Weeks 4, 12, 24, 36, and 48 for determination of minimum plasma concentrations. The removal of PK blood samples was made to this section. Post baseline visits with PK sampling should be scheduled 7± 3 days after the prior injection of study drug during the double blind, placebo-controlled treatment period. Time and date of PK sampling, as well as the date of the last prior administration of study drug should be recorded in the electronic case report form was added. This section removed the reference PK blood sample collections according to the visits indicated in Table 1 and 2, and also removed the measurements of non-compartmental PK parameters and the appropriateness of PK sampling appropriate, for plasma RG456070, RG0005, and SUM.	These changes are for specification of the therapy study design.
Protocol Synopsis	Statistical Analyses was changed to Statistical Considerations.	This change was made to reflect the standard Genzyme Corporation language.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis	Within Statistical Considerations, Sample size was changed to Sample Size Determination.	This change was made to reflect the standard Genzyme Corporation language.
Protocol Synopsis and throughout the entire document	Changes were made to Statistical Consideration to indicate that: the sample size was changed from 40 to 45. The study will randomize the subjects in a 2:1 ratio.	Sample size calculation updated according to new primary efficacy analysis and randomization ratio.
Protocol Synopsis	A section for analysis population was added in the protocol synopsis.	These changes are for specification of the therapy study design.
Protocol Synopsis, Section 7.2.5, and throughout the entire document	The primary efficacy analysis was added to describe that a linear mixed effect model will be fitted to the eGFR from baseline to Week 48. ATHENA Natural History Study (OBS16374) data will be used as prior information supplementing the placebo arm, using a Bayesian approach. The original two-stage analysis which uses ANCOVA model to analyze individual slope obtained from simple linear regression for each subject was removed.	The two-stage model was replaced with the linear mixed effect model because of the advantages of the latter explained in (34).
Protocol Synopsis	Statistical Methods: Summary of changes in baseline in clinical laboratory parameters and vital signs was removed. Description of safety analyses in the synopsis were simplified with details kept in Section 7.2.4. Description of analysis of demographic and baseline characteristics were removed from synopsis and kept in Section 7.2.3.	Changes were made to include only key information of analysis in the Protocol Synopsis.
Protocol Synopsis	Statistical Methods: Supportive analysis of the primary efficacy endpoint and analysis of secondary endpoints were removed from the Protocol Synopsis and discussed in Section 7.2.5. It was added that pharmacodynamics parameters will be summarized and compared between treatment groups at each time point using descriptive statistics.	Changes were made to include only key information of analysis in the Protocol Synopsis.
Protocol Synopsis and throughout the entire document	Statistical Methods: Interim Analysis removal of Regulus language and replaced with: A non-binding interim futility analysis will be performed under the supervision of the DMC when approximately 24 subjects have completed Week 48 visit. Further details are provided in Section 7.2.7. Additional interim analyses for safety assessment only will be performed periodically by the DMC.	These changes are for specification of the therapy study design.
Protocol Synopsis	Schedule of Events Table 1: Change to title to include “and Follow-up Period”	This change is to include language previously omitted.
Protocol Synopsis	Schedule of Events Table 1: Changes were made to the therapy study design.	These changes were implemented to describe therapy study design and to provide clarity of the study design.
Protocol Synopsis and throughout the entire document	Schedule of Events Table 1: Footnotes have been changed to include details and information to describe the requirement for the study design.	These changes are for specification of the therapy study design.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis and throughout the entire document	Schedule of Events Table 2: Changes were made to the therapy study design.	These changes were implemented to describe therapy study design and to provide clarity of the study design.
Section 1.2.3 Justification of Route and Does Regimen	Justification of Route and Dose Regimen has been changed to 110 mg fixed dose, Q1W	The change was made because the weekly administration of SAR339375 is more likely to result in target kidney concentration which had demonstrated efficacy in a nonclinical model, than Q2W administration, whilst still maintaining an acceptable safety margin. The dosing frequency has been increased from Q2W to Q1W based on observed drug concentrations in human kidney samples. (Preliminary data from ongoing kidney biopsy study PDY16327, formerly RG012-06) relative to predicted target kidney concentrations based on nonclinical kidney PK (mouse and NHP) and efficacy (mouse).
Section 1.2.3 Justification of Route and Does Regimen	The justification was updated to reflect changes related to the study therapy. Determination of NHP doses which gave similar kidney SUM concentrations (AUC SUM) to those observed in the mouse models at pharmacologically active doses was added.	These changes were made to show the therapy study design and for clarification.
Section 1.2.3 Justification of Route and Does Regimen	Nonclinical and Clinical data observed and target and Pre-clinical Toxicology were added to reflect reason for therapy study design.	These changes were made for clarity and to describe the rational and basis for the therapy study design.
Section 2.1 Primary Objectives	The Primary Objective has been separated into two objectives. The first primary objective is to assess efficacy of SAR339375 in reducing the decline in renal function. The second primary objective is to assess the safety and tolerability of SAR339375 in subjects with Alport syndrome.	For clarification the primary objective has been separated into two objectives to further determine the effects on safety/tolerability, and efficacy.
Section 2.2 Secondary Objectives	The Secondary Objective has been edited to include specific PK parameters (C_{max} and C_{trough}).	For clarification of the secondary objective the addition of the PK parameters has been added.
Section 2.3 Exploratory Objectives	Exploratory Objective to assess changes in quality of life (QoL) in subject with Alport syndrome following administration of RG-012 was removed	Removal of exploratory endpoints evaluating changes to biomarkers and measurement of quality of life (QoL) of subjects was considered. The assessment of the effect of SAR339375 QoL would add complexity for the conduct of the study and subjects. In addition, there was no change in SF36 data in early CKD subjects from the ATHENA registry (OBS16374, formerly RG012-01), thus the analysis has been removed.
Section 2.3 Exploratory Objectives	Exploratory objectives were added and/or removed.	These changes were implemented to describe therapy study design and to provide clarity of the study design.

