16.1.9 Documentation of Statistical Methods

This section contains the following documents:

- AG10-202 Statistical Analysis Plan, version 1.0, dated 03 July 2019
- AG10-202 Statistical Analysis Plan, version 2.0, dated 11 May 2021
- AG10-202 Statistical Analysis Plan, version 3.0, dated 18 October 2021
- AG10-202 Statistical Analysis Plan, version 4.0, dated 02 May 2023
- AG10-202 Statistical Analysis Plan, version 5.0, dated 05 September 2025

Statistical Analysis Plan

Sponsor:	Eidos Therapeutics, Inc.
Protocol No:	AG10-202
PRA Project Id:	EDS202OL-E202OL
Version Date:	03-July-2019
Version No.:	0.1
Title:	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
CRF Version No./Date:	Version 2.0/24-Sep-2018

1.0 Approvals

Eidos Therapeutics	
Representative/ Title:	Martha Cao/Director of Biostatistics
Signature /Date:	Martha Cao July 3, 2019
PRA	
Project Manager/Title:	Tricia Oehler/ Senior Project Manager
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Biostatistician / Title (Owner):	Sheila A. Quinn/ Senior Principal Biostatistician
Signature /Date:	[redacted]

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Eidos Therapeutics, Inc. Protocol AG10-202.

3.0 Scope

This plan is a living document that will be created during the trial start-up and will be finalized prior to database lock. This SAP will require sign off from the PRA Project Manager, the Biostatistician and the Sponsor.

The Statistical Analysis Plan outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, primary, secondary and exploratory endpoints, concomitant medications, adverse events handling, laboratory data, including pharmacokinetic and pharmacodynamic parameters, and physical examinations

4.0 Introduction

The SAP describes the statistical methods to be used during the reporting and analyses of data collected under Eidos Therapeutics, Inc. Protocol AG10-202.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This SAP version 1.0 was developed using the protocol Amendment 2 dated 06August2018 and CRF version 2.0 dated 25September 2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

4.1 Changes from the Protocol Amendment 2

The following changes from the protocol Amendment 2 are reflected in the SAP version 2.0: These changes will be incorporated in the protocol Amendment 3.

- Baseline values are defined in the protocol Amendment 2 as the last value obtained on or before the date of the first dose from Study AG10-201. For SAP version 1.0, baseline is defined as the last value obtained on or before the first dose of Study AG10-202.
- There are no time to event analyses planned for clinical events as stated in the protocol Amendment 2.
- Since this is a single arm study, data will be not be reported by treatment as stated in the protocol Amendment 2.

5.0 Study Objectives

The primary objective of this study is to evaluate the long-term safety and tolerability of AG10 administered to adult patients with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) who completed the AG10-201 study.

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of AG10 administered orally twice daily in patients with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of AG10 as assessed by established assays of transthyretin (TTR) stabilization, including Fluorescent Probe Exclusion (FPE) assay and Western

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blot, and to describe the PK-PD relationship of AG10 in adult patients with symptomatic ATTR-CM.

Exploratory objective of this study is:

- to describe the long-term effects of AG10 on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.

6.0 Study Design

This study is a Phase 2 long-term, open-label study in up to 55 male and/or female patients with symptomatic ATTR-CM, ≥18 years of age, who have completed participation in the AG10-201 double blind study.

The duration of each patient's participation in the study will continue based on periodic recommendations of the AG10 Data Monitoring Committee (DMC) and/or registration of the product for the treatment of symptomatic ATTR-CM. This prospective multicenter, open-label study will evaluate the long-term safety, tolerability, PK and PD of AG10 administered to eligible patients with stable heart failure therapy.

Eligible patients will begin dosing AG10 800 mg administered twice daily. Information on AEs and concomitant medications will be collected throughout the study. The safety of the study will be monitored by an independent AG10 program-wide Data Monitoring Committee (DMC)

The schedule of assessments is provided in Table 1 below.

Table 1. Schedule of Assessments

	Day 1	Day 14 (±3)	Day 45 (±7)	Visits Every 3 months (±7 days)[f]	7 to 14-day follow-up visit (ET)[a]
Written Informed Consent	X				
Inclusion/Exclusion Criteria Review	X				
Medical History	X				
Physical Exam[b]	X	X	X	X	X
Vital Signs	X	X	X	X	X
Resting transthoracic echocardiogram	X[c]			X	
12-lead resting ECG	X	X	X	X	X
PD assays[d]	X	X	X	X[d]	
PK sample collection[d]	X	X	X	X[d]	
Prealbumin collection[d]	X	X	X	X[d]	
Study drug dosing during visit	X	X	X	X	
Clinical laboratory assessments	X	X	X	X	X
Pregnancy test[e]	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Dispense IMP	X		X	X	
Review Patient Dosing Diary		X	X	X	
Collect Unused IMP			X	X	
Adverse events	X	X	X	X	X

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a. When a patient discontinues study participation, the patient will be asked to return to the study center for the Follow-up Visit. The Follow-up Visit should be performed within 7 to 14 days after last dose.
b. Complete PE including body weight at all visits.
c. Resting echocardiogram at Day 1 and every 3 months.
d. Please refer to updated lab manual on timing of PK, PD and prealbumin collections. Samples will be collected at Day 1, Day 14, Day 45, 3 months and 6 months from Day 1 visit (predose only).
e. Females of Child-Bearing Potential only. Urine pregnancy test at all visits.
f. Visits every 3 months from Day 1 visit.

6.1 Sample Size Considerations

The planned number of patients is determined by the number of eligible and interested patients that have completed the study AG10-201 and therefore is not expected to be greater than 55 patients.

6.2 Randomization

Not Applicable

7.0 Study Endpoints, Variables and Covariates

7.1 Primary Endpoint

The primary objective of this study is to characterize the safety and tolerability of AG10 administered long-term to adult patients with symptomatic ATTR-CM who have completed the study AG10-201. This will be assessed by the following endpoints: Safety will be assessed by collection of treatment-emergent adverse events (AEs), physical examination findings, clinical events (including death, myocardial infarction, stroke, heart failure hospitalization, emergency presentation for worsening heart failure), vital signs, electrocardiogram (ECG) data (PR, RR, QRS, and QT intervals), and clinical laboratory parameters.

7.2 Secondary Endpoints

Pharmacokinetics: Predose PK blood samples will be collected at Day 1, Day 14, Day 45, 3 months and 6 months from Day 1 visit. The PK measurements of plasma concentration of AG10 and metabolite AG10 acylglucuronide will be performed by a designated bioanalytical laboratory.

Pharmacodynamics: Predose PD blood samples will be collected at Day 1, Day 14, Day 45, 3 months and 6 months from Day 1 visit. The PD measurements of AG10 will be assessed by established assays of TTR stabilization, including FPE assay and Western blot, and to describe the PK-PD relationship of AG10 in adult patients with symptomatic ATTR-CM. Changes in circulating prealbumin levels will also be measured as a PD marker.

7.3 Exploratory Endpoints

The exploratory objective of this study is to describe the long-term effects of AG10 on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.

8.0 Definitions

First Study Drug Dose

For all subjects, the first study drug dose date is defined as the date of first dose in AG10-202.

Baseline and Change from Baseline

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Baseline values are defined as the last pre-dose value obtained on or before the date of the first study drug dose.

Change from Baseline = (post-Baseline value – Baseline value).

Completion of study

The completion of study is defined as an answer of “Yes” to the question “Did the subject complete the study (including Follow-Up)?” on the form of End of Study in the CRF.

Completion of treatment

The completion of treatment is defined as an answer of “Completed” to the question “End of Treatment Status” on the form of End of Treatment in the CRF.

Prior and Concomitant Medications

Prior and concomitant medications reported in the AG10-201 study are included (imported) in the AG10-202 database and considered prior medications in the AG10-202 study. Sites were instructed to enter any new medications (started after the end of the AG10-201 study) in the concomitant medication form of EDC. For reporting of AG10-202, prior medications will be any medication with a start date before the date of the first study drug dose as defined above.

Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date on or after the first dose. Consequently, medications ongoing at the start of treatment will be reported as both prior and concomitant medications.

Treatment-Emergent Adverse Events

Adverse events reported in AG10-201 are imported into the AG10-202 database as medical history. Sites are instructed to report any new AEs or any ongoing adverse events with an increase in severity as a new AE in AG10-202. Any newly reported AE (classified by preferred term) that occurs during the AG10-202 treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of IMP or if it was present before the first dose of IMP but increased in severity during the treatment period. If more than 1 AE is reported before the first dose of IMP and is coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that preferred term and that occurred during the period. An AE that occurs more than 14 days after the last dose of IMP will not be counted as a TEAE.

Adverse Events with Outcome of Death

Any AE with an outcome of fatal will be considered as AE with an outcome of death.

Imputation of AE (for determination of TEAE only) and concomitant medication start and stop dates:

Start Date: If only ‘day’ is missing, and the month and year are not the same as the month of first dose, then impute day with ‘01’. Otherwise, if the month and year are the same as the first dose date, use the first dose date. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month and day with month and day of the first dose date (assuming same ‘year’). If ‘day’ and ‘month’ are missing and ‘year’ is not missing and is not the same year as first dose date, then impute with ‘01’ for both ‘day’ and ‘month’. If the start date is completely missing, it will be set to the first dose date.

Stop Date: If only ‘day’ is missing, impute day with last day of the month. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month with ‘12’ and day with ‘31’ (or date of study discontinuation/completion if earlier than 12-31 and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs.

Treatment-related Adverse Events

Any AE with a relationship to study treatment of “Related” or missing will be considered a treatment-related AE as determined by the Investigator. Any AE with a relationship to study treatment of “Unrelated” will be considered not-treatment related.

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Study Day 1

Study Day 1 is defined as the first day of study drug administration in AG10-202.

Study Day

Study day is defined as the number of days from Study Day 1.

- Before Study Day 1, Study Day = (Date of Interest – Date of Study Day 1)
- On or After Study Day 1, Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore, the day prior to Study Day 1 is -1.

Analysis Visit window

Analysis window won't be required for this study but may be noted as protocol deviations. All values will be analyzed for the visit for which they are recorded. The unscheduled post-Baseline values will be excluded from the summary table but will be listed.

9.0 Analysis Sets

9.1 Safety Analysis Set

The safety analysis set will consist of all subjects dosed in AG10-202 and will be used to summarize all safety data.

9.2 PK Analysis Set

The PK analysis set will consist of all subjects receiving at least one dose of AG10 during the AG10-202 treatment period and having at least one quantifiable post-baseline concentration and will be used to summarize all PK data in AG10-202.

9.3 PD Analysis Set

The PD analysis set will consist of all subjects receiving at least one dose of AG10 during the AG10-202 treatment period, and having at least one post-baseline PD assessment, and will be used to summarize all PD data in AG10-202.

10.0 Interim Analyses

No formal interim analyses are planned for this study.

11.0 Data Review

11.1 Data Handling and Transfer

Data will be entered and exported as SAS® (version 9.4 or higher) datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard Data Tabulation Model (CDISC SDTM, version 1.3, Implementation Guide version v3.1.3) conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model (ADaM, version 2.1, Implementation Guide 1.0) standards.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 at the time of the analysis to assign a system organ class (SOC) and preferred term (PT) to each event. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary 2018MAR01 Global B3 at the time of the analysis.

Additional details can be found in the PRA Data Management Plan for AG10-202.

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11.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run on clean subjects and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFL will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

12.0 Statistical Methods

All statistical analyses will be performed using SAS (version 9.4 or higher).

Unless otherwise specified, descriptive data summaries will be tabulated for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place. Counts of zero will not display a percentage.

All continuous variables will be summarized using mean, standard deviation, median, minimum, maximum, and number of subjects with observations. The mean and median will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

12.1 Subject Disposition

The number and percentage of patients treated in the study will be presented, together with the number and percentage of patients who completed and discontinued from the study and who discontinued treatment prematurely and a breakdown of the corresponding reasons for discontinuation.

12.2 Important Protocol Deviations

Per PRA processes, important protocol deviations data will be entered into our Clinical Trials Management System (CTMS). The PRA study team and the sponsor will conduct on-going reviews of the deviation data from CTMS and the resulting set of protocol deviations throughout the study, adjusting the deviation criteria as seems appropriate.

A listing of the important protocol deviations will be provided. No Per Protocol analysis will be performed.

12.3 Treatments

12.3.1 Extent of Study Drug Exposure

Exposure to study drug (e.g. at least 1 dose administered), number of subjects with missed doses (Day 1 - Day 14, Day 15 – Day 45, and every 3 months following and overall), and total number of tablets administered will be summarized for the safety analysis set for exposure during the AG10-202 study. Total number of tablets each subject takes is calculated as the sum of the number of tablets taken at each time point (AM, PM) from Day 1 through the end of the dosing interval (Day 14, Day 15, etc.).

The patient study number, date(s) and visit number when study drug was dispensed, number of bottles of study drug dispensed, number of tablets in each bottle, date of return of each bottle of study medication and number of tablets in each bottle returned will be presented for each subject in listings.

12.3.2 Concomitant Medications

Prior/Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary

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with generic term and therapeutic use [Anatomic Therapeutic Chemical (ATC) code] and summarized by ATC code, WHO generic name, and treatment. The analysis will be performed using the safety analysis set.

The numbers and percentages of subjects using each medication will be displayed. Subjects taking more than one medication in the same ATC class or preferred name will be counted once for the number of subjects taking that preferred name.

12.4 Demographic and Baseline Characteristics

Demographic and Baseline Characteristics (sex, ethnicity, race, gene mutant type, subject's variant type (for subjects with a gene mutation status of mutant), age, age group (<65, ≥65 to <75 or ≥75 [years]), weight [kg], height [cm], body mass index [BMI; kg/m^2]) will be summarized using the descriptive statistics for subjects in the Safety Analysis Set. Qualitative (Categorical) variables (age group, sex, ethnicity, race) will be summarized using frequencies while quantitative (continuous) variables (age, weight, height, BMI) will be summarized using mean, SD, median, minimum, and maximum. Demographic and baseline data will also be listed for subjects in the Safety Analysis Set.

General medical history will be coded by MedDRA (version 21.0 or later), as applicable at time of analysis and will be presented by subject listing only. Medical History for this study will include Medical History and adverse events reported in the AG10-201 study, as well as medical history that occurred after the close of AG10-201.

12.5 PK Analyses

Blood samples for the determination of plasma AG10 and AG10 acylglucuronide will be collected on Days 1, 14, and 45, and months 3 and 6 from Day 1 visit. Only pre-dose samples are planned for collection. Samples that are collected post-dose will not be included in these analyses.

Plasma concentrations of AG10 and AG10 acylglucuronide will be performed by a designated bioanalytical laboratory.

Only patients with sufficient data to calculate each PK parameter will be included in the summary of each PK profile.

Plasma concentrations of AG10 and AG10 acylglucuronide will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration time points (visits).

The level of precision for each concentration will be presented as follows:

- Minimum/Maximum in same precision as in bioanalytical data
- Mean/Median in one more level of precision than Minimum/Maximum
- SD in one more level of precision than Mean/Median
- n will be presented as an integer
- CV% will be presented to the nearest tenth

Excluded subjects will be included in the concentration listings but will be excluded from the summary statistics and noted as such in the tables. All below limit of quantification (BLQ) values will be presented as "BLQ" in the concentration listings and footnoted accordingly.

Box and whisker plots will be presented for PK group analysis with concentration (ug/mL) on the Y

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axis ug/mL, and visit on the x axis. Median concentrations with confidence intervals will be presented.

12.6 PD Analysis

Fluorescent Probe Exclusion Stabilization

For each sample, Fluorescent Probe Exclusion (FPE) reading is measured in duplicate for every 15 min up to 6 hours. The measurement points are pre-probe, 0 min, 15 min, 30 min….360 min (total 26 points × duplicate = 52 data points). Two QC samples (0 µM, 7.5 µM) are included in duplicate in each plate. For each 0 min – 360 min datapoint, the corresponding pre-probe value should be subtracted to derive "adjusted Relative Fluorescence Unit (RFU)".

FPE Percent Target Engagement, at Day X will be derived as follows (using the mean of the duplicates):

$$100 \times \frac{\text{(FPE Day 1 @60 min - FPE Day 1 @pre-probe)-(FPE Day X @60 min-FPE Day X @pre-probe)}}{\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe}}$$

FPE data will be tabulated for time: Y=60 mins for all visits. All timepoints will be used for FPE plots.

Western Blot Stabilization

Western Blot Percent Stabilization at Day X will be derived as follows:

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates, Day\ X)}{mean\ of\ 0\ hour\ acidification\ duplicates, Day\ X}$$

Western Blot data will be tabulated for all visits.

Overall percent stabilization of ≥ 75%, defined as a subject having a stabilization greater than or equal to 75% at greater than or equal to 75% of their measurements, will be summarized for both FPE and Western Blot.

Overall percent stabilization of ≥ 90%, defined as a subject having a stabilization greater than or equal to 90% at greater than or equal to 90% of their measurements, will be summarized for both FPE and Western Blot.

Overall percent stabilization of ≥ 99%, defined as a subject having a stabilization greater than or equal to 99% at greater than or equal to 99% of their measurements, will be summarized for both FPE and Western Blot.

Percent stabilization of each category (≥75%, ≥90%, ≥95%, and ≥99%) was defined as a patient having a stabilization greater than or equal to 75%, 90%, 95%, and 99%, respectively, at ***any*** of their measurements.