Section # and Name	Description of Change	Brief Rationale
Section 3.1 Overall Study Design	The number of subjects was increased from 40 to 45	The changes were made to include recruitment of approximately 45 adult subjects both male and female preventing the exposure of children at this early stage of development of SAR339375.
Section 3.1 Overall Study Design	The description of the study design was revised to include and clarify study treatment design for the double-blind, placebo-controlled treatment period, the open label treatment extension period, for dose reduction, and the follow up period.	These changes were implemented to describe therapy study design and to provide clarity of the study design.
Section 3.2.1 Inclusion Criteria	I01, I02, I03, I04, and I05 were modified to clarify the inclusion criteria in the study	The study is modified to update inclusion criteria to include recruitment both male and female subjects and preventing the exposure of children at this early stage of development of SAR339375. The updated inclusion criteria will allow for expansion of the study population and prohibit limitation to X-linked Alport Syndrome. In order to better identify rapid progressors, additional renal function inclusion criteria were added based on the baseline eGFR and proteinuria. These new criteria are based on the analysis of the ATHENA registry data. Inclusion criteria were also updated to include ACE/ARB treatment at stable dose for at least 30 days since ACE/ARB are the current standard of care.
Section 3.2.2 Exclusion Criteria	E01, E03, and E05 were modified to provide clarity of exclusion criteria of the study, E09, E12, E13, E14 were added.	These changes were implemented to describe therapy study design and to provide clarity of the study design.
Section 3.2.3.2 Follow-up for Drug Discontinuation/Subject Withdrawal from the Study	Subjects who are withdrawn from the study will not be replaced was removed from this section.	This change was made to provide specification to the therapy study design.
Section 3.3 Screen Failures	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 3.4 Discontinuation of the Study	Study stopping criteria was modified to include Grade 3 (or higher) AEs, or any death or two SAEs considered at least possibly related to participation in the clinical trial.	This criteria has been modified to reflect the information we have for the rate of occurrence of AEs and SAEs in the other trials and particularly on the ATHENA registry study.
Section 4.1.1 Identity of Investigation Products	Table 3 Identity of Investigational Products has been removed and replaced with descriptive text about the study drug dosage form.	The changes are specifications for the therapy study design.
Section 4.1.2 Packaging and Labeling, Handling and Accountability	Details were modified in this section to describe how the study drug and placebo dosage forms each will be supplied.	This change was made to provide specification to the therapy study design.