A table of the FPE variations in QC readings will be presented.

Figures for FPE assay will include the complete time course of Fluorescence generation for each viable

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serum sample at each blood draw time point by subject.

Figures for RFU and by percent target engagement by AG10 concentration will be presented for all subjects and by mutant types (a total of six panels).

In addition, box and whisker plots by mutant type will be presented for FPE percent target engagement by visit (Day 15, Day 45, Month 3, Month 6, etc.). Mean and 95% confidence intervals will be included on the plots.

FPE mean percent target engagement and Western Blot mean percent stabilization will all be presented by visit (Day 1, Day 14, Month 3, Month 6, etc.) overall and by mutation type. This will be presented with both standard error and standard deviation of the mean.

Figures for WB assay will include percent stabilization by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.) by subject.

In addition, box and whisker plots by mutant type will be presented for WB percent stabilization by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.). Mean and 95% confidence intervals will be included on the plots.

Figures for percent change from baseline in Prealbumin levels by visit (Day 1, Day 14, etc.) will be presented overall and by mutant type.

In addition, box and whisker plots overall and by mutant type will be presented for prealbumin level (mg/dL) by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.). Mean and 95% confidence intervals will be included on the plots.

Correlation plots will be provided comparing the relationships of prealbumin with AG10 concentration, RFU at 60 minutes, and percent stabilization (as defined by FPE and WB, separately).

12.7 Safety Analyses

The safety analysis set will be used for all safety analyses.

12.7.1 Adverse Events

Only TEAEs will be included in the summary tables.

A high level overall summary of TEAEs will be presented to summarize all AEs, treatment-related AEs, AEs with outcome of death, serious AEs, AEs that lead to discontinuation of study drug, and AEs leading to discontinuation of study.

Subject incidence of the following AEs will be tabulated by SOC and PT. The number and percentage of each TEAE will be calculated.

- TEAEs
- TEAEs by maximum severity
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to discontinuation of the study

Subjects will be counted only once within each SOC or PT. For tables categorized by severity, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event for that SOC or PT. Treatment-related TEAEs include AEs from AE CRF page where relationship to study

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treatment is checked as either Related', or 'Unrelated'. Missing values for severity will be considered as 'Severe' and missing value for relationship to treatment will be considered as 'Related' in the summary.

AEs leading to discontinuation of study drug are those with an action taken with study treatment on the AE CRF page of 'Drug Withdrawn'.

AEs leading to discontinuation from the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

By-subject listings will be provided for the following: All TEAEs, non-TEAEs, TEAEs leading to discontinuation of study drug and TEAEs leading to discontinuation from the study.

The duration of AEs in days will be derived as the AE end date (including imputation date for incomplete AE end date) – AE onset date (imputed date for incomplete AE onset date) +1.

12.7.2 Deaths and Serious Adverse Events

Subject incidence of the following SAEs will be tabulated by SOC and PT. The number and percentage of each SAE will be calculated.

- SAEs with an outcome of death
- SAEs that are life threatening
- SAEs that require inpatient hospitalization or prolongation of existing hospitalization
- SAEs that result in persistent or significant disability/incapacity
- SAEs that result in a congenital anomaly or birth defect

By-subject listings will be also provided for the following: All Deaths, SAEs.

12.7.3 Clinical Events

The total number of clinical events will be summarized broken down to each event of interest (death, myocardial infarction, stroke, heart failure hospitalization, emergency presentation for worsening heart failure, and atrial fibrillation). A listing of clinical events will also be presented.

12.7.4 Laboratory Data

Laboratory test results are reported in conventional units provided by the laboratory.

Descriptive summaries of observed values and changes from baseline will be provided for numerical laboratory assessments by visit. The categorical lab results will be summarized by frequency and percentage and by visit.

Laboratory parameters with abnormal results as identified by the central lab will be listed.

12.7.5 Vital Signs

Descriptive summaries of observed values and changes from baseline will be provided for vital signs by visit.

12.7.6 Physical Examinations, ECGs, Echocardiogram and Other Observations Related to Safety

Descriptive summaries of observed values and changes from baseline will be provided for ECGs (aggregate RR interval, aggregate PR interval, aggregate QRS duration, aggregate QT interval) by visit. Physical Exam and Echocardiogram results will be provided in listings only.

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13.0 Validation

The goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

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14.0 References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomic Therapeutic Classification
ATTR	TTR amyloidosis
ATTR-CM	TTR cardiomyopathy
BLQ	Below Level of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CSR	Clinical Study Report
CTMS	Clinical Trials Management System
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FPE	Fluorescent Probe Exclusion
IMP	Investigational Medicinal Product
LC-MS/MS	liquid chromatography–mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PD	Pharmacodynamic
PT	Preferred Term
RFU	Relative Fluorescence Unit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
STDM	Standard Data Tabulation Model
TEAE	Treatment-emergent adverse event
TFL	Tables, Figures and Listings
TTR	transthyretin
WHO	World Health Organization

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Statistical Analysis Plan

Protocol Title:	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
Protocol Version No./Date:	Amendment 3 / 03Dec2019
CRF Version No./Date:	5.0 / 20APR2021
SAP Version No./Date:	2.0 / 11MAY2021

Approvals

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

Sponsor	
Sponsor Name:	Eidos Therapeutics
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1.0 List of Abbreviatons

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
BLQ	Below limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CTMS	Clinical Trials Management System
CV%	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ET	Early Termination
FPE	Fluorescent Probe Exclusion
HCl	Hydrochloride
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
n	Number of Subjects
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PD	Pharmacodynamic
PN	Preferred Name
PT	Preferred Term
QTcB	QT corrected interval with Bazett's formula
QTcF	QT corrected interval with Fridericia's formula
RFU	Relative Fluorescence Unit
SAE	Serious Adverse Event

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SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SEM	Standard Error of The Mean
SOC	System Organ Class
STDM	Standard Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
TTR	Transthyretin
ULN	Upper Limit of Normal
WB	Western blot
WHODrug	World Health Organization Drug Dictionary

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2.0 Introduction

The purpose of the statistical analysis plan (SAP) is to provide a detailed description of the principal features of the analysis described in the protocol and to include detailed procedures for executing the statistical analysis of the primary, secondary, and exploratory endpoints and other data collected under Eidos Therapeutics, Inc. Study AG10-202. Acoramidis hydrochloride (HCl), and Investigational Medicinal Product (IMP) are used interchangeably in this document. In Study AG10-202 Study Protocol Amendment 3, AG10 is used to refer to acoramidis and AG10 HCl is used to refer to acoramidis HCl.

This document describes study objectives, analysis sets, outcome measures, the timing of statistical analyses, data analysis methods, and data summaries for this protocol. Analysis approaches detailed within this document supersede the analyses and summaries presented in the protocol.

This plan is a living document that will be created during the trial start-up and will be finalized prior to database lock. This SAP will require sign off from the PRA Biometrics Project Manager, the Biostatistician and the Sponsor.

2.1 Objectives of Study

The primary objective of this study is to evaluate the long-term safety and tolerability of IMP administered to adult subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) who completed the AG10-201 study.

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of IMP administered orally twice daily in subjects with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of IMP as assessed by established assays of transthyretin (TTR) stabilization, including Fluorescent Probe Exclusion (FPE) assay and Western blot (WB), and to describe the PK-PD relationship of IMP in adult subjects with symptomatic ATTR-CM.

The exploratory objective of this study is:

- to describe the long-term effects of IMP on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.

2.2 Study Design

This study is a prospective, multicenter, Phase 2, long-term, open-label study in up to 55 male and/or female subjects with symptomatic ATTR-CM, ≥18 years of age, who have completed participation in Study AG10-201. This prospective multicenter, open-label study will evaluate the long-term safety, tolerability, PK and PD of IMP administered to eligible subjects with stable heart failure therapy. An open-label design is considered to be the most appropriate study design for meeting this objective.

The study will continue at the Sponsor's discretion, or until registration of the product for the treatment of symptomatic ATTR-CM.

Eligible subjects will begin dosing acoramidis HCl 800 mg administered twice daily. Information on Adverse Events (AEs) and concomitant medications will be collected throughout the study. The safety of the study will be monitored by an independent acoramidis HCl program-wide Data Monitoring Committee (DMC).

The schedule of assessments is provided in Table 1.

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Table 1: Schedule of Assessments

	Day 1	Day 14 (±3)	Day 45 (±7)	Visits Every 3 months (±7 days)[c,d,f]	ET Visit [g]	Follow-up Visit 30 days after date of last dose (±7 days) [a]	Unscheduled Visit [h]
Written Informed Consent	X						
Inclusion/Exclusion Criteria Review	X						
Medical History	X						
Physical Exam[b]	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Resting transthoracic echocardiogram[c]	X[c]			X[c]	X[c]		X[c]
12-lead resting ECG[c]	X	X	X	X[c]	X	X	X
PD assays[d]	X	X	X	X[d]			
PK sample collection[d]	X	X	X	X[d]			
Prealbumin collection[d]	X	X	X	X[d]			
Study drug dosing during visit	X	X	X	X			
Clinical laboratory assessments	X	X	X	X	X	X	X
Pregnancy test[e]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Dispense IMP	X		X	X			
Review Subject Dosing Record		X	X	X	X		
Collect Unused IMP			X	X	X		X
Adverse events	X	X	X	X	X	X	X

Abbreviations: ECG: Electrocardiogram; ET: Early termination; IMP: Investigational Medicinal Product; PD: Pharmacodynamics; PK: Pharmacokinetics.

[a] When a subject discontinues study participation, the subject will be asked to return to the study center for the Follow-up Visit. The Follow-up Visit should be performed 30 days after date of last dose.

[b] Complete Physical Examination including body weight at all visits.

[c] Resting 12-lead electrocardiogram and echocardiogram at Day 1, every 3 months until Month 12 then annually. Perform echocardiogram at ET Visit unless obtained in prior 6 months and at Unscheduled Visit only if clinically indicated.

[d] Samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 and then every 3 months after Month 15 (pre-dose only)

[e] Females of Child-Bearing Potential only. Urine pregnancy test at all visits.

[f] Visits every 3 months from Day 1 visit.

[g] If a subject discontinues study participation, the subject will be asked to return to the study center for the ET Visit as soon as possible and to return any unused IMP.

[h] For assessment or follow up of an adverse event, only procedures that are indicated as needed by the investigator should be performed (e.g., physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test).

2.3 Study Population

The study will enroll up to 55 males and/or females ≥18 years of age with chronic, stable, symptomatic ATTR-CM will be enrolled and begin dosing with acoramidis HCl 800 mg twice daily. See sections 8.3.1 and 8.3.2 of the study protocol for Inclusion and Exclusion criteria.

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2.4 Study Dosage and Administration

IMP doses chosen for this study are based on results from nonclinical PK studies, data from the first-in-human single ascending dose and multiple ascending dose study, and data from a Phase 2 study (AG10-201). Further detail on dose selection can be found in the Investigator's Brochure (IB).

Dosing should occur twice daily, once in the morning and once in the evening.

Subjects will be dosed with acoramidis HCl 800 mg administered twice daily. Downward adjustment of dose or interruption of IMP is discouraged but permitted if necessary, in the event of intolerance to IMP. Subsequent upward adjustment of IMP back to the target dose should be attempted whenever possible. If it is believed that an AE may be drug-related, and depending on its severity, the IMP may be reduced from 800 mg twice daily to 400 mg twice daily.

2.5 Sample Size Determination

The planned number of subjects is determined by the number of eligible and interested subjects that have completed the Study AG10-201 and therefore is not expected to be greater than 55 subjects.

2.6 Blinding

This is an open-label study.

2.7 Interim Analysis

There will be a data snapshot to generate an interim clinical study report to support planned regulatory activities.

3.0 General Analysis Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS) version 9.4 or higher.

Unless otherwise specified, descriptive data summaries will be tabulated for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place. Counts of zero will not display a percentage.

All continuous variables will be summarized using mean, standard deviation (SD), median, minimum, maximum, 25th percentile, 75th percentile and number of subjects with observations. Unless otherwise specified, the mean, median, 25th percentile and 75th percentile will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

3.1 Analysis Sets

Safety Analysis Set

The safety analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period. The safety analysis set will be used to summarize all safety data.

PK Analysis Set

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The PK analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one quantifiable post-baseline concentration. The PK analysis set will be used to summarize all PK data in Study AG10-202.

PD Analysis Set

The PD analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one post-baseline PD assessment. The PD analysis set will be used to summarize all PD data in Study AG10-202.

3.2 Study Day Derivations

Study Day 1

Study Day 1 is defined as the first day of IMP administration in Study AG10-202.

Study Day

Study day is defined as the number of days from Study Day 1. Before Study Day 1, Study Day = (Date of Interest – Date of Study Day 1). Therefore, the day prior to Study Day 1 is -1.

On or After Study Day 1, Study Day = (Date of Interest – Date of Study Day 1) + 1.

A month is defined as 30.4375 days and a year is defined as 365.25 days.

First IMP Dose

For all subjects, the first IMP dose date is defined as the date of first dose in Study AG10-202. Date of first dose is recorded on the Exposure-First Dose Case Report Form (CRF).

Baseline and Change from Baseline

Baseline values are defined as the last pre-dose value obtained on or before the date of the first IMP dose in Study AG10-202.

Change from Baseline = (post-Baseline value – Baseline value).

Completion of study

Subject completion of the study is defined as an answer of “Yes” to the question “Did the subject complete the study (including Follow-Up)?” on the form of End of Study in the CRF.

Completion of treatment

Subject completion of treatment is defined as an answer of “Completed” to the question “End of Treatment Status” on the form of End of Treatment in the CRF.

3.3 Visit Window for Analysis

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows. The actual visit date is allowed to fall within a specified interval of the target day.

In general, if more than one actual visit (including unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit

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dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

Analysis window are as follows:

Table 2: Analysis Visit Windows

Study Analysis Visit	Target Day	Analysis Window
Baseline	1	≤1
Day 14	14	2-29
Day 45	45	30-68
Month 3	90	69-134
Month 6	180	135-314
Month 15	450	315-494
Month 18	540	495-584
Month 21	630	585-674
Month 24	720	675-764
Month 27	810	765-854
Month 30	900	855-944
Month X[a]	Every 90 days thereafter	Target day – 45 days to target day + 44 days

[a] For visits occurring every 3 months after Month 30, Month X is 3 months after the previous visit.

3.4 Handling of Dropouts and Missing Data

Subjects who discontinue from the study will not be replaced.

An AE will be considered treatment-emergent if the entered data (e.g., the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria.

Imputation of AE (for determination of treatment-emergent adverse event [TEAE] only) and **concomitant medication** start and stop dates:

- **Start Date:** If only ‘day’ is missing, and the month and year are not the same as the month and year of first dose, then impute day with the first of the month. Otherwise, if the month and year are the same as the first dose date, use the first dose date. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month and day with month and day of the first dose date (assuming same ‘year’). If ‘day’ and ‘month’ are missing and ‘year’ is not missing and is not the same year as first dose date, then impute with 1st of January. If the start date is completely missing, it will be set to the first dose date.
- **Stop Date:** If only ‘day’ is missing, impute day with last day of the month. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month with the 31st of December’ (or date of study discontinuation/completion if earlier than 31st of December and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. Stop date will not be imputed for ongoing AEs.

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4.0 Subject Disposition

Subject disposition will be presented including numbers and percentages of subjects: treated in the study; who completed the study; who discontinued from the study; who completed treatment, and who discontinued treatment prematurely. Reasons for discontinuation of IMP and of the study will be summarized.

5.0 Protocol Deviations

Important protocol deviations data have been entered into the PRA Clinical Trials Management System (CTMS) and the SimpleTrials system. The Sponsor will conduct on-going reviews of the deviation data from CTMS and SimpleTrials system and the resulting set of protocol deviations throughout the study, adjusting the deviation criteria as seems appropriate. Data from the SimpleTrials system will be imported into the PRA system for combination with CTMS data for reporting. In the SimpleTrials CTMS, Important protocol deviations are entered as 'Major'; other protocol deviations (not important) are entered as 'Minor'.

A listing of the important protocol deviations will be provided. No Per Protocol analysis will be performed.

6.0 Demographics and Baseline Characteristics

Demographic data are imported from the Study AG10-201 database. Demographic and Baseline Characteristics (sex, ethnicity, race, gene mutation status, subject's variant type (for subjects with a gene mutation status of mutant), age [years], age group (<65, ≥65 to <75 or ≥75 [years] and <78, ≥78 [years]) and weight [kg], will be summarized using the descriptive statistics for subjects in the Safety Analysis Set. Qualitative (categorical) variables (age group, sex, ethnicity, race) will be summarized using frequencies while quantitative (continuous) variables (age and weight) will be summarized using mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum. Demographic and baseline data will also be listed for subjects in the Safety Analysis Set.

7.0 Medical History

Medical history for this study will include imported Medical history and AEs initially reported in the AG10-201 study, as well as medical history that occurred after the close of Study AG10-201 and before enrollment in Study AG10-202.

Medical history and AEs reported in Study AG10-201 were imported into the Study AG10-202 database as medical history. Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database.

General medical history will be coded by Medical Dictionary for Regulatory Activities ([MedDRA] version 23.1 or later), as applicable at time of analysis and will be presented in a summary table and with a subject listing.