Section # and Name	Description of Change	Brief Rationale
Section 4.2 Treatment Assignment	For open label period, addition of details that subjects who require dose reduction will receive SAR339375 as per the same dose that they received in the blinded.	This change was made to provide specification to the therapy study design.
Section 4.3 Treatment Administration	Modification to this section was made to describe the frequency of obtaining a subject's platelet count and when the platelet count will be obtained.	This change was made to provide specification to the therapy study design.
Section 4.4 Home Injection	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 4.5 Dose Reduction	Modification to this section was made to describe the frequency of obtaining a subject's platelet count and when the platelet count will be obtained.	This change was made to provide specification to the therapy study design.
Section 4.7 Prior and Concomitant Medications	Removal of text: Prior/concomitant medication data collected in the ATHENA study may be used for this study.	The information obtained from the ATHENA study about prior or concomitant medications will not be used in this study.
Section 5 Study Procedures	Change to this section to include rescreening of subject will be permitted with consultation of the Study Medical Manager.	This change was made for clarification.
Section 5.1 Screening	Modification in schedule of events to screenings was made to describe screenings required prior to drug administration.	This change was made for clarification.
Section 5.2 Double-blind, placebo-controlled treatment period	Details were added to this section to describe dose modifications to IMP dose, and the schedule of events for the study drug.	This change was made for clarification.
Section 5.3 Open-label extension treatment period	Details were added to this section to describe dose modifications to IMP dose, and the schedule of events for the study drug.	This change was made for clarification.
Section 5.4 Early termination	Details were added to this section to describe the schedule of events for a subject that discontinues before completing the treatment period for the study drug.	This change was made for clarification.
Section 5.5 Follow up period	Details were added to this section to provide clarification of the follow up weeks from the last scheduled study visit in the active treatment period.	This change was made for clarification
Section 6.2.1 Adverse events	Details were added to this section to provide clarification on information about collection of information about AEs.	This change was made for clarification.
Section 6.2.1 Adverse events	Table 4 was modified to include another column that addressed Life Threatening Event (Grade 4).	These changes were implemented align with standard Genzyme Corporation data collection process.
Section 6.2.1 Adverse events	Table 6 was removed.	This change was made to incorporate standard Genzyme Corporation processes.

Section # and Name	Description of Change	Brief Rationale
Section 6.2.3 Procedures in case of pregnancy	Collection of pregnancy information was added to this section.	These changes were made to align with standard Genzyme Corporation process.
Section 6.2.4 Sponsor Obligation	This section was added and details about the Sponsor' Obligations through the course of the study were provided about the storage, dispensing, handling, and quality of the SAR339375 drug product.	These changes were made to align with standard Genzyme Corporation process.
Section 6.2.5 Guidelines for Reporting Product Complaints (SAR339375)	This section was added that provide guidelines for reporting product complaints (SAR339375).	These changes were made to align with standard Genzyme Corporation process.
Section 6.2.11 Monitoring of Platelet Count	Modification to this section was made to describe the frequency of obtaining a subject's platelet count and when the platelet count will be obtained.	This change was made to provide specification to the therapy study design.
Section 6.2.13 Safety Oversight	Details were added to this section to include information about the internal Data Monitoring Committee and their review of data throughout the study.	These changes were made to align with standard Genzyme Corporation process.
Section 6.3.1 Estimated GFR	Changes to the information about the calculation of eGFR were provided. Removed Section 6.3.2 of SF-36 from previous version of protocol.	This change was made to provide clarification.
Section 6.4 Pharmacodynamic Assessments and Biomarkers	Modification to this section included the removal of several assessments listed in the Schedule of Events table.	This change was made to provide specification to the therapy study design.
Section 6.5 Pharmacokinetic Assessments	Modifications to this section were made to provide details of the changes to the pharmacokinetic assessments.	These changes are for specification of the therapy study design.
Section 6.6 Disposition of Samples after Study Completion	Modification to this section was made to provide clarity on the disposal of PK samples following completion of CSR and the disposal of ADA samples.	These changes were made to align with standard Genzyme Corporation process.
Section 7.1.1 Safety Endpoints and Protocol Synopsis	Addition of safety endpoint association of AE with ADA was added to this section.	This change was made to provide specification to the therapy study design.
Section 7.1.2 Efficacy Endpoints and Protocol Synopsis	Modifications to this section provided clarity on primary endpoint and secondary endpoints. Absolute and percentage change in eGFR values from baseline at Week 96 was moved to Section 7.1.3.	This change was made to provide clarification of the open label extension period of the therapy study design.
Section 7.1.3 Exploratory Endpoints: Efficacy, Pharmacodynamic and Biomarker Endpoints	Modifications to this section added exploratory endpoint of absolute and percentage change in eGFR values from baseline at Week 96, and also removed assessments no longer performed during the treatment period for this study.	These changes are for specification of the therapy study design.