8.0 Prior and Concomitant Medications/Procedures

Prior and concomitant medications reported in the Study AG10-201 study are included (imported) in the Study AG10-202 database and considered prior medications in the AG10-202 study. Sites were instructed to enter any new medications (started after the end of the Study AG10-201) in the concomitant medication form of the CRF. For reporting of Study AG10-202, prior medications will be any medication with a start date before the date of the first IMP dose as defined above.

Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date on or after the first dose. Consequently, medications ongoing at the start of treatment will be reported as both prior and concomitant medications.

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Prior and concomitant medications will be coded according to the AG10-202 Coding Conventions using the World Health Organization Drug Dictionary (WHODrug). The prior and concomitant medication analyses will be performed using the Safety Analysis Set.

Summaries and listings of prior and concomitant medications by Preferred Name (PN) and ATC codes will be provided. In the summaries, subjects taking more than one medication in the same PN will be counted once for the number of subjects taking the medication of that PN.

Summaries and listings of prior and concomitant diuretics and cardiovascular medications may be presented.

9.0 Extent of Exposure to Study Drug

The extent of exposure will be presented as duration (months). The number of months of exposure will be defined as: (last dose of IMP date – first dose of IMP date +1) / 30.4375, regardless of intermittent discontinuations or dose reductions. Non-integer values will be rounded to one decimal place. The number of months of actual exposure will be defined as: (last dose of IMP date – first dose of IMP date – number of days where no medication was taken +1) / 30.4375.

As context for the extent of exposure, the proportion of subjects receiving at least one dose and the proportion of tablets taken out of the originally dispensed number will be presented.

The subject number, date(s) and visit number when IMP was dispensed, number of bottles of IMP dispensed, number of tablets in each bottle, date of return of each bottle of IMP and number of tablets in each bottle returned will be presented for each subject in listings.

10.0 Safety Evaluations

The Safety Analysis Set will be used for all safety analyses.

Safety parameters to be assessed include: TEAEs, treatment-emergent serious adverse events (SAEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal electrocardiogram (ECG) parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern.

10.1 Adverse Events

Only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables. Serious TEAEs and Treatment-Emergent Serious Adverse Events are used interchangeably in this document.

10.1.1 All Treatment-Emergent Adverse Events

For the purposes of data collection for this study, any untoward event that is reported from the time that the subject signs the Informed Consent Form (ICF) until 30 days after the last dose of IMP is to be considered an AE. An AE will be considered a TEAE if it was not present before the first dose of IMP for the Study AG10-202 study or if it was present before the first dose of IMP but increased in severity during the treatment period. Only TEAEs will be included in the summary tables.

An AE that occurs more than 30 days after the last dose of IMP will not be counted as a TEAE. For interim reporting, the last dose of IMP for the determination of treatment emergence will be assigned as the date of the data extract for ongoing subjects. For subjects that have discontinued IMP, the date of last dose will be as recorded on the End of Treatment CRF. For subjects that died during the reporting period, if a date of last dose is not reported, the date of death will be used for the date of last dose.

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A summary of the following will be presented: all TEAEs; treatment-related TEAEs; TEAEs with outcome of death; Serious TEAEs; treatment-related Serious TEAEs; non-serious TEAEs; TEAEs leading to discontinuation of IMP, and TEAEs leading to discontinuation of study.

Tabular summaries with numbers and percentages of subjects that have the following TEAEs will be provided by System Organ Class (SOC) and PT.

- All TEAEs;
- TEAEs by maximum severity;
- Treatment-related TEAEs;
- Non-serious TEAEs;
- TEAEs leading to discontinuation of IMP;
- TEAEs leading to discontinuation of study.

At each level of summarization (e.g., all TEAEs, SOC, and PT), subjects will be counted only once. For tables categorized by severity, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event for that SOC or PT. Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing values for severity will be considered as 'Severe' and missing value for relationship to IMP will be considered as 'Related' in the summary.

TEAEs leading to discontinuation of IMP are those with an action taken with IMP on the AE CRF page of 'Drug Withdrawn'.

TEAEs leading to discontinuation of the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

By-subject listings will be provided for the following: All TEAEs, non-TEAEs, TEAEs leading to discontinuation of study drug and TEAEs leading to discontinuation of study.

The duration of AEs in days will be derived as the AE end date (including imputation date for incomplete AE end date) – AE onset date (imputed date for incomplete AE onset date) +1.

10.1.2 Treatment-Related Adverse Events

Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing value for relationship to treatment will be considered as 'Related' in the summary.

Subject incidence of the treatment-related TEAEs will be tabulated by SOC and PT and associated listing will be provided.

Subject incidence of the treatment-related serious TEAEs will be tabulated by SOC and PT and associated listing will be provided.

10.1.3 Treatment-Emergent Serious Adverse Events

The number and percentage of subjects and the number of SAEs reported for the following categories of SAEs will be presented.

- SAEs;
- SAEs with an outcome of death;
- SAEs leading to discontinuation of IMP;
- SAEs leading to discontinuation of study.

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In addition, subject incidence of the treatment-emergent SAEs will be tabulated by SOC and PT for the above categories. Subjects will be counted only once within each SOC or PT. By-subject listings will be also provided for the each of the above categories.

10.1.4 Adverse Events Leading to Discontinuation of Study Drug and/or the Study

AEs leading to discontinuation of IMP are those with an action taken with regard to IMP of 'Drug Withdrawn'. AEs leading to discontinuation from the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

Subject incidence of the TEAEs leading to discontinuation of IMP will be tabulated by SOC and PT and associated listing will be provided.

Subject incidence of the TEAEs leading to discontinuation of study will be tabulated by SOC and PT and associated listing will be provided.

10.1.5 Adverse Events with an Outcome of Death

An AE with an outcome of fatal reported will be considered as AE with an outcome of death.

Subject incidence of the TEAEs with an outcome of death will be tabulated by SOC and PT and an associated listing will be provided.

10.2 Clinical Laboratory Tests

Descriptive summaries of observed values and changes from baseline will be provided for numerical laboratory assessments by visit. The categorical laboratory results will be summarized by frequency and percentage and by visit.

Laboratory values will also be tabulated in shift tables from baseline where available. For the shift tables, laboratory results will be categorized by the central laboratory (when normal ranges have been defined) as high (higher than the upper limit of the normal range), normal (within the normal range) or low (lower than the lower limit of the normal range).

Where applicable, figures of mean laboratory values and of individual subject's laboratory parameters (spaghetti plots) by visit will be presented.

The number and proportion of subjects with liver test elevations will be presented. Liver test elevations are assessed by using post-Baseline results for ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), and total bilirubin based on the definitions presented in Table 3.

Table 3: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN - < 3 x ULN ALT or AST ≥ 3 x to < 5 x ULN ALT or AST ≥ 5 x to < 10 x ULN ALT or AST ≥ 10 x to < 20 x ULN ALT or AST ≥ 20 x ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

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The number and percentage of subjects with concurrent (defined as measurements on the same day) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times upper limit of normal (ULN) and total bilirubin > 2 times ULN will also be presented.

Laboratory parameters with abnormal results as identified by the central lab will be listed. Subject listings will also be provided for all laboratory tests.

10.3 Vital Signs

Descriptive summaries of observed values and changes from baseline will be provided for vital signs by visit.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for vital signs parameters.

10.4 Physical Examination

Physical examination will be provided in listings only.

10.5 Electrocardiogram

Descriptive summaries of observed values and changes from baseline will be provided for ECGs (PR interval, QRS duration, QT interval, QT corrected interval with Bazett's formula [QTcB] and with Fridericia's formula [QTcF]) by visit.

Number and percentage of subjects for each the following categories (based on the International Council for Harmonisation [ICH] E14 guidance) will be tabulated by visit:

- QT interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcB interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcF interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- Increase in change from baseline in QT interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- Increase in change from baseline in QTcB interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- Increase in change from baseline in QTcF interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- PR interval greater than 200 msec and change from baseline in PR interval > 25%;
- QRS interval greater than 120 msec and change from baseline in QRS interval > 25%.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for all ECG parameters.

Subject listings will also be provided for all ECG results.

10.6 COVID-19 Related Analysis

Any deviations from the protocol related to COVID-19 control measures will be summarized and a listing will be generated.

Listings may be provided for subjects with the following: visits altered by or missed due to COVID-19 control measures; visits missed due to COVID-19 Infection Related Adverse Event; subjects with study discontinuations due to COVID-19 control measures; subjects with IMP discontinuation due to COVID-19

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control measures; subjects with missed IMP doses related to COVID-19 control measures, and subjects with COVID-19, or COVID-19 vaccine adverse events.

11.0 Pharmacokinetics and Pharmacodynamics

11.1 Pharmacokinetics

Pre-dose blood samples for the determination of plasma acoramidis and acoramidis acylglucuronide will be collected on Days 1, 14, and 45, and months 3, 6 and 15 and then every 3 months after Month 15. Only pre-dose samples are planned for collection. Samples that are collected post-dose will not be included in these analyses.

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be performed by a designated bioanalytical laboratory, which will report the concentrations in ng/ml. The acoramidis molar concentration will be derived using the molecular weight of 292.31g/mol as freebase.

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, 25th percentile, 75th percentile and maximum will be calculated for all nominal concentration time points (visits).

The level of precision for each concentration will be presented as follows:

- Minimum and Maximum in same precision as in bioanalytical data;
- Mean, Median, 25th percentile and 75th percentile in one more level of precision than Minimum and Maximum;
- SD and SEM in one more level of precision than Mean;
- n will be presented as an integer;
- CV% will be presented to the nearest tenth.

All below limit of quantification (BLQ) values will be presented as “BLQ” in the concentration listings and footnoted accordingly.

Box and whisker plots will be presented for PK group analysis with concentration (ng/mL) on the y-axis and visit on the x-axis. The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker.

11.2 Pharmacodynamics

Pre-dose PD blood samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 and then every 3 months after Month 15. The PD of acoramidis will be assessed by established assays of TTR stabilization, including FPE assay and WB, and to describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM.

Note: Observed values and change from baseline in circulating prealbumin levels will also be measured as a PD marker.

Fluorescent Probe Exclusion (FPE) Stabilization

For each sample, FPE reading is measured in duplicate for every 15 min up to 6 hours. The measurement points are pre-probe, 0 min, 15 min, 30 min….360 min (total 26 points × duplicate = 52 data points). Two QC samples (0 µM, 7.5 µM) are included in duplicate in each plate. For each 0 min – 360 min datapoint, the corresponding pre-probe value should be subtracted to derive “adjusted Relative Fluorescence Unit (RFU)”.

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FPE Percent Target Engagement, at Day X will be derived as follows (using the mean of the duplicates):

$$100 \times \frac{(\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe }) - (\text{FPE Day X @60 min-FPE Day X @pre-probe})}{\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe}}$$

FPE data will be tabulated for time: Y=60 mins for all visits. All timepoints will be used for FPE plots.

Western Blot (WB) Stabilization

WB Percent Stabilization at Day X will be derived as follows:

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates, Day\ X)}{mean\ of\ 0\ hour\ acidification\ duplicates,\ Day\ X}$$

WB data will be tabulated for all visits.

Number and percentage of subjects with FPE % target engagement ≥ 75%, ≥ 90%, ≥ 99% will be summarized for each visit.

Number and percentage of subjects with WB % stabilization ≥ 75%, ≥ 90%, ≥ 99% will be summarized for each visit.

A table of the FPE variations in QC readings will be presented.

Figures for FPE assay will include the complete time course of Fluorescence generation for each viable serum sample at each blood draw time point by subject.

FPE mean percent target engagement and WB mean percent stabilization will be presented by visit (Day 1, Day 14, Month 3, Month 6,etc.) overall and by mutation type. This will be presented with both standard error and standard deviation of the mean. At Day 1 FPE percent target engagement is by definition zero and doesn't need to be presented.

In addition, box and whisker plots by mutant type will be presented for WB percent stabilization and FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6, … etc.). The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker.

Mean percent change from baseline in prealbumin levels by visit (Day 1, Day 14, etc.) will be presented overall and by mutant type. This will be presented with both standard error and standard deviation of the mean.

In addition, box and whisker plots overall and by mutant type will be presented for percent change from baseline in prealbumin level (mg/dL) by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

A summary of subjects who reached certain thresholds (10%, 25%, and 50%) of percent increase in prealbumin at each visit may be provided.

A subject data listing will include WB percent stabilization by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.). Another subject data listing will include FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6,.. etc.). Finally, a subject data listing will include prealbumin concentration and percent change from baseline by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

11.3 Pharmacodynamics and Pharmacokinetics Relationship

Correlation plots will be provided as follows.

1. Acoramidis concentration vs. FPE percent target engagement

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2. Acoramidis concentration vs. WB percent stabilization
3. Acoramidis concentration vs. Prealbumin percent change from baseline

12.0 Echocardiographic Parameters (Exploratory)

Descriptive summaries of observed values and changes from baseline for echocardiographic parameters may be provided. A listing of echocardiogram parameters will also be provided.

13.0 References

ICH E3 Structure and content of clinical study reports. https://www.ema.europa.eu/en/ich-e3-structure-content-clinical-study-reports.

ICH E9 Statistical principles for clinical trials. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials.

ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. https://www.ema.europa.eu/en/ich-e14-clinical-evaluation-qtqtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic.

14.0 Summary of Changes from the protocol

The following changes from Protocol Amendment 3 are reflected in the SAP version 2.0:

- Baseline values are defined in the protocol Amendment 3 as the last value obtained on or before the date of the first dose from Study AG10-201. For SAP version 2.0, baseline is defined as the last value obtained on or before the first dose of Study AG10-202.
- There are no time-to-event analyses planned for clinical events as stated in protocol Amendment 3.
- Since this is a single arm study, data will not be reported by treatment group as stated in protocol Amendment 3.
- Safety parameters to be assessed include: TEAEs, treatment-emergent SAEs, AEs leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern. More details were added for clarity.
- Summary of clinical events will not be performed as data wasn't collected to support such an analysis.

15.0 Validation

The goal is to ensure that each Table; Figure, and Listing (TFL) delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

Data Handling and Transfer

Data will be entered and exported as SAS (version 9.4 or higher) datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard (CDISC) Data Tabulation Model ([SDTM], version 1.4 or higher, Implementation Guide version v3.2 or

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higher) conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model ([ADaM], version 2.1 or higher, Implementation Guide 1.1) standards.

Medical history and AEs will be coded using the MedDRA, version 23.1 or higher at the time of the analysis to assign a SOC and PT to each event. Prior and concomitant medications will be coded using the WHODrug 2020SEP01 Global B3 or higher at the time of the analysis.

Additional details can be found in the PRA Data Management Plan for Study AG10-202.

16.0 Summary of Changes

Date	Description
03-Jul-2019	Initial version
11-May-2021	Version 2.0 • Document was reformatted for clarity. • Document was aligned with protocol amendment 3 and CRF version 5.0. • Updated the List of Abbreviations. • Updated AG10 to acoramidis. • Consistent use of IMP instead of study drug or study treatment. • Consistent use of subject to refer to individuals participating in the study instead of patient. • Added 25th and 75th percentile statistics to the summary statistics, wherever applicable. • Removed original section 7 (Study Endpoints, Variables and Covariate). This is now covered under each corresponding analysis method section. • Removed original section 12.7.3 (Clinical Events) as data was not collected and

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Date	Description
	analysis is not applicable. • **Section 2.0:** Updated incorporating details of study purpose and scope. • **Section 2.2:** Study design was updated in alignment with study protocol amendment 3. • **Section 2.3:** Added a separate section for study population. • **Section 2.4:** Added a section for study dosage and administration with more details. • **Section 2.6:** Removed the randomization section and added this blinding section clarifying that AG10-202 is an open label study. • **Section 2.7**: Updated interim analysis section. There will be a data snapshot to generate an interim clinical study report in support planned regulatory activities. • **Section 3.3**: Section updated to specify the derivations of analysis windows for the reporting of the study results (previously nominal visits were to be used). • **Section 3.4**: o Added this section to compile all imputation rules handling of dropouts and missing data. o Added clarify to missing data imputation rule. An AE will be considered treatment-emergent if the entered data (e.g. the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria. • **Section 4.0:** Added completed treatment to subject disposition analysis. • **Section 5.0**: Added details explaining that PRA and SimpleTrials CTMS hold the protocol deviations for the study. • **Section 6.0**: Added (<78, ≥78 [years]) to age group. • **Section 7.0**: o Added a separate section for medical history with more details for clarity. o Indicated that Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database. • **Section 8.0**: o Added summaries and listings of prior and concomitant diuretics and cardiovascular medications, which may be presented. • **Section 9.0**: o Summary of doses missed was removed. o Duration of exposure derivation was clarified. • **Section 10.0:** Added list of safety parameters. • **Section 10.1**: Stated that only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables. • **Section 10.1.1**: o Added clarity to treatment emergent adverse event definitions.

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Date	Description
	○ Added treatment-related Serious TEAEs and non-serious TEAEs to the overall TEAE summary. • **Section 10.1.2:** Added a separate section to outline analysis for treatment-related adverse events. • **Section 10.1.3:** ○ Added overall SAE summaries for SAE, SAEs leading to IMP discontinuation and SAEs leading to discontinuation. ○ Removed the breakdown into all different serious criteria. ○ Added summaries by SOC and PT and additional listings for SAEs. • **Section 10.1.4:** Added a separate section to outline analysis for adverse events leading to discontinuation of study drug and/or the study. • **Section 10.1.5:** Added a separate section to outline analysis for adverse events with an outcome of death. • **Section 10.2**: ○ Added shift tables, where available. ○ Added table and listing for liver test elevations. ○ Added mean and individual spaghetti plots. • **Section 10.3**: Added mean and individual spaghetti plots. • **Section 10.5**: ○ Added a separate section to outline all ECG related analysis. ○ Additional summaries tables added for potentially abnormal QT, QTcB, QTcF, PR and QRS intervals parameters. ○ Added mean and individual spaghetti plots. • **Section 10.6**: New section for COVID-19 related analysis. • **Section 11.1:** ○ Added details for the derivation of PK concentration to molar concentration. ○ Removed median concentrations with confidence intervals figure. ○ Removed the sentences of subject's inclusion or exclusion for PK analysis as data from all subjects in the PK analysis set will be included. • **Section 11.2**: ○ Clarified that prealbumin levels are a PD parameter. ○ Clarified that listings for the WB and FPE will be provided. ○ Clarified that listing for prealbumin and percent change in prealbumin levels will be provided. ○ Added summary of subjects with percent increase in prealbumin levels above certain thresholds. ○ Clarified figures presentation/contents.

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Date	Description
	○ Removed figures presenting RFU and by percent target engagement by AG10 concentration. ○ Removed figures presenting mean and 95% confidence intervals for FPE and WB percent stabilization. ○ Removed figure presenting mean and 95% confidence intervals for prealbumin. ○ Removed summary table of the overall percent stabilization for both WB and FPE. • **Section 11.3**: ○ Added a separate section to outline the PD/PK correlation plots. ○ Specify that percentage change from baseline prealbumin levels is used in the correlation plots instead of prealbumin levels. ○ Removed correlation plot between prealbumin and RFU. • **Section 12.0**: Added descriptive summaries of observed values and changes from baseline for echocardiographic parameters. • **Section 13.0**: Included ICH E3, E9 and E14 as references. • **Section 14.0**: ○ Updated current text to refer to protocol amendment 3. ○ Added clarification of the safety parameters assessed. ○ Clarify that the summary of clinical events will not be performed. • **Section 15.0**: ○ Moved original section 11.0 Data Review under this Validation section. ○ Updated versions for SDTM and ADaM. ○ Updated versions for MedDRA and WHO dictionaries. ○ Removed Data Screening paragraph as this is governed by Data Management Plan and is not within the scope of SAP. • **Section 16.0:** Added summary of changes.

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Statistical Analysis Plan

Protocol Title:	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
Protocol Version No./Date:	Amendment 3 / 03Dec2019
CRF Version No./Date:	5.0 / 20APR2021
SAP Version No./Date:	3.0 / 18OCT2021

Approvals

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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Signature /Date:	DocuSigned by Jing Du Jing Du I approve this document 10/18/2021 | 10:32 PM PDT
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1.0 List of Abbreviatons

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
BLQ	Below limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CTMS	Clinical Trials Management System
CV%	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ET	Early Termination
FPE	Fluorescent Probe Exclusion
HCl	Hydrochloride
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
n	Number of Subjects
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PD	Pharmacodynamic
PN	Preferred Name
PT	Preferred Term
QTcB	QT corrected interval with Bazett's formula
QTcF	QT corrected interval with Fridericia's formula
RFU	Relative Fluorescence Unit
SAE	Serious Adverse Event

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SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SEM	Standard Error of The Mean
SI	International System of Units
SOC	System Organ Class
STDM	Standard Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
TTR	Transthyretin
ULN	Upper Limit of Normal
WB	Western blot
WHODrug	World Health Organization Drug Dictionary

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2.0 Introduction

The purpose of the statistical analysis plan (SAP) is to provide a detailed description of the principal features of the analysis described in the protocol and to include detailed procedures for executing the statistical analysis of the primary, secondary, and exploratory endpoints and other data collected under Eidos Therapeutics, Inc. Study AG10-202. Acoramidis hydrochloride (HCl), and Investigational Medicinal Product (IMP) are used interchangeably in this document. In Study AG10-202 Study Protocol Amendment 3, AG10 is used to refer to acoramidis and AG10 HCl is used to refer to acoramidis HCl.

This document describes study objectives, analysis sets, outcome measures, the timing of statistical analyses, data analysis methods, and data summaries for this protocol. Analysis approaches detailed within this document supersede the analyses and summaries presented in the protocol.

This plan is a living document that will be created during the trial start-up and will be finalized prior to database lock. This SAP will require sign off from the PRA Biometrics Project Manager, the Biostatistician and the Sponsor.

2.1 Objectives of Study

The primary objective of this study is to evaluate the long-term safety and tolerability of IMP administered to adult subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) who completed the AG10-201 study.

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of IMP administered orally twice daily in subjects with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of IMP as assessed by established assays of transthyretin (TTR) stabilization, including Fluorescent Probe Exclusion (FPE) assay and Western blot (WB), and to describe the PK-PD relationship of IMP in adult subjects with symptomatic ATTR-CM.

The exploratory objective of this study is:

- to describe the long-term effects of IMP on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.

2.2 Study Design

This study is a prospective, multicenter, Phase 2, long-term, open-label study in up to 55 male and/or female subjects with symptomatic ATTR-CM, ≥18 years of age, who have completed participation in Study AG10-201. This prospective multicenter, open-label study will evaluate the long-term safety, tolerability, PK and PD of IMP administered to eligible subjects with stable heart failure therapy. An open-label design is considered to be the most appropriate study design for meeting this objective.

The study will continue at the Sponsor's discretion, or until registration of the product for the treatment of symptomatic ATTR-CM.

Eligible subjects will begin dosing acoramidis HCl 800 mg administered twice daily. Information on Adverse Events (AEs) and concomitant medications will be collected throughout the study. The safety of the study will be monitored by an independent acoramidis HCl program-wide Data Monitoring Committee (DMC).

The schedule of assessments is provided in Table 1.

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Table 1: Schedule of Assessments

	Day 1	Day 14 (±3)	Day 45 (±7)	Visits Every 3 months (±7 days)[c,d,f]	ET Visit [g]	Follow-up Visit 30 days after date of last dose (±7 days) [a]	Unscheduled Visit [h]
Written Informed Consent	X						
Inclusion/Exclusion Criteria Review	X						
Medical History	X						
Physical Exam[b]	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Resting transthoracic echocardiogram[c]	X[c]			X[c]	X[c]		X[c]
12-lead resting ECG[c]	X	X	X	X[c]	X	X	X
PD assays[d]	X	X	X	X[d]			
PK sample collection[d]	X	X	X	X[d]			
Prealbumin collection[d]	X	X	X	X[d]			
Study drug dosing during visit	X	X	X	X			
Clinical laboratory assessments	X	X	X	X	X	X	X
Pregnancy test[e]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Dispense IMP	X		X	X			
Review Subject Dosing Record		X	X	X	X		
Collect Unused IMP			X	X	X		X
Adverse events	X	X	X	X	X	X	X

Abbreviations: ECG: Electrocardiogram; ET: Early termination; IMP: Investigational Medicinal Product; PD: Pharmacodynamics; PK: Pharmacokinetics.

[a] When a subject discontinues study participation, the subject will be asked to return to the study center for the Follow-up Visit. The Follow-up Visit should be performed 30 days after date of last dose.

[b] Complete Physical Examination including body weight at all visits.

[c] Resting 12-lead electrocardiogram and echocardiogram at Day 1, every 3 months until Month 12 then annually. Perform echocardiogram at ET Visit unless obtained in prior 6 months and at Unscheduled Visit only if clinically indicated.

[d] Samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 and then every 3 months after Month 15 (pre-dose only)

[e] Females of Child-Bearing Potential only. Urine pregnancy test at all visits.

[f] Visits every 3 months from Day 1 visit.

[g] If a subject discontinues study participation, the subject will be asked to return to the study center for the ET Visit as soon as possible and to return any unused IMP.

[h] For assessment or follow up of an adverse event, only procedures that are indicated as needed by the investigator should be performed (e.g., physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test).

2.3 Study Population

The study will enroll up to 55 males and/or females ≥18 years of age with chronic, stable, symptomatic ATTR-CM will be enrolled and begin dosing with acoramidis HCl 800 mg twice daily. See sections 8.3.1 and 8.3.2 of the study protocol for Inclusion and Exclusion criteria.

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2.4 Study Dosage and Administration

IMP doses chosen for this study are based on results from nonclinical PK studies, data from the first-in-human single ascending dose and multiple ascending dose study, and data from a Phase 2 study (AG10-201). Further detail on dose selection can be found in the Investigator's Brochure (IB).

Dosing should occur twice daily, once in the morning and once in the evening.

Subjects will be dosed with acoramidis HCl 800 mg administered twice daily. Downward adjustment of dose or interruption of IMP is discouraged but permitted if necessary, in the event of intolerance to IMP. Subsequent upward adjustment of IMP back to the target dose should be attempted whenever possible. If it is believed that an AE may be drug-related, and depending on its severity, the IMP may be reduced from 800 mg twice daily to 400 mg twice daily.

2.5 Sample Size Determination

The planned number of subjects is determined by the number of eligible and interested subjects that have completed the Study AG10-201 and therefore is not expected to be greater than 55 subjects.

2.6 Blinding

This is an open-label study.

2.7 Interim Analysis

There will be a data snapshot to generate an interim clinical study report to support planned regulatory activities.

3.0 General Analysis Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS) version 9.4 or higher.

Unless otherwise specified, descriptive data summaries will be tabulated for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place. Counts of zero will not display a percentage.

All continuous variables will be summarized using mean, standard deviation (SD), median, minimum, maximum, 25th percentile, 75th percentile and number of subjects with observations. Unless otherwise specified, the mean, median, 25th percentile and 75th percentile will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

3.1 Analysis Sets

Safety Analysis Set

The safety analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period. The safety analysis set will be used to summarize all safety data.

PK Analysis Set

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The PK analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one quantifiable post-baseline concentration. The PK analysis set will be used to summarize all PK data in Study AG10-202.

PD Analysis Set

The PD analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one post-baseline PD assessment. The PD analysis set will be used to summarize all PD data in Study AG10-202.

3.2 Study Day Derivations

Study Day 1

Study Day 1 is defined as the first day of IMP administration in Study AG10-202.

Study Day

Study day is defined as the number of days from Study Day 1. Before Study Day 1, Study Day = (Date of Interest – Date of Study Day 1). Therefore, the day prior to Study Day 1 is -1.

On or After Study Day 1, Study Day = (Date of Interest – Date of Study Day 1) + 1.

A month is defined as 30.4375 days and a year is defined as 365.25 days.

First IMP Dose

For all subjects, the first IMP dose date is defined as the date of first dose in Study AG10-202. Date of first dose is recorded on the Exposure-First Dose Case Report Form (CRF).

Baseline and Change from Baseline

Baseline values are defined as the last pre-dose value obtained on or before the date of the first IMP dose in Study AG10-202.

Change from Baseline = (post-Baseline value – Baseline value).

Completion of study

Subject completion of the study is defined as an answer of “Yes” to the question “Did the subject complete the study (including Follow-Up)?” on the form of End of Study in the CRF.

Completion of treatment

Subject completion of treatment is defined as an answer of “Completed” to the question “End of Treatment Status” on the form of End of Treatment in the CRF.

3.3 Visit Window for Analysis

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows. The actual visit date is allowed to fall within a specified interval of the target day.

In general, if more than one actual visit (including unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit

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dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

Analysis window are as follows:

Table 2: Analysis Visit Windows

Study Analysis Visit	Target Day	Analysis Window
Baseline	1	≤1
Day 14	14	2-29
Day 45	45	30-68
Month 3	90	69-134
Month 6	180	135-224
Month 9	270	225-314
Month 12	360	315-404
Month 15	450	404-494
Month 18	540	495-584
Month 21	630	585-674
Month 24	720	675-764
Month 27	810	765-854
Month 30	900	855-944
Month X[a]	Every 90 days thereafter	Target day – 45 days to target day + 44 days

[a] For visits occurring every 3 months after Month 30, Month X is 3 months after the previous visit.

3.4 Handling of Dropouts and Missing Data

Subjects who discontinue from the study will not be replaced.

An AE will be considered treatment-emergent if the entered data (e.g., the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria.

Imputation of AE (for determination of treatment-emergent adverse event [TEAE] only) and **concomitant medication** start and stop dates:

- **Start Date:** If only ‘day’ is missing, and the month and year are not the same as the month and year of first dose, then impute day with the first of the month. Otherwise, if the month and year are the same as the first dose date, use the first dose date. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month and day with month and day of the first dose date (assuming same ‘year’). If ‘day’ and ‘month’ are missing and ‘year’ is not missing and is not the same year as first dose date, then impute with 1st of January. If the start date is completely missing, it will be set to the first dose date.
- **Stop Date:** If only ‘day’ is missing, impute day with last day of the month. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month with the 31st of December’ (or date of study discontinuation/completion if earlier than 31st of December and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. Stop date will not be imputed for ongoing AEs.

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4.0 Subject Disposition

Subject disposition will be presented including numbers and percentages of subjects: treated in the study; who completed the study; who discontinued from the study; who completed treatment, and who discontinued treatment prematurely. Reasons for discontinuation of IMP and of the study will be summarized.

5.0 Protocol Deviations

Important protocol deviations data have been entered into the PRA Clinical Trials Management System (CTMS) and the SimpleTrials system. The Sponsor will conduct on-going reviews of the deviation data from CTMS and SimpleTrials system and the resulting set of protocol deviations throughout the study, adjusting the deviation criteria as seems appropriate. Data from the PRA CTMS was imported into the SimpleTrials CTMS data for reporting. In the SimpleTrials CTMS, Important protocol deviations are entered as 'Major'; other protocol deviations (not important) are entered as 'Minor'.

A listing of the important protocol deviations will be provided. No Per Protocol analysis will be performed.

6.0 Demographics and Baseline Characteristics

Demographic data are imported from the Study AG10-201 database. Demographic and Baseline Characteristics (sex, ethnicity, race, gene mutation status, subject's variant type (for subjects with a gene mutation status of mutant), age [years], age group (<65, ≥65 to <75 or ≥75 [years], <65, ≥65 [years] and <78, ≥78 [years]) and weight [kg], will be summarized using the descriptive statistics for subjects in the Safety Analysis Set. Qualitative (categorical) variables (age group, sex, ethnicity, race) will be summarized using frequencies while quantitative (continuous) variables (age and weight) will be summarized using mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum. Demographic and baseline data will also be listed for subjects in the Safety Analysis Set.

7.0 Medical History

Medical history for this study will include imported Medical history and AEs initially reported in the AG10-201 study, as well as medical history that occurred after the close of Study AG10-201 and before enrollment in Study AG10-202.

Medical history and AEs reported in Study AG10-201 were imported into the Study AG10-202 database as medical history and was coded by Medical Dictionary for Regulatory Activities ([MedDRA] version 21.0). Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database and coded by MedDRA (version 23.1 or later) as applicable at time of analysis and will be presented in a summary table and with a subject listing.

8.0 Prior and Concomitant Medications/Procedures

Prior and concomitant medications reported in the Study AG10-201 study are included (imported) in the Study AG10-202 database and considered prior medications in the AG10-202 study. Sites were instructed to enter any new medications (started after the end of the Study AG10-201) in the concomitant medication form of the CRF. For reporting of Study AG10-202, prior medications will be any medication with a start date before the date of the first IMP dose as defined above.

Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date on or after the first dose. Consequently, medications ongoing at the start of treatment will be reported as both prior and concomitant medications.

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Prior and concomitant medications initially reported in AG10-202 will be coded according to the AG10-202 Coding Conventions using the World Health Organization Drug Dictionary (WHODrug) i.e. using the WHODrug dictionary version 2020SEP01. Prior and concomitant medications reported in the Study AG10-201 and imported in the Study AG10-202 database are coded with WHODrug dictionary version 2018MAR01. The prior and concomitant medication analyses will be performed using the Safety Analysis Set.

Summaries and listings of prior and concomitant medications by Preferred Name (PN) and each Anatomic Therapeutic Classification (ATC) levels (1 to 4) will be provided and by PN and ATC levels 1 to 2. In the summaries, subjects taking more than one medication in the same PN will be counted once for the number of subjects taking the medication of that PN.

Summaries and listings of prior and concomitant diuretics and cardiovascular medications will be presented by ATC levels 1 to 4 and PN as well as for ATC levels 1 to 2 and PN. Diuretics medications are medications classified under the ATC Level 2 of Diuretics and Cardiovascular medications are medications classified under the ATC Level 1 of Cardiovascular System.

9.0 Extent of Exposure to Study Drug

The extent of exposure will be presented as duration (months). The number of months of exposure will be defined as: (last dose of IMP date – first dose of IMP date +1) / 30.4375, regardless of intermittent discontinuations or dose reductions. Non-integer values will be rounded to one decimal place.

The number of months of actual exposure will be defined as: (last dose of IMP date – first dose of IMP date – number of days where no medication was taken +1) / 30.4375. The number of days when no medication was taken will be derived from the 'Exposure-Missed Doses' eCRF page. The number of days with no medications is derived as the number of missed doses divided by 2. The IMP is taken twice per day and one missed dose (AM or PM) corresponds to half a day.