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Statistical Methods and Analyses	Changes were made to this section to describe the statistical analysis plan development. This section is modified to include primary and secondary analyses.	These changes were made to align with standard Genzyme Corporation process.
Section 7.2.2 Analysis Populations	Modifications to this section removed the per protocol population and also included considerations on the subjects who only receive a partial dose.	These changes are for specification of the therapy study design.
Section 7.2.4 Safety Analysis	Changes to this section include information about the way safety analyses will be performed on the safety population.	These changes are made to align with the standard Genzyme Corporation process.
Section 7.2.5 Efficacy Analysis	This section has been updated with replacement of primary efficacy analysis and changes according to the modifications made to efficacy endpoint.	These changes were made to align with standard Genzyme Corporation process.
Section 7.2.6 Pharmacodynamic Analysis	This section has been removed; information has been incorporated into Section 7.2.6 Other Analyses.	These changes were made to align with standard Genzyme Corporation process.
Section 7.2.7 Pharmacokinetic Analysis	This section has been removed, information has been incorporated into Section 7.2.6 Other Analyses.	These changes were made to align with standard Genzyme Corporation process.
Section 7.2.7 Interim Analysis	Modification to this section provide information on nonbinding interim futility analysis and when this will be performed.	These changes were made to align with standard Genzyme Corporation process.
Section 9.1.1 Rapid Notification on Serious Adverse Events	Slight rewordings and additional details were added regarding exam and laboratory information to report, and regarding the timeframes in which to report. A statement about what to do when the eCRF does not work was added.	These changes were made to align with standard Genzyme Corporation process.
Section 9.1.2 Dosing Deviations	Modification to this section provided information on procedure for symptomatic overdose with IMP.	These changes were made to align with standard Genzyme Corporation process.
Section 9.2.2 Ethical Review	Section Header was changed from “Institutional Review Board/Ethics Committee” to “Ethical Review”. This section also provides details on review by IRB/IEC for approval before implementation of changes made to the study design.	These changes were made to align with standard Genzyme Corporation process.
Section 9.2.3 Informed Consent	Changes were made to this section to provide information about informed consent for participation in this study.	These changes were made to align with standard Genzyme Corporation process.
Section 9.2.4 Regulatory and Ethical Considerations	Section Header was changed from “Ethical Considerations” to “Regulatory and Ethical Considerations” in order to incorporate information about the study being conducted in accordance with the protocol.	These changes were made to align with standard Genzyme Corporation process.

Section # and Name	Description of Change	Brief Rationale
Section 9.2.5 Sponsor Obligation	Section Header was changed from "sponsor" to "Sponsor Obligation" additional details were added regarding the Sponsor's reporting obligations. IN addition, details were added regarding the storage, dispensing, handling and quality of SAR339375 drug product.	These changes were made to align with standard Genzyme Corporation process.
Section 9.2.7 Guidelines for reporting product complaints (SAR339375)	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.3 Study Documentation, Confidentiality, and Records Retention	Section Header was changed from "Records Retention" to "Study Documentation, Confidentiality, and Records Retention" The information in this section was modified to provide details about storage of subject data.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.4 Data Quality Control and Quality Assurance	This entire section and its subsection were changed in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.5 Audits and Inspections	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.7 Publication Policy	Section Header was changed from "Publication Policy/Disclosure of Data" to Publication Policy" and describes that the results of the study may be published or presented at scientific meetings.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.8 Dissemination of Clinical Study Data	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.9 Data Protection	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.10 Data Quality Assurance	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.11 Source Documents	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 9.3.12 Study and site closure	This entire section was added in the amended protocol.	These changes were made to align with standard Genzyme Corporation process.
Section 10 Supporting Documentation and operational Considerations, and Section 11 References	Section 10 (Supporting Documentation and Operational Considerations) was created and the prior Section 10 (References) was renumbered to Section 11.	Section 10 was inserted to align with the Genzyme Corporation standard, following transfer in the development and commercialization of RG-012.

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical error corrections) were implemented throughout the protocol.