As context for the extent of exposure, the proportion of subjects receiving at least one dose and the proportion of tablets taken out of the expected number of tablets to be taken. The strength of the tablets dispensed during the study is 200 mg (kits starting by '3') and 400 mg (kits starting by '4' or '5'). The subjects are expected to take a total of 4 tablets daily (strength 400 mg) or a total of 8 tablets daily (strength 200mg).

If one or multiple kits have not been returned, the following assumption will be followed:

- If a subject discontinued from the study and their last dispensed kits were not returned, it will be assumed that the subject took their IMP as planned per the study (i.e. 800 mg twice daily) up to their last dose date.
- Otherwise, if a kit was not returned at the following visit, it is assumed that all IMP was taken from that kit.
- Lastly, for the interim snapshot, if the kits were not returned and no visit was performed after the kits were dispensed (ongoing subjects), it will be assumed that the subject took their IMP as planned per the study (i.e. 800 mg twice daily) up to the data cut-off date.

The subject number, date(s) when IMP was dispensed, number of tablets dispensed in each bottle, date of return of each bottle of IMP and number of tablets in each bottle returned will be presented for each subject in listings.

10.0 Safety Evaluations

The Safety Analysis Set will be used for all safety analyses.

Safety parameters to be assessed include: TEAEs, treatment-emergent serious adverse events (SAEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance,

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abnormal vital signs of clinical relevance, abnormal electrocardiogram (ECG) parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern.

10.1 Adverse Events

Only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables. Serious TEAEs and Treatment-Emergent Serious Adverse Events are used interchangeably in this document.

10.1.1 All Treatment-Emergent Adverse Events

For the purposes of data collection for this study, any untoward event that is reported from the time that the subject signs the Informed Consent Form (ICF) until 30 days after the last dose of IMP is to be considered an AE. An AE will be considered a TEAE if it was not present before the first dose of IMP for the Study AG10-202 study or if it was present before the first dose of IMP but increased in severity during the treatment period. Only TEAEs will be included in the summary tables.

An AE that occurs more than 30 days after the last dose of IMP will not be counted as a TEAE. For interim reporting, the last dose of IMP for the determination of treatment emergence will be assigned as the date of the data extract for ongoing subjects. For subjects that have discontinued IMP, the date of last dose will be as recorded on the End of Treatment CRF. For subjects that died during the reporting period, if a date of last dose is not reported, the date of death will be used for the date of last dose.

A summary of the following will be presented: all TEAEs; treatment-related TEAEs; TEAEs with outcome of death; Serious TEAEs; treatment-related Serious TEAEs; non-serious TEAEs; TEAEs leading to discontinuation of IMP, and TEAEs leading to discontinuation of study.

Tabular summaries with numbers and percentages of subjects that have the following TEAEs will be provided by System Organ Class (SOC) and Preferred Term (PT).

- All TEAEs;
- TEAEs by maximum severity;
- Treatment-related TEAEs;
- Non-serious TEAEs;
- TEAEs leading to discontinuation of IMP;
- TEAEs leading to discontinuation of study.

The summary of TEAEs will also be repeated by SOC only and by PT only. The most frequent TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

At each level of summarization (e.g., all TEAEs, SOC, and PT), subjects will be counted only once. For tables categorized by severity, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event for that SOC or PT. Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as ‘Related’. Missing values for severity will be considered as ‘Severe’ and missing value for relationship to IMP will be considered as ‘Related’ in the summary.

TEAEs leading to discontinuation of IMP are those with an action taken with IMP on the AE CRF page of ‘Drug Withdrawn’.

TEAEs leading to discontinuation of the study are those on the AE CRF page with “YES” for the question “Did the adverse event cause the subject to be discontinued from the study?”

By-subject listings will be provided for the following: All TEAEs, non-TEAEs, TEAEs leading to discontinuation of study drug and TEAEs leading to discontinuation of study.

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The duration of AEs in days will be derived as the AE end date (including imputation date for incomplete AE end date) – AE onset date (imputed date for incomplete AE onset date) +1.

10.1.2 Treatment-Related Adverse Events

Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing value for relationship to treatment will be considered as 'Related' in the summary.

Subject incidence of the treatment-related TEAEs will be tabulated by SOC and PT and associated listing will be provided. The summary of treatment-related TEAEs will also be repeated by SOC only and by PT only. The most frequent treatment-related TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

Subject incidence of the treatment-related serious TEAEs will be tabulated by SOC and PT and associated listing will be provided.

10.1.3 Treatment-Emergent Serious Adverse Events

The number and percentage of subjects and the number of SAEs reported for the following categories of SAEs will be presented.

- SAEs;
- SAEs with an outcome of death;
- Treatment-related SAEs;
- SAEs leading to discontinuation of IMP;
- SAEs leading to discontinuation of study.

In addition, subject incidence of the treatment-emergent SAEs will be tabulated by SOC and PT for the above categories. Subjects will be counted only once within each SOC or PT.

The summary of serious TEAEs will also be repeated by SOC only and by PT only. The most frequent serious TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

By-subject listings will be also provided for the each of the above categories.

10.1.4 Adverse Events Leading to Discontinuation of Study Drug and/or the Study

AEs leading to discontinuation of IMP are those with an action taken with regard to IMP of 'Drug Withdrawn'. AEs leading to discontinuation from the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

Subject incidence of the TEAEs leading to discontinuation of IMP will be tabulated by SOC and PT and associated listing will be provided.

Subject incidence of the TEAEs leading to discontinuation of study will be tabulated by SOC and PT and associated listing will be provided.

10.1.5 Adverse Events with an Outcome of Death

An AE with an outcome of fatal reported will be considered as AE with an outcome of death.

Subject incidence of the TEAEs with an outcome of death will be tabulated by SOC and PT and an associated listing will be provided.

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10.1.6 Exposure-Adjusted Incidence Rate Adverse Events

Exposure-adjusted incidence rate will be derived for TEAEs, serious TEAEs and treatment-related TEAEs, overall and at each SOC and PT levels.

At each level of the summary, the subject-years of exposure is the sum of the duration from the first dose of IMP to the start date of the first event of interest (for the subjects with an event of interest) plus the duration from the first dose of IMP to the last dose of IMP + 30 days or data cut-off date (for subjects with no event of interest) divided by 365.25. The incidence rate is the number of subjects with the event of interest divided by subject-years multiplied by 100.

10.2 Clinical Laboratory Tests

Descriptive summaries of observed values and changes from baseline will be provided for numerical laboratory assessments by visit based on International System of Units (SI). If a result begins with a "<", then the result will be imputed by the numeric part divided by the square root of 2. If a result begins with a ">", then the result will be imputed by the numeric. The categorical laboratory results will be summarized by frequency and percentage and by visit.

Laboratory values will also be tabulated in shift tables from baseline where available. For the shift tables, laboratory results will be categorized by the central laboratory (when normal ranges have been defined) as high (higher than the upper limit of the normal range), normal (within the normal range) or low (lower than the lower limit of the normal range). Unavailable results (samples not collected, visit not done, discontinuation) will also be summarized and included in the total count. The percentages will be based on the number of subjects at baseline within each category, (for example, for a given parameter, regardless of the visit, the percentage of subjects with low post-baseline results and low baseline results will be based on the number of subjects with low baseline results). Shift from baseline to worst post-baseline will also be summarized, if a subjects has both a low and high post-baseline results, the subjects will be summarized under High category.

Where applicable, figures of mean laboratory values and of individual subject's laboratory parameters (spaghetti plots) by visit will be presented.

The number and proportion of subjects with liver test elevations will be presented. Liver test elevations are assessed by using post-Baseline results for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin based on the definitions presented in Table 3.

Table 3: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN - < 3 x ULN ALT or AST ≥ 3 x to < 5 x ULN ALT or AST ≥ 5 x to < 10 x ULN ALT or AST ≥ 10 x to < 20 x ULN ALT or AST ≥ 20 x ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

The number and percentage of subjects with concurrent (defined as measurements on the same day) ALT or AST ≥ 3 times upper limit of normal (ULN) and total bilirubin > 2 times ULN will also be presented.

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In addition, tables for the numeric laboratory parameters presenting the normal ranges in both reported units and SI units will be provided.

Laboratory parameters with abnormal results as identified by the central lab will be listed. Subject listings will also be provided for all laboratory tests.

10.3 Vital Signs

Descriptive summaries of observed values and changes from baseline will be provided for vital signs by visit.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for vital signs parameters.

10.4 Physical Examination

Physical examination will be provided in listings only.

10.5 Electrocardiogram

Descriptive summaries of observed values and changes from baseline will be provided for ECGs (PR interval, QRS duration, QT interval, QT corrected interval with Bazett's formula [QTcB] and with Fridericia's formula [QTcF]) by visit.

Number and percentage of subjects for each the following categories (based on the International Council for Harmonisation [ICH] E14 guidance) will be tabulated by visit:

- QT interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcB interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcF interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- Increase in change from baseline in QT interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- Increase in change from baseline in QTcB interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- Increase in change from baseline in QTcF interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- PR interval greater than 200 msec and change from baseline in PR interval > 25%;
- QRS interval greater than 120 msec and change from baseline in QRS interval > 25%.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for all ECG parameters.

Subject listings will also be provided for all ECG results.

10.6 COVID-19 Related Analysis

Any deviations from the protocol related to Coronavirus disease 2019 (COVID-19) control measures will be summarized and a listing will be generated.

Listings may be provided for subjects with the following: visits altered by or missed due to COVID-19 control measures; visits missed due to COVID-19 Infection Related Adverse Event; subjects with study discontinuations due to COVID-19 control measures; subjects with IMP discontinuation due to COVID-19 control measures; subjects with missed IMP doses related to COVID-19 control measures, and subjects with COVID-19adverse events. COVID-19 AEs will be identified using Standardised MedDRA Query on COVID-

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19 with a narrow scope.

11.0 Pharmacokinetics and Pharmacodynamics

11.1 Pharmacokinetics

Pre-dose blood samples for the determination of plasma acoramidis and acoramidis acylglucuronide will be collected on Days 1, 14, and 45, and months 3, 6 and 15 and then every 3 months after Month 15. Only pre-dose samples are planned for collection. Samples that are collected post-dose will not be included in these analyses.

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be performed by a designated bioanalytical laboratory, which will report the concentrations in ng/ml. The acoramidis molar concentration will be derived using the molecular weight of 292.31g/mol as freebase, and the acoramidis acylglucuronide concentration will be derived using the molecular weight of 468.43 g/mol as freebase

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, 25th percentile, 75th percentile and maximum will be calculated for all nominal concentration time points (visits).

The level of precision for each concentration will be presented as follows:

- Minimum and Maximum in same precision as in bioanalytical data;
- Mean, Median, 25th percentile and 75th percentile in one more level of precision than Minimum and Maximum;
- SD and SEM in one more level of precision than Mean;
- n will be presented as an integer;
- CV% will be presented to the nearest tenth.

All below limit of quantification (BLQ) values will be presented as “BLQ” in the concentration listings and footnoted accordingly.

Box and whisker plots will be presented for PK group analysis with concentration (ng/mL) on the y-axis and visit on the x-axis. The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker. The box and whisker plots will be presented overall and by gene mutation type.

11.2 Pharmacodynamics

Pre-dose PD blood samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 and then every 3 months after Month 15. The PD of acoramidis will be assessed by established assays of TTR stabilization, including FPE assay and WB, and to describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM.

Note: Observed values and change from baseline in circulating prealbumin levels will also be measured as a PD marker.

Fluorescent Probe Exclusion (FPE) Stabilization

For each sample, FPE reading is measured in duplicate for every 15 min up to 6 hours. The measurement points are pre-probe, 0 min, 15 min, 30 min….360 min (total 26 points × duplicate = 52 data points). Two QC samples (0 µM, 7.5 µM) are included in duplicate in each plate. For each 0 min – 360 min datapoint, the corresponding pre-probe value should be subtracted to derive “adjusted Relative Fluorescence Unit (RFU)”.

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FPE Percent Target Engagement, at Day X will be derived as follows (using the mean of the duplicates):

$$100 \times \frac{(\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe }) - (\text{FPE Day X @60 min-FPE Day X @pre-probe})}{\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe}}$$

FPE data will be tabulated for time: Y=60 mins for all visits. All timepoints will be used for FPE plots.

Western Blot (WB) Stabilization

WB Percent Stabilization at Day X will be derived as follows:

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates, Day\ X)}{mean\ of\ 0\ hour\ acidification\ duplicates,\ Day\ X}$$

WB data will be tabulated for all visits.

Number and percentage of subjects with FPE % target engagement ≥ 75%, ≥ 90%, ≥ 99% will be summarized overall and by gene mutation type for each visit. Descriptive summary of FPE % target engagement will be presented overall and by gene mutation type for each visit,

Number and percentage of subjects with WB % stabilization ≥ 75%, ≥ 90%, ≥ 99% will be summarized overall and by gene mutation type for each visit. Descriptive summary of WB % stabilization and its change from baseline will be presented overall and by gene mutation type for each visit,

A table of the FPE variations in QC readings (mean and CV% of the duplicates at 60 min minus the mean of the pre-probes duplicates) will be presented for 0 µM QC samples and 7.5 µM QC samples for each plate. Percent target engagement for each plate will be provided and is defined as follow:

$$100 \times \frac{(\text{FPE 0 µM @60 min - FPE 0 µM @pre-probe}) - (\text{FPE 7.5 µM @60 min - FPE 7.5 µM @pre-probe})}{\text{FPE 0 µM @60 min - FPE 0 µM @pre-probe}}$$

Where 0 µM denotes the 0 µM QC samples and 7.5 µM denotes the 7.5 µM QC samples.

A table of the WB variations in QC readings (means and CV% of the duplicate for 0 hour acidification and 72 hour acidification) for each control (DMSO and 5 µM acoramidis) will be presented by gel. Percent stabilization for each gel will be summarized for each control type and is defined as follow.

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates)}{mean\ of\ 0\ hour\ acidification\ duplicates}$$

Figures for FPE assay will include the complete time course of Fluorescence generation for each viable serum sample at each blood draw time point by subject.

FPE mean percent target engagement and WB mean percent stabilization will be presented (bar chart) by visit (Day 1, Day 14, Month 3, Month 6,etc.) overall and by gene mutation type. This will be presented with both standard error and standard deviation of the mean. At Day 1 FPE percent target engagement is by definition zero and doesn't need to be presented.

FPE mean percent target engagement ± SD and WB mean percent stabilization ± SD will be presented (mean plot) by visit. At Day 1 FPE percent target engagement is by definition zero and will be display as 0 on the plot.

In addition, box and whisker plots by gene mutation type will be presented for WB percent stabilization and FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6, … etc.). The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker.

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Mean percent change from baseline in prealbumin levels by visit (Day 1, Day 14, etc.) will be presented (bar chart) overall and by gene mutation type. This will be presented with both standard error and standard deviation of the mean.

Mean prealbumin levels ± SD by visit will be presented (mean plot).

In addition, box and whisker plots overall and by gene mutation type will be presented for prealbumin level (mg/dL) by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

A summary of subjects who reached certain thresholds (10%, 25%, and 50%) of percent increase in prealbumin overall and by gene mutation type for each visit will be provided. In addition, descriptive summary of prealbumin levels, change from baseline in prealbumin levels and percent change from baseline in prealbumin levels will be presented overall and by gene mutation type for each visit,

A subject data listing will include WB percent stabilization by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.). Another subject data listing will include FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6,. etc.). Finally, a subject data listing will include prealbumin concentration and percent change from baseline by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

11.3 Pharmacodynamics and Pharmacokinetics Relationship

Correlation plots will be provided overall and by mutant type as follows. Spearman correlation will be provided overall and by gene mutation type at each visits up to Month 30.

1. Acoramidis concentration vs. FPE percent target engagement
2. Acoramidis concentration vs. WB percent stabilization
3. Acoramidis concentration vs. Prealbumin percent change from baseline

12.0 Echocardiographic Parameters (Exploratory)

Descriptive summaries of observed values and changes from baseline for echocardiographic parameters of LV mass, stroke volume index and global longitudinal strain will be provided. A listing of echocardiogram parameters (LV mass, stroke volume index and global longitudinal strain) will also be provided.

13.0 References

ICH E3 Structure and content of clinical study reports..

ICH E9 Statistical principles for clinical trials. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials.

ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. https://www.ema.europa.eu/en/ich-e14-clinical-evaluation-qtqtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic.

14.0 Summary of Changes from the protocol

The following changes from Protocol Amendment 3 are reflected in the SAP version 2.0:

- Baseline values are defined in the protocol Amendment 3 as the last value obtained on or before the date of the first dose from Study AG10-201. For SAP version 2.0, baseline is defined as the last value obtained on or before the first dose of Study AG10-202.
- There are no time-to-event analyses planned for clinical events as stated in protocol Amendment 3.

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- Since this is a single arm study, data will not be reported by treatment group as stated in protocol Amendment 3.
- Safety parameters to be assessed include: TEAEs, treatment-emergent SAEs, AEs leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern. More details were added for clarity.
- Summary of clinical events will not be performed as data wasn't collected to support such an analysis.

15.0 Validation

The goal is to ensure that each Table; Figure, and Listing (TFL) delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

Data Handling and Transfer

Data will be entered and exported as SAS (version 9.4 or higher) datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard (CDISC) Data Tabulation Model ([SDTM], version 1.4 or higher, Implementation Guide version v3.2 or higher) conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model ([ADaM], version 2.1 or higher, Implementation Guide 1.1) standards.

Medical history and AEs will be coded using the MedDRA, version 23.1 or higher at the time of the analysis to assign a SOC and PT to each event. Prior and concomitant medications will be coded using the WHODrug 2020SEP01 Global B3 or higher at the time of the analysis.

Additional details can be found in the PRA Data Management Plan for Study AG10-202.

16.0 Summary of Changes

Date	Description
03-Jul-2019	Initial version
11-May-2021	Version 2.0 • Document was reformatted for clarity. • Document was aligned with protocol amendment 3 and CRF version 5.0. • Updated the List of Abbreviations. • Updated AG10 to acoramidis. • Consistent use of IMP instead of study drug or study treatment. • Consistent use of subject to refer to individuals participating in the study instead of

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Date	Description
	patient. • Added 25th and 75th percentile statistics to the summary statistics, wherever applicable. • Removed original section 7 (Study Endpoints, Variables and Covariate). This is now covered under each corresponding analysis method section. • Removed original section 12.7.3 (Clinical Events) as data was not collected and analysis is not applicable. • **Section 2.0:** Updated incorporating details of study purpose and scope. • **Section 2.2:** Study design was updated in alignment with study protocol amendment 3. • **Section 2.3:** Added a separate section for study population. • **Section 2.4:** Added a section for study dosage and administration with more details. • **Section 2.6:** Removed the randomization section and added this blinding section clarifying that AG10-202 is an open label study. • **Section 2.7**: Updated interim analysis section. There will be a data snapshot to generate an interim clinical study report in support planned regulatory activities. • **Section 3.3**: Section updated to specify the derivations of analysis windows for the reporting of the study results (previously nominal visits were to be used). • **Section 3.4**: o Added this section to compile all imputation rules handling of dropouts and missing data. o Added clarify to missing data imputation rule. An AE will be considered treatment-emergent if the entered data (e.g. the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria. • **Section 4.0:** Added completed treatment to subject disposition analysis. • **Section 5.0**: Added details explaining that PRA and SimpleTrials CTMS hold the protocol deviations for the study. • **Section 6.0**: Added (<78, ≥78 [years]) to age group. • **Section 7.0**: o Added a separate section for medical history with more details for clarity. o Indicated that Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database. o Dictionary version was updated to the latest version used. • **Section 8.0**: o Added summaries and listings of prior and concomitant diuretics and cardiovascular medications, which may be presented. o Moved definition of prior and concomitant medications from Section 8.0 definition (initial version) to Section 8.0 Prior and Concomitant Medications/Procedures.

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Date	Description

	• **Section 9.0**:
	  ○ Summary of doses missed was removed.
	  ○ Duration of exposure derivation was clarified.
	  ○ Number of tablets administrated summary replaced by proportion of tablets taken out of dispensed.
	• **Section 10.0:** List of safety parameters was updated and moved from previous Section 7.0..
	• **Section 10.1**: Stated that only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables.
	• **Section 10.1.1**:
	  ○ Added clarity to treatment emergent adverse event definitions.
	  ○ Added treatment-related Serious TEAEs and non-serious TEAEs to the overall TEAE summary.
	• **Section 10.1.2:** Added a separate section to outline analysis for treatment-related adverse events.
	• **Section 10.1.3:**
	  ○ Added overall SAE summaries for SAE, SAEs leading to IMP discontinuation and SAEs leading to discontinuation.
	  ○ Removed the breakdown into all different serious criteria.
	  ○ Added summaries by SOC and PT and additional listings for SAEs.
	• **Section 10.1.4:** Added a separate section to outline analysis for adverse events leading to discontinuation of study drug and/or the study.
	• **Section 10.1.5:** Added a separate section to outline analysis for adverse events with an outcome of death.
	• **Section 10.2**:
	  ○ Added shift tables, where available.
	  ○ Added table and listing for liver test elevations.
	  ○ Added mean and individual spaghetti plots.
	• **Section 10.3**: Added mean and individual spaghetti plots.
	• **Section 10.5**:
	  ○ Added a separate section to outline all ECG related analysis.
	  ○ Additional summaries tables added for potentially abnormal QT, QTcB, QTcF, PR and QRS intervals parameters.
	  ○ Added mean and individual spaghetti plots.
	• **Section 10.6**: New section for COVID-19 related analysis.
	• **Section 11.1:**
	  ○ Added details for the derivation of PK concentration to molar concentration.

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Date	Description
	○ Removed median concentrations with confidence intervals figure. ○ Removed the sentences of subject's inclusion or exclusion for PK analysis as data from all subjects in the PK analysis set will be included. • **Section 11.2**: ○ Clarified that prealbumin levels are a PD parameter. ○ Clarified that listings for the WB and FPE will be provided. ○ Clarified that listing for prealbumin and percent change in prealbumin levels will be provided. ○ Added summary of subjects with percent increase in prealbumin levels above certain thresholds. ○ Clarified figures presentation/contents. ○ Removed figures presenting RFU and by percent target engagement by AG10 concentration. ○ Removed figures presenting mean and 95% confidence intervals for FPE and WB percent stabilization. ○ Removed figure presenting mean and 95% confidence intervals for prealbumin. ○ Removed summary table of the overall percent stabilization for both WB and FPE. • **Section 11.3**: ○ Added a separate section to outline the PD/PK correlation plots. ○ Specify that percentage change from baseline prealbumin levels is used in the correlation plots instead of prealbumin levels. ○ Removed correlation plot between prealbumin and RFU. • **Section 12.0**: Added descriptive summaries of observed values and changes from baseline for echocardiographic parameters. • **Section 13.0**: Included ICH E3, E9 and E14 as references. • **Section 14.0**: ○ Updated current text to refer to protocol amendment 3. ○ Added clarification of the safety parameters assessed. ○ Clarify that the summary of clinical events will not be performed. • **Section 15.0**: ○ Moved original section 11.0 Data Review under this Validation section. ○ Updated versions for SDTM and ADaM. ○ Updated versions for MedDRA and WHO dictionaries. ○ Removed Data Screening paragraph as this is governed by Data Management Plan and is not within the scope of SAP. • **Section 16.0:** Added summary of changes.

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Date	Description

18-Oct-2021	• **Section 1.0**: added abbreviation for SI
	• **Section 3.3:**
	  ○ Corrected visit windows (added Month 9 and Month 12).
	• **Section 5.0**:
	  ○ Clarified that protocol deviations reported in the PRA CTMS were imported into the SimpleTrials CTMS.
	• **Section 6.0**:
	  ○ Added summary for age group of <65, ≥65 years.
	• **Section 7.0**:
	  ○ Clarified that data imported from AG10-201 was coded using MedDRA version 21.0 and the medical history and AE reported after close of Study AG10-201 were coded by MedDRA version 23.1.
	• **Section 8.0**:
	  ○ Clarified that data imported from AG10-201 was coded using WHO Drug dictionary version 2018MAR01 and the medications reported after close of Study AG10-201 were coded by WHO Drug dictionary version 2020SEP01.
	  ○ Clarified that the summary for prior/concomitant medications will include each of the ATC levels (1 to 4) and additional tables will be created for the summary with ATC levels 1, level 2 and PN.
	  ○ Added details on how Cardiovascular medications and Diuretics medications are selected.
	• **Section 9.0**:
	  ○ Clarified that days where no medication was taken is derived from the 'Exposure-Missed Doses' eCRF page. Clarified how missed days were derived as the IMP is taken twice daily.
	  ○ Updated proportion of tablets taken out of dispensed by proportion of tablets taken out of number of tablets expected to be taken to have a measure of compliance
	  ○ Provided details for kits not returned.
	  ○ Provided details on the different strengths of tablets dispensed during the study.
	  ○ Removed visit and number of bottled of IMP dispensed from the data listing as those field are not included in the listing.
	• **Section 10.1.1**:
	  ○ Added summary of TEAE by SOC only and by PT only
	  ○ Added summary for the most frequent TEAE by PT.
	• **Section 10.1.2**:
	  ○ Added summary of treatment-related TEAE by SOC only and by PT only
	  ○ Added summary for the most frequent treatment-related TEAE by PT.

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Date	Description

	• **Section 10.1.3**:
	  ○ Added summary of treatment-related serious TEAE in the overall table.
	  ○ Added summary of serious TEAE by SOC only and by PT only
	  ○ Added summary for the most frequent serious TEAE by PT.
	• **Section 10.1.6**:
	  ○ New section to describe summary for exposure-related incidence rate.
	• **Section 10.2**:
	  ○ Clarified that tables will present SI results.
	  ○ Added rules for imputation for the results beginning with '>' or '<'.
	  ○ Provided details for the percentages derivation for the shift tables and added definition for non-available category.
	  ○ Added details for shift tables from baseline to worst post-baseline.
	  ○ Added tables for the normal ranges in reported and SI units.
	• **Section 10.6**:
	  ○ Removed COVID-19 vaccine AEs from the list of data listings.
	  ○ Added details on selection for COVID-19 AEs.
	• **Section 11.1**:
	  ○ Added molecular weight for acoramidis acylglucuronide.
	  ○ Box and whisker plots will be presented overall and by gene mutation type
	• **Section 11.2**:
	  ○ Specified that summary tables are overall and by gene mutation type.
	  ○ Added details for the summary of the FPE QC samples.
	  ○ Added tables for the summary of the WB QC samples.
	  ○ Added new table for descriptive summary for FPE percent target engagement.
	  ○ Added mean plots (mean ± SD) for FPE percent target engagement.
	  ○ Added new table for descriptive summary for WB percent stabilization (actual and change from baseline).
	  ○ Added mean plots (mean ± SD) for WB percent stabilization.
	  ○ Box and whisker plots will present prealbumin levels and not percent change from baseline in prealbumin levels
	  ○ Added new table for descriptive summary for prealbumin levels (actual, change from baseline and percent change from baseline).
	  ○ Added mean plot (mean ± SD) for prealbumin levels.
	• **Section 11.3**:
	  ○ Added that figures will be provided overall and by mutant type

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Date	Description
	○ Added Spearman correlation for the overall and by gene mutation type at each visit up to Month 30. • **Section 12.0**: Added list of parameters included in tables and listings. • **Section 16.0:** (version 11-May-2021): ○ Sections 7.0, 8.0, 9.0 and 10.0 added minor clarifications.

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Statistical Analysis Plan

Protocol Title:	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
Protocol Version No./Date:	Amendment 4 / 09Sep2022
CRF Version No./Date:	5.0 / 20APR2021
SAP Version No./Date:	4.0 / 02MAY2023

Approvals

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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Signature /Date:	DocuSigned by Jing Du Jing Du I approve this document 5/2/2023 | 6:12 PM PDT
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1.0 List of Abbreviatons

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
BLQ	Below limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CTMS	Clinical Trials Management System
CV%	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ET	Early Termination
FPE	Fluorescent Probe Exclusion
HCl	Hydrochloride
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
n	Number of Subjects
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PD	Pharmacodynamic
PN	Preferred Name
PT	Preferred Term
QTcB	QT corrected interval with Bazett's formula
QTcF	QT corrected interval with Fridericia's formula
RFU	Relative Fluorescence Unit
SAE	Serious Adverse Event

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SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SEM	Standard Error of The Mean
SI	International System of Units
SOC	System Organ Class
STDM	Standard Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
TTR	Transthyretin
ULN	Upper Limit of Normal
WB	Western blot
WHODrug	World Health Organization Drug Dictionary

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2.0 Introduction

The purpose of the statistical analysis plan (SAP) is to provide a detailed description of the principal features of the analysis described in the protocol and to include detailed procedures for executing the statistical analysis of the primary, secondary, and exploratory endpoints and other data collected under Eidos Therapeutics, Inc. Study AG10-202. Acoramidis hydrochloride (HCl), and Investigational Medicinal Product (IMP) are used interchangeably in this document. In Study AG10-202 Study Protocol Amendment 3, AG10 is used to refer to acoramidis and AG10 HCl is used to refer to acoramidis HCl.

This document describes study objectives, analysis sets, outcome measures, the timing of statistical analyses, data analysis methods, and data summaries for this protocol. Analysis approaches detailed within this document supersede the analyses and summaries presented in the protocol.

This plan is a living document that will be created during the trial start-up and will be finalized prior to database lock. This SAP will require sign off from the PRA Biometrics Project Manager, the Biostatistician and the Sponsor.

2.1 Objectives of Study

The primary objective of this study is to evaluate the long-term safety and tolerability of IMP administered to adult subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) who completed the AG10-201 study.

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of IMP administered orally twice daily in subjects with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of IMP as assessed by established assays of transthyretin (TTR) stabilization, including Fluorescent Probe Exclusion (FPE) assay and Western blot (WB), and to describe the PK-PD relationship of IMP in adult subjects with symptomatic ATTR-CM.

The exploratory objective of this study is:

- to describe the long-term effects of IMP on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.

2.2 Study Design

This study is a prospective, multicenter, Phase 2, long-term, open-label study in up to 55 male and/or female subjects with symptomatic ATTR-CM, ≥18 years of age, who have completed participation in Study AG10-201. This prospective multicenter, open-label study will evaluate the long-term safety, tolerability, PK and PD of IMP administered to eligible subjects with stable heart failure therapy. An open-label design is considered to be the most appropriate study design for meeting this objective**.**

The study will continue at the Sponsor's discretion, or until registration of the product for the treatment of symptomatic ATTR-CM.

Eligible subjects will begin dosing acoramidis HCl 800 mg administered twice daily. Information on Adverse Events (AEs) and concomitant medications will be collected throughout the study. The safety of the study will be monitored by an independent acoramidis HCl program-wide Data Monitoring Committee (DMC).

The schedule of assessments is provided in Table 1.

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Table 1: Schedule of Assessments

	Day 1	Day 14 (±3 days)	Day 45 (±7 days)	To Month 54: Visits Every 3 Months (±7 days) to Month 54[a, b, c]	After Month 54: Telephone Contact Every 3 Months (±7 days)[d]	After Month 54: Visits Every 6 Months (±7 days)[a, c]	ET Visit[e]	Follow-up Visit 30 days after date of last dose (±7 days)[f]	Unsched-uled Visit[g]
Written Informed Consent	X								
Inclusion/ Exclusion Criteria Review	X								
Medical History	X								
Physical Exam[h]	X	X	X	X		X	X	X	X
Vital Signs	X	X	X	X		X	X	X	X
Resting transthoracic echocardiogram[a]	X[a]			X[a]		X[a]	X[a]		X[a]
12-lead resting ECG[a]	X	X	X	X[a]		X[a]	X	X	X
PD assays[c]	X	X	X	X[c]		X[c]			
PK sample collection[c]	X	X	X	X[c]		X[c]			
Prealbumin collection[c]	X	X	X	X[c]		X[c]			
Study drug dosing during visit	X	X	X	X		X			
Clinical laboratory assessments	X	X	X	X		X	X	X	X
Pregnancy test[i]	X	X	X	X		X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dispense IMP	X		X	X		X			

a. Resting 12-lead electrocardiogram and echocardiogram at Day 1, every 3 months until Month 12 then annually. Perform echocardiogram at ET Visit unless obtained in prior 6 months and at Unscheduled Visit only if clinically indicated.
b. Visits every 3 months from Day 1 visit until Month 54.
c. Samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 (predose only) and every 3 months after Month 15 up to Month 54. After the Month 54 clinic visit, samples will be collected every 6 months.
d. After Month 54, telephone contact will occur every 3 months after on-site clinic visits and include AE collection, concomitant medication use assessment, and IMP compliance assessment.
e. If a patient discontinues study participation, the patient will be asked to return to the study center for the ET Visit as soon as possible and to return any unused IMP.
f. When a patient discontinues study participation, the patient will be asked to return to the study center for the Follow-up Visit. The Follow-up Visit should be performed 30 days after date of last dose.
g. For assessment or follow up of an adverse event, only procedures that are indicated as needed by the investigator should be performed (eg, physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test).
h. Complete Physical Exam including body weight at all visits.
i. Females of Child-Bearing Potential only. Urine pregnancy test at all visits.

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2.3 Study Population

The study will enroll up to 55 males and/or females ≥18 years of age with chronic, stable, symptomatic ATTR-CM will be enrolled and begin dosing with acoramidis HCl 800 mg twice daily. See sections 8.3.1 and 8.3.2 of the study protocol for Inclusion and Exclusion criteria.

2.4 Study Dosage and Administration

IMP doses chosen for this study are based on results from nonclinical PK studies, data from the first-in-human single ascending dose and multiple ascending dose study, and data from a Phase 2 study (AG10-201). Further detail on dose selection can be found in the Investigator's Brochure (IB).

Dosing should occur twice daily, once in the morning and once in the evening.

Subjects will be dosed with acoramidis HCl 800 mg administered twice daily. Downward adjustment of dose or interruption of IMP is discouraged but permitted if necessary, in the event of intolerance to IMP. Subsequent upward adjustment of IMP back to the target dose should be attempted whenever possible. If it is believed that an AE may be drug-related, and depending on its severity, the IMP may be reduced from 800 mg twice daily to 400 mg twice daily.

2.5 Sample Size Determination

The planned number of subjects is determined by the number of eligible and interested subjects that have completed the Study AG10-201 and therefore is not expected to be greater than 55 subjects.

2.6 Blinding

This is an open-label study.

2.7 Interim Analysis

There will be a data snapshot to generate an interim clinical study report to support planned regulatory activities.

3.0 General Analysis Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS) version 9.4.

Unless otherwise specified, descriptive data summaries will be tabulated for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place. Counts of zero will not display a percentage.