10.8.10 Clinical study protocol Version 3.0 (16 August 2017)

Table 8 - Summary of key changes to Protocol RG012-03, Version 3.0

Heading	Summary of Change
CONTACT LIST	Has been removed from the protocol; A full list of study contacts is provided in the Study Reference Manual. Removed Clinical Project Manager, Clinical Operations.
PROTOCOL SYNOPSIS	Synopsis changes have been made to harmonize the synopsis with the multiple changes specified in this summary of changes.
Section 1.1.4.2 Study RG012-05	Has been updated to include additional details regarding the changes in platelet counts observed in the 220 mg dose cohort.
Section 1.3.1 Potential Risks	'Potential for Thrombocytopenia', has been updated to include class related side effects (decreased complement and elevated liver function tests) and added injection site reactions as potential side effects as observed in RG-012 clinical trials. Thresholds for increased monitoring and dose reduction have been removed.
Section 3.1 Overall Study Design	Has been modified to state that the threshold for pausing study drug dosing is platelets <100 000/microL consistent with the new Grading System for Adverse Events of Interest and that AEs must return to normal or >= Grade 1 for injection site reactions.
Section 3.2.2 Exclusion Criteria	Has been modified to: • Exclude those with a weight >110 kg (this negates the need for two SC injections when study drug is administered).
Section 3.2.3.1 Individual Treatment Stopping Criteria	Has been modified to: • Be consistent with the new Grading System for Adverse Events of Interest. • Adjusted the unintended weight loss to >= 9% to be consistent with a Grade 3 (severe) severity per the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017. • Added guidance to pausing dosing with any Grade 2 AE that is not addressed in the Grading System for Adverse Events of Interest.
Section 3.3 Discontinuation of Study	Was modified to clarify the study stopping criteria and the potential outcomes from the SRC review of significant AEs.
Section 4.4 Dose Reduction	Has been modified to reflect the new Grading System for Adverse Events of Interest. Moderate (Grade 2) AEs will result in a pause in dosing. Additional details are provided for dose reduction rules for AEs of Interest (thrombocytopenia, liver dysfunction, renal function, and injection site reactions).
Section 5.2 Double-Blind, Placebo-Controlled Treatment Period	Has the following modifications: Hearing Assessment added at baseline, Week 48, and early termination visits. Hearing loss can occur in Alport syndrome. • For subjects age 12-17, physical exam to include height and Tanner stage at baseline, Week 24, and Week 48. In addition, FSH, LH, and total testosterone will be measured at baseline, Week 24, and Week 48. This is to assess pubertal development. • Clarified that a 2 hr observation period is required after administration of the first dose at the baseline visit.

Heading	Summary of Change
Section 5.3 Open-Label Extension Treatment Period	Has the following modifications: • Hearing Assessment added at Week 96 and early termination visits. • For subjects age 12-17, physical exam to include height and Tanner stage at Weeks 48, 72, and 96. In addition, FSH, LH, and total testosterone will be measured at Weeks 48, 72, and 96.
Section 5.4 Early Termination	Was modified to include: • Hearing Assessment. • For subjects age 12-17 physical exam to include height and Tanner stage. In addition, FSH, LH, and total testosterone will be measured.
Section 6.2.1 Adverse Events	Was modified with: • A new protocol-defined Grading System for Adverse Events of Interest (Table 4) was updated. Thrombocytopenia, liver function abnormalities, renal function, and weight loss (Injection site reactions are also considered an adverse event of interest but are covered separately in Section 6.1.9 and Table 8) were identified as adverse events of interest based upon nonclinical toxicology studies with RG456070 as well as clinical experience with RG-012 and other oligonucleotides. This new grading system is based upon the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017. This grading system is more conservative than the CTCAE grading system for oncology subjects. • For AEs not considered an event of interest, the Classification of Adverse Events by Severity (Table 5) was modified.
Section 6.2.4 Physical Examination/Body System Assessment	Was modified to add height and Tanner staging for subjects 12 to 17.
Section 6.2.7 Hearing Assessment	Added. Hearing will be assessed during the, Treatment Period and Extension Period, using a pure tone audiometry (air only) test at defined frequencies at baseline, Week 48 and 96.
Section 6.2.8 Gonadotropins	Added. For subjects ages 12-17 FSH, LH, and total testosterone will be measured.
Section 6.2.9 Monitoring of Platelet Count	Common Terminology Criteria for Adverse Events [CTCAE] ≥ Grade 1 thrombocytopenia), <125 000/microL was deleted and information on Total protein and monitoring platelets was added to Section 6.2.8.
Section 6.4 Pharmacodynamic Assessments and Biomarkers	Was modified to remove the specific podocyte assay.
Section 7.2.1 Determination of Sample Size	Changed to: Probability of observing a 50% effect size is provided rather that for a 40% effect.
Section 10 REFERENCES	Removed reference to CTCAE v4.03 (2010) and added website links.