All continuous variables will be summarized using mean, standard deviation (SD), median, minimum, maximum, 25th percentile, 75th percentile and number of subjects with observations. Unless otherwise specified, the mean, median, 25th percentile and 75th percentile will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

3.1 Analysis Sets

Safety Analysis Set

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The safety analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period. The safety analysis set will be used to summarize all safety data.

PK Analysis Set

The PK analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one quantifiable post-baseline concentration. The PK analysis set will be used to summarize all PK data in Study AG10-202.

PD Analysis Set

The PD analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one post-baseline PD assessment. The PD analysis set will be used to summarize all PD data in Study AG10-202.

3.2 Study Day Derivations

Study Day 1

Study Day 1 is defined as the first day of IMP administration in Study AG10-202.

Study Day

Study day is defined as the number of days from Study Day 1. Before Study Day 1, Study Day = (Date of Interest – Date of Study Day 1). Therefore, the day prior to Study Day 1 is -1.

On or After Study Day 1, Study Day = (Date of Interest – Date of Study Day 1) + 1.

A month is defined as 30.4375 days and a year is defined as 365.25 days.

First IMP Dose

For all subjects, the first IMP dose date is defined as the date of first dose in Study AG10-202. Date of first dose is recorded on the Exposure-First Dose Case Report Form (CRF).

Baseline and Change from Baseline

Baseline values are defined as the last pre-dose value obtained on or before the date of the first IMP dose in Study AG10-202.

Change from Baseline = (post-Baseline value – Baseline value).

Completion of study

Subject completion of the study is defined as an answer of “Yes” to the question “Did the subject complete the study (including Follow-Up)?” on the form of End of Study in the CRF.

Completion of treatment

Subject completion of treatment is defined as an answer of “Completed” to the question “End of Treatment Status” on the form of End of Treatment in the CRF.

3.3 Visit Window for Analysis

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Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows. The actual visit date is allowed to fall within a specified interval of the target day.

In general, if more than one actual visit (including unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

Analysis window are as follows:

Table 2: Analysis Visit Windows

Visit	Target Study Day	Analysis Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	≤1	1
Day 14	15	2	31
Day 45	46	32	69
Month 3	92	70	138
Month 6	184	139	230
Month 9	275	231	321
Month 12	366	322	412
Month 15	458	413	504
Month 18	549	505	595
Month 21	640	596	686
Month 24	732	687	778
Month 27	823	779	869
Month 30	914	870	960
Month 33	1005	961	1051
Month 36	1097	1052	1143
Month 39	1188	1144	1234
Month 42	1279	1235	1325
Month 45	1371	1326	1417
Month 48	1462	1418	1508
Month 51	1553	1509	1599
Month 54	1645	1600	1736
Month 60	1827	1737	1919
Month 66	2010	1920	2102
Month 72	2193	2103	≥2103

3.4 Handling of Dropouts and Missing Data

Subjects who discontinue from the study will not be replaced.

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An AE will be considered treatment-emergent if the entered data (e.g., the answer to "Did this AE start before the first dose for the AG10-202 study was taken?" on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria.

Imputation of AE (for determination of treatment-emergent adverse event [TEAE] only) and **concomitant medication** start and stop dates:

- **Start Date:** If only 'day' is missing, and the month and year are not the same as the month and year of first dose, then impute day with the first of the month. Otherwise, if the month and year are the same as the first dose date, use the first dose date. If 'day' and 'month' are missing, and 'year' is not missing, then impute month and day with month and day of the first dose date (assuming same 'year'). If 'day' and 'month' are missing and 'year' is not missing and is not the same year as first dose date, then impute with 1st of January. If the start date is completely missing, it will be set to the first dose date.
- **Stop Date:** If only 'day' is missing, impute day with last day of the month. If 'day' and 'month' are missing, and 'year' is not missing, then impute month with the 31st of December' (or date of study discontinuation/completion if earlier than 31st of December and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. Stop date will not be imputed for ongoing AEs.

Imputation of incomplete date of last dose of IMP: if a subject discontinued the treatment but the date of last dose is incomplete, the date of completion/discontinuation from the End of Study CRF page will be used.

4.0 Subject Disposition

Subject disposition will be presented including numbers and percentages of subjects: treated in the study; who completed the study; who discontinued from the study; who completed treatment, and who discontinued treatment prematurely. Reasons for discontinuation of IMP and of the study will be summarized.

5.0 Protocol Deviations

Important protocol deviations data have been entered into the PRA Clinical Trials Management System (CTMS) and the SimpleTrials system. The Sponsor will conduct on-going reviews of the deviation data from CTMS and SimpleTrials system and the resulting set of protocol deviations throughout the study, adjusting the deviation criteria as seems appropriate. Data from the PRA CTMS was imported into the SimpleTrials CTMS data for reporting. In the SimpleTrials CTMS, Important protocol deviations are entered as 'Major'; other protocol deviations (not important) are entered as 'Minor'.

A listing of the important protocol deviations will be provided. No Per Protocol analysis will be performed.

6.0 Demographics and Baseline Characteristics

Demographic data are imported from the Study AG10-201 database. Demographic and Baseline Characteristics (sex, ethnicity, race, gene mutation status, subject's variant type (for subjects with a gene mutation status of mutant), age [years], age group (<65, ≥65 to <75 or ≥75 [years], <65, ≥65 [years] and <78, ≥78 [years]) and weight [kg], will be summarized using the descriptive statistics for subjects in the Safety Analysis Set. Qualitative (categorical) variables (age group, sex, ethnicity, race) will be summarized using frequencies while quantitative (continuous) variables (age and weight) will be summarized using mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum. Demographic and baseline data will also be listed for subjects in the Safety Analysis Set.

7.0 Medical History

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Medical history for this study will include imported medical history and AEs initially reported in the AG10-201 study, as well as medical history that occurred after the close of Study AG10-201 and before enrollment in Study AG10-202.

Medical history and AEs reported in Study AG10-201 were imported into the Study AG10-202 database as medical history and was coded by Medical Dictionary for Regulatory Activities ([MedDRA] version 21.0). Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database and coded by MedDRA version 24.1 as applicable at time of analysis and will be presented in a summary table and with a subject listing.

8.0 Prior and Concomitant Medications/Procedures

Prior and concomitant medications reported in the Study AG10-201 study are included (imported) in the Study AG10-202 database and considered prior medications in the AG10-202 study. Sites were instructed to enter any new medications (started after the end of the Study AG10-201) in the concomitant medication form of the CRF. For reporting of Study AG10-202, prior medications will be any medication with a start date before the date of the first IMP dose as defined above.

Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date on or after the first dose. Consequently, medications ongoing at the start of treatment will be reported as both prior and concomitant medications.

Prior and concomitant medications initially reported in AG10-202 will be coded according to the AG10-202 Coding Conventions using the World Health Organization Drug Dictionary (WHODrug) i.e. using the WHODrug dictionary version 2022SEP01 Prior and concomitant medications reported in the Study AG10-201 and imported in the Study AG10-202 database are coded with WHODrug dictionary version 2018MAR01. The prior and concomitant medication analyses will be performed using the Safety Analysis Set.

Summaries and listings of prior and concomitant medications by Preferred Name (PN) and each Anatomic Therapeutic Classification (ATC) levels (1 to 4) will be provided and by PN and ATC levels 1 to 2. In the summaries, subjects taking more than one medication in the same PN will be counted once for the number of subjects taking the medication of that PN.

Summaries and listings of prior and concomitant diuretics and cardiovascular medications will be presented by ATC levels 1 to 4 and PN as well as for ATC levels 1 to 2 and PN. Diuretics medications are medications classified under the ATC Level 2 of Diuretics and Cardiovascular medications are medications classified under the ATC Level 1 of Cardiovascular System.

9.0 Extent of Exposure to Study Drug

The extent of exposure will be presented as duration (months). The number of months of exposure will be defined as: (last dose of IMP date – first dose of IMP date +1) / 30.4375, regardless of intermittent discontinuations or dose reductions. Non-integer values will be rounded to one decimal place.

The number of months of actual exposure will be defined as: (last dose of IMP date – first dose of IMP date – number of days where no medication was taken +1) / 30.4375. The number of days when no medication was taken will be derived from the ‘Exposure-Missed Doses’ eCRF page. The number of days with no medications is derived as the number of missed doses divided by 2. The IMP is taken twice per day and one missed dose (AM or PM) corresponds to half a day.

As context for the extent of exposure, the proportion of subjects receiving at least one dose and the proportion of tablets taken out of the expected number of tablets to be taken. The strength of the tablets dispensed during the study is 200 mg (kits starting by ‘3’) and 400 mg (kits starting by ‘4’ or ‘5’). The subjects are expected to take a total of 4 tablets daily (strength 400 mg) or a total of 8 tablets daily (strength 200mg).

If one or multiple kits have not been returned, the following assumption will be followed:

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- If a subject discontinued from the study and their last dispensed kits were not returned, it will be assumed that the subject took their IMP as planned per the study (i.e. 800 mg twice daily) up to their last dose date.
- Otherwise, if a kit was not returned at the following visit, it is assumed that all IMP was taken from that kit.
- Lastly, for the interim snapshot, if the kits were not returned and no visit was performed after the kits were dispensed (ongoing subjects), it will be assumed that the subject took their IMP as planned per the study (i.e. 800 mg twice daily) up to the data cut-off date.

The subject number, date(s) when IMP was dispensed, number of tablets dispensed in each bottle, date of return of each bottle of IMP and number of tablets in each bottle returned will be presented for each subject in listings.

10.0 Safety Evaluations

The Safety Analysis Set will be used for all safety analyses.

Safety parameters to be assessed include: TEAEs, treatment-emergent serious adverse events (SAEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal electrocardiogram (ECG) parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern.

10.1 Adverse Events

Only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables. Serious TEAEs and Treatment-Emergent Serious Adverse Events are used interchangeably in this document.

10.1.1 All Treatment-Emergent Adverse Events

For the purposes of data collection for this study, any untoward event that is reported from the time that the subject signs the Informed Consent Form (ICF) until 30 days after the last dose of IMP is to be considered an AE. An AE will be considered a TEAE if it was not present before the first dose of IMP for the Study AG10-202 study or if it was present before the first dose of IMP but increased in severity during the treatment period. Only TEAEs will be included in the summary tables.

An AE that occurs more than 30 days after the last dose of IMP will not be counted as a TEAE. For interim reporting, the last dose of IMP for the determination of treatment emergence will be assigned as the date of the data extract for ongoing subjects. For subjects that have discontinued IMP, the date of last dose will be as recorded on the End of Treatment CRF. For subjects that died during the reporting period, if a date of last dose is not reported, the date of death will be used for the date of last dose.

A summary of the following will be presented: all TEAEs; treatment-related TEAEs; TEAEs with outcome of death; Serious TEAEs; treatment-related Serious TEAEs; non-serious TEAEs; TEAEs leading to discontinuation of IMP, and TEAEs leading to discontinuation of study.

Tabular summaries with numbers and percentages of subjects that have the following TEAEs will be provided by System Organ Class (SOC) and Preferred Term (PT).

- All TEAEs;
- TEAEs by maximum severity;
- Treatment-related TEAEs;
- Non-serious TEAEs;

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- TEAEs leading to discontinuation of IMP;
- TEAEs leading to discontinuation of study.

The summary of TEAEs will also be repeated by SOC only and by PT only. The most frequent TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

At each level of summarization (e.g., all TEAEs, SOC, and PT), subjects will be counted only once. For tables categorized by severity, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event for that SOC or PT. Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing values for severity will be considered as 'Severe' and missing value for relationship to IMP will be considered as 'Related' in the summary.

TEAEs leading to discontinuation of IMP are those with an action taken with IMP on the AE CRF page of 'Drug Withdrawn'.

TEAEs leading to discontinuation of the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

By-subject listings will be provided for the following: All TEAEs, non-TEAEs, TEAEs leading to discontinuation of study drug and TEAEs leading to discontinuation of study.

The duration of AEs in days will be derived as the AE end date (including imputation date for incomplete AE end date) – AE onset date (imputed date for incomplete AE onset date) +1.

10.1.2 Treatment-Related Adverse Events

Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing value for relationship to treatment will be considered as 'Related' in the summary.

Subject incidence of the treatment-related TEAEs will be tabulated by SOC and PT and associated listing will be provided. The summary of treatment-related TEAEs will also be repeated by SOC only and by PT only. The most frequent treatment-related TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

Subject incidence of the treatment-related serious TEAEs will be tabulated by SOC and PT and associated listing will be provided.

10.1.3 Treatment-Emergent Serious Adverse Events

The number and percentage of subjects and the number of SAEs reported for the following categories of SAEs will be presented.

- SAEs;
- SAEs with an outcome of death;
- Treatment-related SAEs;
- SAEs leading to discontinuation of IMP;
- SAEs leading to discontinuation of study.

In addition, subject incidence of the treatment-emergent SAEs will be tabulated by SOC and PT for the above categories. Subjects will be counted only once within each SOC or PT.

The summary of serious TEAEs will also be repeated by SOC only and by PT only. The most frequent serious TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

By-subject listings will be also provided for the each of the above categories.

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10.1.4 Adverse Events Leading to Discontinuation of Study Drug and/or the Study

AEs leading to discontinuation of IMP are those with an action taken with regard to IMP of 'Drug Withdrawn'. AEs leading to discontinuation from the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

Subject incidence of the TEAEs leading to discontinuation of IMP will be tabulated by SOC and PT and associated listing will be provided.

Subject incidence of the TEAEs leading to discontinuation of study will be tabulated by SOC and PT and associated listing will be provided.

10.1.5 Adverse Events with an Outcome of Death

An AE with an outcome of fatal reported will be considered as AE with an outcome of death.

Subject incidence of the TEAEs with an outcome of death will be tabulated by SOC and PT and an associated listing will be provided.

10.1.6 Exposure-Adjusted Incidence Rate Adverse Events

Exposure-adjusted incidence rate will be derived for TEAEs, serious TEAEs and treatment-related TEAEs, overall and at each SOC and PT levels.

At each level of the summary, the subject-years of exposure is the sum of the duration from the first dose of IMP to the start date of the first event of interest (for the subjects with an event of interest) plus the duration from the first dose of IMP to the last dose of IMP + 30 days or data cut-off date (for subjects with no event of interest) divided by 365.25. The incidence rate is the number of subjects with the event of interest divided by subject-years multiplied by 100.

10.2 Clinical Laboratory Tests

Descriptive summaries of observed values and changes from baseline will be provided for numerical laboratory assessments by visit based on International System of Units (SI). If a result begins with a "<", then the result will be imputed by the numeric part divided by the square root of 2. If a result begins with a ">", then the result will be imputed by the numeric. The categorical laboratory results will be summarized by frequency and percentage and by visit.

Laboratory values will also be tabulated in shift tables from baseline where available. For the shift tables, laboratory results will be categorized by the central laboratory (when normal ranges have been defined) as high (higher than the upper limit of the normal range), normal (within the normal range) or low (lower than the lower limit of the normal range). Unavailable results (samples not collected, visit not done, discontinuation) will also be summarized and included in the total count. The percentages will be based on the number of subjects at baseline within each category, (for example, for a given parameter, regardless of the visit, the percentage of subjects with low post-baseline results and low baseline results will be based on the number of subjects with low baseline results). Shift from baseline to worst post-baseline will also be summarized, if a subjects has both a low and high post-baseline results, the subjects will be summarized under High category.

Where applicable, figures of mean laboratory values and of individual subject's laboratory parameters (spaghetti plots) by visit will be presented.

The number and proportion of subjects with liver test elevations will be presented. Liver test elevations are assessed by using post-Baseline results for alanine aminotransferase (ALT), aspartate aminotransferase

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(AST), alkaline phosphatase (ALP), and total bilirubin based on the definitions presented in Table 3.

Table 3: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN - < 3 x ULN ALT or AST ≥ 3 x to < 5 x ULN ALT or AST ≥ 5 x to < 10 x ULN ALT or AST ≥ 10 x to < 20 x ULN ALT or AST ≥ 20 x ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

The number and percentage of subjects with concurrent (defined as measurements on the same day) ALT or AST ≥ 3 times upper limit of normal (ULN) and total bilirubin > 2 times ULN will also be presented.

In addition, tables for the numeric laboratory parameters presenting the normal ranges in both reported units and SI units will be provided.

Laboratory parameters with abnormal results as identified by the central lab will be listed. Subject listings will also be provided for all laboratory tests.

10.3 Vital Signs

Descriptive summaries of observed values and changes from baseline will be provided for vital signs by visit.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for vital signs parameters.

10.4 Physical Examination

Physical examination will be provided in listings only**.**

10.5 Electrocardiogram

Descriptive summaries of observed values and changes from baseline will be provided for ECGs (PR interval, QRS duration, QT interval, QT corrected interval with Bazett's formula [QTcB] and with Fridericia's formula [QTcF]) by visit.

Number and percentage of subjects for each the following categories (based on the International Council for Harmonisation [ICH] E14 guidance) will be tabulated by visit:

- QT interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcB interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcF interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- Increase in change from baseline in QT interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- Increase in change from baseline in QTcB interval greater than 10 msec, 30 msec, 60 msec and 90 msec;

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- Increase in change from baseline in QTcF interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- PR interval greater than 200 msec and change from baseline in PR interval > 25%;
- QRS interval greater than 120 msec and change from baseline in QRS interval > 25%.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for all ECG parameters.