10.8.11 Clinical study protocol Version 2.0 (29 June 2017)

Table 9 - Summary of key changes to Protocol RG012-03, Version 2.0

Heading	Summary of Change
Protocol Title	Change was made due and dose regimen from weekly to every two weeks. A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics of RG-012 for Injection Administered Every 2 Weeks in Patients with Alport Syndrome
Synopsis	Changes have been made to harmonize the synopsis with the multiple changes specified in this summary of changes. Additionally, the following changes are made: • Study personnel and contact details were updated including new contact details for reporting of Serious Adverse Events and Anti-Drug Antibody laboratory. • The Independent Data Monitoring Committee has been replaced by a Safety Review Committee who will review safety data on a monthly and ad-hoc basis. Changes to reflect this have been made in the Synopsis, Section 3.3 'Discontinuation of the Study', addition of the new Section 6.1.9 "Safety Oversight" and deletion of Section 9.1.3 Independent Data Monitoring Committee. The synopsis section has been expanded to include further details to outline Safety Management: • Monitoring of platelet count • Option for dose reduction • Individual treatment stopping criteria and study stopping criteria added to the synopsis
Section 1 'Introduction' 1.1 'Background'	• Additional information provided on Alport Syndrome, RG-012 and its target, micro-RNA-21 • More information is provided on the non-clinical studies conducted to date, including in vivo studies, and the GLP 26-week mice and 39-week monkey studies, with the conclusion updated to reflect the higher dose implemented with this amendment. • An update is provided from the ongoing Phase 1 study, RG012-05 in healthy subjects, in which dose escalation from fixed doses of 55 mg, 110 mg (corresponds approximately to 1.5 mg/kg in a 73 kg subject) and 220 mg have completed and follow up is ongoing.
Section 1.2 'Rationale'	Updated with information on the justification of the target and the study design. The justification of the route and dose regimen have also been updated to reflect the increased dose and new regimen of 1.5 mg/kg Q2W.
Section 1.3 'Potential Risks and Benefits'	New section added.
Section 2 'Study Objectives'	• Efficacy of RG-012 (in reducing the decline in renal function) is now included as a primary objective of the study. This is reflected in the study title, which is changed on the title page, Investigator protocol agreement page and synopsis. • The secondary objectives have been revised to focus on the plasma PK (including the individual concentrations and sum of the parent compound and it's major metabolite) and potential formation of anti-drug antibodies. As such, the objective "To assess the effect of RG-012 on endogenous renal microRNA-21 (miR-21)" has been removed. • The biomarker objective has been moved from a secondary objective to be exploratory objective

Heading	Summary of Change
Section 3 'Investigational Plan'	• The sample size has been increased from 30 to approximately 40 subjects. • The double-blind, placebo controlled treatment period has increased from 24 to 48 weeks. • The dose has been changed to be 1.5 mg/kg or placebo (ratio 1:1) for 48 weeks (previously was 110 mg or 220 mg RG-012, or placebo for 24 weeks). • RG-012 will be administered every 2 weeks instead of weekly. • Details of the open-label extension have been added. This is available to subjects who complete the original 48-week study. All subjects will receive Q2W active treatment with RG-012. As a result 'Active treatment period' has been replaced with 'Double-Blind, Placebo-Controlled Treatment period' throughout the protocol to distinguish from the 'Open Label Extension Period'. • Visits previously assigned to be performed as 'Home visits' have been reassigned as study site visits, with the option for them to be performed at an Alternate Location. (Further details as to the training, qualification and delegation of the personnel performing these visits is provided in Section 5.7 'Alternate Location Visits'.) • Study center information has been updated. • Information on what and how data from the ATHENA study can be used has been updated (some information moved to Section 3.2.1 Inclusion Criteria) • Due to the multiple ascending dose study having completing, details of the Sentinel cohort and how the study will progress as planned have been removed. • Details of assessments to be performed in the Double-Blind, Placebo-Controlled Treatment Period have been removed with reference made to Table 1 instead. • The text was updated to align with changes in the eligibility criteria and Section 4.6 Prior and Concomitant Medication, to state that for concomitant medication other than ACE and ARBs, the dose can be adjusted to maintain standard of care. • Dose reductions are now allowed in response to a Grade 2 treatment-emergent adverse event or thrombocytopenia. (Full details of this are provided in Section 4.3 'Dose Reductions') • Patients will be followed up for 6 weeks upon completion of either the double-blind, placebo controlled treatment period or the open-label extension (previously a 12 week follow up was specified following completion of the main part of the study). • The overall duration is increased from approximately 60 weeks to approximately 106 weeks (from screening through completion of follow-up).

Heading	Summary of Change
Section 3.2 'Study Population'	• Removed the requirement to be able to provide written informed consent • Women have been excluded from the study. Related eligibility criteria have been removed (contraception requirements and exclusion of female subjects who are pregnant or lactating) • The age requirement has been revised to include the option to include subjects aged 12 to 60 years following SRC review of the data from the first 10 subjects (previously was 18 to 65 years). • Specified that subjects must have a diagnosis of X-linked Alport syndrome (clinical and genetic diagnosis) • eGFR related inclusion criteria have been simplified and updated to reflect the increased age range. Revised to: - Baseline eGFR value must be between 40 and 90 mL/min/1.73 m^2 (previously was a first screening eGFR of 45 to 90 ml/min/1.73 m^2 and final screening/baseline eGFR >30 ml/min/1.73 m^2) - eGFR Slope criteria are now only applicable for subjects aged 31-60. For these subjects, the Baseline eGFR progression criteria revised to broaden the amount of time the measurements can be collected from. - Changes were also made on how the data from subjects participating in the ATHENA study can be used • The proteinuria limit was reduced from ≥500 mg to ≥300 mg protein/g creatinine, which needs to be met at the screening visit (previously was initial screening and baseline visits) • Clarified that subjects currently taking an ACE inhibitor and/or ARB, the dosing regimen should be stable for ≥30 days prior to screening. • Contraception have been simplified, to require the subject to agree to use a condom during heterosexual intercourse from screening through to 65 days after the last dose of study drug (previously additional measures were an option and restriction was applicable for 30 days after the last dose of study drug) • Drug screen requirements/options for Investigator discretion updated to include cannabinoids. • Simplified requirements for platelets, hemoglobin and total white cell count to be within normal limits • ALT, AST and GGT must now all be less than 1.5 x ULN (previously was 3 x ULN) • Concomitant medication (prescribed and over the counter) exclusion criteria have been updated to reflect that changes to concomitant medication are no longer prohibited but must be reported to the study staff. • Greater clarity has been provided to the description clinically significant illnesses that would prevent a subject from joining the study. Evidence of urinary obstruction or difficulty in voiding and history of hypocomplemtemia have been added as exclusionary concomitant illnesses. • Other criteria have been combined and/or reworded for greater clarity.

Heading	Summary of Change
Section 3.2.1 Inclusion Criteria	Information on what and how data from the ATHENA study can be used has been updated and some information moved to Section 3.2.1 Inclusion criteria
Section 3.2.3.1 'Individual Treatment Stopping Criteria'	• Hyperkalemia (K >6.0 mEq/L) (removed the need to be demonstrated at 2 sequential study visits) • Unexplained decrease in body weight >7% or >5 kg from baseline (previously was >10% form baseline) • Anemia as indicated by hemoglobin ≤10 g/dL (previously was <9 g/dL) • Hypoalbuminemia <2.4 g/dL (previously was <2 g/dL) or a decrease in albumin of >1 g/L from baseline (previously this was only applicable to subjects with a baseline albumin of <3 g/dL) • Platelets <50 x 10^9/L (≥Grade 3 thrombocytopenia) (previously was an error in the unit) • Added: Prothrombin time (PT) and aPTT >2 x ULN*
Section 3.2.3 'Withdrawal, Removal, and Replacement of Subjects'	• Section 3.2.3 'Withdrawal, Removal, and Replacement of Subjects' has been revised as follows: • Differentiation has been made between a subject choosing to discontinue study drug and to withdraw from the study. Any subject who prematurely discontinues study drug should be followed until the scheduled end of follow up period, whereas subjects who withdraw consent will not be followed. It has been noted that subjects will be replaced at the discretion of the Sponsor.
3.2.3.2 'Follow-up for Drug Discontinuation/Subject Withdrawal'	• Changes have been made in section 3.2.3.2 Follow-up for Drug Discontinuation/Subject Withdrawal from the Study to reflect these changes. • Section 3.2.3.2 'Follow-up for Drug Discontinuation/Subject Withdrawal' has also been updated with regards to the need to follow up of any subjects that discontinue study drug due to an AE.
Section 3.3 'Discontinuation of the Study'	• Section 3.3 'Discontinuation of the Study' has been updated to reflect that additional enrollment and/or dosing (previously was just enrollment) will be suspended pending review and recommendation by the SRC.
Section 4 "Treatment Procedures" Section 4.1.2 "Packaging and Labeling"	• Previous Section 4.1.2 and Table 4 'Treatments Administered' has been replaced by section (new) 4.3 Treatment Administration, with the wording revised • Packaging and Labeling section (old 4.1.3, new 4.1.2) have been updated to state that all labels will be in English and the local language will meet CFR 312.6 requirements and meet EudraLex Annex 13 requirements specific to each country.
Section 4.1.3 'Study Drug Supply', Storage, and Tracking	Section 4.1.3 Study Drug Supply, Storage, and Tracking wording has been updated to state that the Sponsor or designee is responsible for monitoring the logistics of supply, that supplies can only be dispensed in accordance with the protocol and more details on the requirement of the drug inventory have been added.
Section 4.2 'Treatment Assignment'	Section 4.2 'Treatment Assignment' has been updated to reflect the changes in the new study design.

Heading	Summary of Change
Section 4.3 'Treatment Administration'	Previous Section 4.1.2 and Table 4 'Treatments Administered' has been replaced by section (new) 4.3 Treatment Administration, with the wording revised.
Section 4.4 'Dose Reduction'	New Section 4.4 'Dose Reduction' has been introduced to allow dose reductions in response to CTCAE Grade 2 treatment-emergent AEs.
Section 4.5 'Medical History and Prior/Concomitant Medications'	Section 4.5 Medical History and Prior/Concomitant Medications has been split, with Medical History moved to Section 6 and updated to collect Family History relevant to Alport syndrome and renal disease, in addition to the subjects significant ongoing illnesses.
Section 4.6 'Prior and Concomitant Medications'	Prior and Concomitant Medications have been split into their own section, Section 4.6. This section has been updated to allow subjects to start taking new or adjust the dose of prescription or over-the-counter medications or herbal supplements and that any changes need to be reported to the site. Concomitant medications should still be maintained at a stable dose and regimen, particularly if they affect blood pressure or renal function, however they may be adjusted to maintain standard of care.
Section 5 'Study Procedures'	Table 1, Table 2 and Section 5 'Study Procedures' have been revised to: • Remove pregnancy and FSH tests as women are excluded from the study. • Additional visits have been added to reflect the longer study duration. • Visit windows have been added. • Week/day numbering has been simplified in Section 5, to just refer to the Week number. • Revise PK and complement profiles on applicable days so only collected until 4 hours post dose (was up to 24 hours). • Biomarkers have been grouped together in Section 5
Section 5.3 'Open Label Extension Period'	Table 2 and Section 5.3 have been added to describe the assessments required for the Open Label Extension Period.
Section 5.6 'Contraception'	Section 5.6 'Contraception' has been removed since women are excluded form participation in the study and contraception for male subjects has been specified in the inclusion criteria as to be required to use a condom.
Section 6, 'Background, Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Assessments'	• Section 6, 'Background, Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Assessments' revised to add 'Background' assessments. • Treatment-emergent AEs have been defined. • Follow up of AEs present at the time of subject withdrawal has been defined. • Table 6 Adverse Event Outcome has been updated to add 'recover' in the same instances as resolved was recorded. 'Lost to follow-up' has been changed to 'Unknown'. 'Death' has been changed to 'Fatal'. • Procedures in Case of Pregnancy has been revised considering the exclusion of women from the study, but remains to describe requirements if the partner of a male subject should become pregnant. • The Renal biopsy has been removed as a study assessment

Heading	Summary of Change
Section 6.1 'Medical History and Family History'	Medical History and Family History has been added as Section 6.1 described above so all section numbers have increased by one.
Section 6.2.8 'Monitoring of Platelet Count and Total protein decrease'	New section 6.1.8 'Monitoring of Platelet Count and Total protein decrease' has been added to describe the reflex testing in response to a decrease in total protein or platelet count and outline the required monitoring and response to changes in platelet count.
Section 6.2 'Safety Assessments'	(New) Section 6.2 'Safety Assessments' has been updated to provide more details as to the areas included in the clinical laboratory tests.
Section 6.3.1 'Estimated GFR'	Additional information on the options to determine the estimated GFR have been added to Section 6.3.1 Estimated GFR.
Section 6.4 'The Biomarker'	The Biomarker section 6.4 has been updated to detail all pharmacodynamic and biomarker assessments.
Section 6.5 'Pharmacokinetic Assessments '	Section 6.5 Pharmacokinetic Assessments has been updated to reflect the reduced PK sampling profiles for the study and to state the Sum of the parent and major metabolite will be measured.
Section 7 'Statistical Analysis' Section 7.1.1 'Safety Endpoints'	Updates were made to the statistical section in response to the change in the study design, with the increased sample size, extended treatment period and visits, optional extension treatment period, inclusion of Treatment-emergent AEs.
7.1.2 "'Efficacy Endpoints'	Safety comparisons will be assessed through change from baseline, incidence and titer of ADA's has been reclassified as a safety endpoint.
7.1.3 'Exploratory Endpoints: Efficacy, Pharmacodynamic and Biomarker Endpoints'	Efficacy endpoints have been revised and updated to reflect the new treatment duration, with comparisons being made at Weeks 24, 48 and 96. Additional efficacy and exploratory efficacy endpoints have been included.
Section 7.2.8. 'Interim Analysis'	• Interim Analysis details have been added in a new section, Section 7.2.8. • Exploratory endpoints were updated to reflect the objectives and changes in podocyturia was added as an exploratory endpoint (updates made to Table 1 and Section 5 'Study Procedures' to reflect sample collection). • The efficacy analysis was updated in line with the inclusion of efficacy as the primary endpoint of the study. • Details were added to describe the analysis for the pharmacodynamic endpoints. • The pharmacokinetic analysis section was expanded and PK parameter definitions added. • Interim Analysis details have been added in a new section, Section 7.2.8.
Section 10 'References'	Section 10, References was updated with new references

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