Subject listings will also be provided for all ECG results.

10.6 COVID-19 Related Analysis

Any deviations from the protocol related to Coronavirus disease 2019 (COVID-19) control measures will be summarized and a listing will be generated.

Listings may be provided for subjects with the following: visits altered by or missed due to COVID-19 control measures; visits missed due to COVID-19 Infection Related Adverse Event; subjects with study discontinuations due to COVID-19 control measures; subjects with IMP discontinuation due to COVID-19 control measures; subjects with missed IMP doses related to COVID-19 control measures, and subjects with COVID-19adverse events. COVID-19 AEs will be identified using Standardised MedDRA Query on COVID-19 with a narrow scope.

11.0 Pharmacokinetics and Pharmacodynamics

11.1 Pharmacokinetics

Pre-dose blood samples for the determination of plasma acoramidis and acoramidis acylglucuronide will be collected on Days 1, 14, and 45, and months 3, 6 and 15 and then every 3 months after Month 15. Only pre-dose samples are planned for collection. Samples that are collected post-dose will not be included in these analyses.

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be performed by a designated bioanalytical laboratory, which will report the concentrations in ng/ml. The acoramidis molar concentration will be derived using the molecular weight of 292.31g/mol as freebase, and the acoramidis acylglucuronide concentration will be derived using the molecular weight of 468.43 g/mol as freebase

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, 25th percentile, 75th percentile and maximum will be calculated for all nominal concentration time points (visits).

The level of precision for each concentration will be presented as follows:

- Minimum and Maximum in same precision as in bioanalytical data;
- Mean, Median, 25th percentile and 75th percentile in one more level of precision than Minimum and Maximum;
- SD and SEM in one more level of precision than Mean;
- n will be presented as an integer;
- CV% will be presented to the nearest tenth.

All below limit of quantification (BLQ) values will be presented as “BLQ” in the concentration listings and footnoted accordingly.

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Box and whisker plots will be presented for PK group analysis with concentration (ng/mL) on the y-axis and visit on the x-axis. The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker. The box and whisker plots will be presented overall and by gene mutation type.

11.2 Pharmacodynamics

Pre-dose PD blood samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 and then every 3 months after Month 15. The PD of acoramidis will be assessed by established assays of TTR stabilization, including FPE assay and WB, and to describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM.

Note: Observed values and change from baseline in circulating prealbumin levels will also be measured as a PD marker.

Fluorescent Probe Exclusion (FPE) Stabilization

For each sample, FPE reading is measured in duplicate for every 15 min up to 6 hours. The measurement points are pre-probe, 0 min, 15 min, 30 min….360 min (total 26 points × duplicate = 52 data points). Two QC samples (0 µM, 7.5 µM) are included in duplicate in each plate. For each 0 min – 360 min datapoint, the corresponding pre-probe value should be subtracted to derive “adjusted Relative Fluorescence Unit (RFU)”.

FPE Percent Target Engagement, at Day X will be derived as follows (using the mean of the duplicates):

$$100 \times \frac{(\text{FPE Day 1 @60 min} - \text{FPE Day 1 @pre-probe}) - (\text{FPE Day X @60 min} - \text{FPE Day X @pre-probe})}{\text{FPE Day 1 @60 min} - \text{FPE Day 1 @pre-probe}}$$

FPE data will be tabulated for time: Y=60 mins for all visits. All timepoints will be used for FPE plots.

Western Blot (WB) Stabilization

WB Percent Stabilization at Day X will be derived as follows:

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates, Day\ X)}{mean\ of\ 0\ hour\ acidification\ duplicates,\ Day\ X}$$

WB data will be tabulated for all visits.

Number and percentage of subjects with FPE % target engagement ≥ 75%, ≥ 90%, ≥ 99% will be summarized overall and by gene mutation type for each visit. Descriptive summary of FPE % target engagement will be presented overall and by gene mutation type for each visit,

Number and percentage of subjects with WB % stabilization ≥ 75%, ≥ 90%, ≥ 99% will be summarized overall and by gene mutation type for each visit. Descriptive summary of WB % stabilization and its change from baseline will be presented overall and by gene mutation type for each visit,

A table of the FPE variations in QC readings (mean and CV% of the duplicates at 60 min minus the mean of the pre-probes duplicates) will be presented for 0 µM QC samples and 7.5 µM QC samples for each plate. Percent target engagement for each plate will be provided and is defined as follow:

$$100 \times \frac{(\text{FPE 0 µM @60 min} - \text{FPE 0 µM @pre-probe}) - (\text{FPE 7.5 µM @60 min} - \text{FPE 7.5 µM @pre-probe})}{\text{FPE 0 µM @60 min} - \text{FPE 0 µM @pre-probe}}$$

Where 0 µM denotes the 0 µM QC samples and 7.5 µM denotes the 7.5 µM QC samples.

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A table of the WB variations in QC readings (means and CV% of the duplicate for 0 hour acidification and 72 hour acidification) for each control (DMSO and 5 µM acoramidis) will be presented by gel. Percent stabilization for each gel will be summarized for each control type and is defined as follow.

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates)}{mean\ of\ 0\ hour\ acidification\ duplicates}$$

Figures for FPE assay will include the complete time course of Fluorescence generation for each viable serum sample at each blood draw time point by subject.

FPE mean percent target engagement and WB mean percent stabilization will be presented (bar chart) by visit (Day 1, Day 14, Month 3, Month 6,etc.) overall and by gene mutation type. This will be presented with both standard error and standard deviation of the mean. At Day 1 FPE percent target engagement is by definition zero and doesn't need to be presented.

FPE mean percent target engagement ± SD and WB mean percent stabilization ± SD will be presented (mean plot) by visit. At Day 1 FPE percent target engagement is by definition zero and will be display as 0 on the plot.

In addition, box and whisker plots by gene mutation type will be presented for WB percent stabilization and FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6, … etc.). The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker.

Mean percent change from baseline in prealbumin levels by visit (Day 1, Day 14, etc.) will be presented (bar chart) overall and by gene mutation type. This will be presented with both standard error and standard deviation of the mean.

Mean prealbumin levels ± SD by visit will be presented (mean plot).

In addition, box and whisker plots overall and by gene mutation type will be presented for prealbumin level (mg/dL) by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

A summary of subjects who reached certain thresholds (10%, 25%, and 50%) of percent increase in prealbumin overall and by gene mutation type for each visit will be provided. In addition, descriptive summary of prealbumin levels, change from baseline in prealbumin levels and percent change from baseline in prealbumin levels will be presented overall and by gene mutation type for each visit,

A subject data listing will include WB percent stabilization by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.). Another subject data listing will include FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6,. etc.). Finally, a subject data listing will include prealbumin concentration and percent change from baseline by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

11.3 Pharmacodynamics and Pharmacokinetics Relationship

Correlation plots will be provided overall and by mutant type as follows. Spearman correlation will be provided overall and by gene mutation type at each visits up to Month 30.

1. Acoramidis concentration vs. FPE percent target engagement
2. Acoramidis concentration vs. WB percent stabilization
3. Acoramidis concentration vs. Prealbumin percent change from baseline

12.0 Echocardiographic Parameters (Exploratory)

Descriptive summaries of observed values and changes from baseline for echocardiographic parameters of LV mass, stroke volume index and global longitudinal strain will be provided. A listing of echocardiogram parameters (LV mass, stroke volume index and global longitudinal strain) will also be provided.

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13.0 References

ICH E3 Structure and content of clinical study reports..

ICH E9 Statistical principles for clinical trials. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials.

ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. https://www.ema.europa.eu/en/ich-e14-clinical-evaluation-qtqtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic.

14.0 Summary of Changes from the protocol

The following changes from Protocol Amendment 3 are reflected in the SAP version 2.0:

- Baseline values are defined in the protocol Amendment 3 as the last value obtained on or before the date of the first dose from Study AG10-201. For SAP version 2.0, baseline is defined as the last value obtained on or before the first dose of Study AG10-202.
- There are no time-to-event analyses planned for clinical events as stated in protocol Amendment 3.
- Since this is a single arm study, data will not be reported by treatment group as stated in protocol Amendment 3.
- Safety parameters to be assessed include: TEAEs, treatment-emergent SAEs, AEs leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern. More details were added for clarity.
- Summary of clinical events will not be performed as data wasn't collected to support such an analysis.

15.0 Validation

The goal is to ensure that each Table; Figure, and Listing (TFL) delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

Data Handling and Transfer

Data will be entered and exported as SAS (version 9.4) datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard (CDISC) Data Tabulation Model ([SDTM], version 1.4, Implementation Guide version version 3.2) conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model ([ADaM], version 2.1, Implementation Guide version 1.1) standards.

Medical history and AEs will be coded using the MedDRA, version 24.1 at the time of the analysis to assign a SOC and PT to each event. Prior and concomitant medications will be coded using the WHODrug 2022SEP01 Global B3 at the time of the analysis.

Additional details can be found in the PRA Data Management Plan for Study AG10-202.

16.0 Summary of Changes

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Date	Description
03-Jul-2019	Initial version

11-May-2021	Version 2.0
	• Document was reformatted for clarity.
	• Document was aligned with protocol amendment 3 and CRF version 5.0.
	• Updated the List of Abbreviations.
	• Updated AG10 to acoramidis.
	• Consistent use of IMP instead of study drug or study treatment.
	• Consistent use of subject to refer to individuals participating in the study instead of patient.
	• Added 25th and 75th percentile statistics to the summary statistics, wherever applicable.
	• Removed original section 7 (Study Endpoints, Variables and Covariate). This is now covered under each corresponding analysis method section.
	• Removed original section 12.7.3 (Clinical Events) as data was not collected and analysis is not applicable.
	• **Section 2.0:** Updated incorporating details of study purpose and scope.
	• **Section 2.2:** Study design was updated in alignment with study protocol amendment 3.
	• **Section 2.3:** Added a separate section for study population.
	• **Section 2.4:** Added a section for study dosage and administration with more details.
	• **Section 2.6:** Removed the randomization section and added this blinding section clarifying that AG10-202 is an open label study.
	• **Section 2.7**: Updated interim analysis section. There will be a data snapshot to generate an interim clinical study report in support planned regulatory activities.
	• **Section 3.3**: Section updated to specify the derivations of analysis windows for the reporting of the study results (previously nominal visits were to be used).
	• **Section 3.4**:
	  ○ Added this section to compile all imputation rules handling of dropouts and missing data.
	  ○ Added clarify to missing data imputation rule. An AE will be considered treatment-emergent if the entered data (e.g. the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria.
	• **Section 4.0:** Added completed treatment to subject disposition analysis.
	• **Section 5.0**: Added details explaining that PRA and SimpleTrials CTMS hold the protocol deviations for the study.
	• **Section 6.0**: Added (<78, ≥78 [years]) to age group.
	• **Section 7.0**:
	  ○ Added a separate section for medical history with more details for clarity.

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Date	Description
	○ Indicated that Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database. ○ Dictionary version was updated to the latest version used. • **Section 8.0**: ○ Added summaries and listings of prior and concomitant diuretics and cardiovascular medications, which may be presented. ○ Moved definition of prior and concomitant medications from Section 8.0 definition (initial version) to Section 8.0 Prior and Concomitant Medications/Procedures. • **Section 9.0**: ○ Summary of doses missed was removed. ○ Duration of exposure derivation was clarified. ○ Number of tablets administrated summary replaced by proportion of tablets taken out of dispensed. • **Section 10.0:** List of safety parameters was updated and moved from previous Section 7.0.. • **Section 10.1**: Stated that only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables. • **Section 10.1.1**: ○ Added clarity to treatment emergent adverse event definitions. ○ Added treatment-related Serious TEAEs and non-serious TEAEs to the overall TEAE summary. • **Section 10.1.2:** Added a separate section to outline analysis for treatment-related adverse events. • **Section 10.1.3:** ○ Added overall SAE summaries for SAE, SAEs leading to IMP discontinuation and SAEs leading to discontinuation. ○ Removed the breakdown into all different serious criteria. ○ Added summaries by SOC and PT and additional listings for SAEs. • **Section 10.1.4:** Added a separate section to outline analysis for adverse events leading to discontinuation of study drug and/or the study. • **Section 10.1.5:** Added a separate section to outline analysis for adverse events with an outcome of death. • **Section 10.2**: ○ Added shift tables, where available. ○ Added table and listing for liver test elevations. ○ Added mean and individual spaghetti plots. • **Section 10.3**: Added mean and individual spaghetti plots.

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Date	Description

	• **Section 10.5**:
	  ○ Added a separate section to outline all ECG related analysis.
	  ○ Additional summaries tables added for potentially abnormal QT, QTcB, QTcF, PR and QRS intervals parameters.
	  ○ Added mean and individual spaghetti plots.
	• **Section 10.6**: New section for COVID-19 related analysis.
	• **Section 11.1:**
	  ○ Added details for the derivation of PK concentration to molar concentration.
	  ○ Removed median concentrations with confidence intervals figure.
	  ○ Removed the sentences of subject's inclusion or exclusion for PK analysis as data from all subjects in the PK analysis set will be included.
	• **Section 11.2**:
	  ○ Clarified that prealbumin levels are a PD parameter.
	  ○ Clarified that listings for the WB and FPE will be provided.
	  ○ Clarified that listing for prealbumin and percent change in prealbumin levels will be provided.
	  ○ Added summary of subjects with percent increase in prealbumin levels above certain thresholds.
	  ○ Clarified figures presentation/contents.
	  ○ Removed figures presenting RFU and by percent target engagement by AG10 concentration.
	  ○ Removed figures presenting mean and 95% confidence intervals for FPE and WB percent stabilization.
	  ○ Removed figure presenting mean and 95% confidence intervals for prealbumin.
	  ○ Removed summary table of the overall percent stabilization for both WB and FPE.
	• **Section 11.3**:
	  ○ Added a separate section to outline the PD/PK correlation plots.
	  ○ Specify that percentage change from baseline prealbumin levels is used in the correlation plots instead of prealbumin levels.
	  ○ Removed correlation plot between prealbumin and RFU.
	• **Section 12.0**: Added descriptive summaries of observed values and changes from baseline for echocardiographic parameters.
	• **Section 13.0**: Included ICH E3, E9 and E14 as references.
	• **Section 14.0**:
	  ○ Updated current text to refer to protocol amendment 3.
	  ○ Added clarification of the safety parameters assessed.

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Date	Description
	○ Clarify that the summary of clinical events will not be performed. • **Section 15.0**: ○ Moved original section 11.0 Data Review under this Validation section. ○ Updated versions for SDTM and ADaM. ○ Updated versions for MedDRA and WHO dictionaries. ○ Removed Data Screening paragraph as this is governed by Data Management Plan and is not within the scope of SAP. • **Section 16.0:** Added summary of changes.
18-Oct-2021	• **Section 1.0**: added abbreviation for SI • **Section 3.3:** ○ Corrected visit windows (added Month 9 and Month 12). • **Section 5.0**: ○ Clarified that protocol deviations reported in the PRA CTMS were imported into the SimpleTrials CTMS. • **Section 6.0**: ○ Added summary for age group of <65, ≥65 years. • **Section 7.0**: ○ Clarified that data imported from AG10-201 was coded using MedDRA version 21.0 and the medical history and AE reported after close of Study AG10-201 were coded by MedDRA version 23.1. • **Section 8.0**: ○ Clarified that data imported from AG10-201 was coded using WHO Drug dictionary version 2018MAR01 and the medications reported after close of Study AG10-201 were coded by WHO Drug dictionary version 2020SEP01.

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Date	Description
	○ Clarified that the summary for prior/concomitant medications will include each of the ATC levels (1 to 4) and additional tables will be created for the summary with ATC levels 1, level 2 and PN. ○ Added details on how Cardiovascular medications and Diuretics medications are selected. • **Section 9.0**: ○ Clarified that days where no medication was taken is derived from the 'Exposure-Missed Doses' eCRF page. Clarified how missed days were derived as the IMP is taken twice daily. ○ Updated proportion of tablets taken out of dispensed by proportion of tablets taken out of number of tablets expected to be taken to have a measure of compliance ○ Provided details for kits not returned. ○ Provided details on the different strengths of tablets dispensed during the study. ○ Removed visit and number of bottled of IMP dispensed from the data listing as those field are not included in the listing. • **Section 10.1.1**: ○ Added summary of TEAE by SOC only and by PT only ○ Added summary for the most frequent TEAE by PT. • **Section 10.1.2**: ○ Added summary of treatment-related TEAE by SOC only and by PT only ○ Added summary for the most frequent treatment-related TEAE by PT. • **Section 10.1.3**: ○ Added summary of treatment-related serious TEAE in the overall table. ○ Added summary of serious TEAE by SOC only and by PT only ○ Added summary for the most frequent serious TEAE by PT. • **Section 10.1.6**: ○ New section to describe summary for exposure-related incidence rate. • **Section 10.2**: ○ Clarified that tables will present SI results. ○ Added rules for imputation for the results beginning with '>' or '<'. ○ Provided details for the percentages derivation for the shift tables and added definition for non-available category. ○ Added details for shift tables from baseline to worst post-baseline. ○ Added tables for the normal ranges in reported and SI units. • **Section 10.6**: ○ Removed COVID-19 vaccine AEs from the list of data listings.

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Date	Description
	○ Added details on selection for COVID-19 AEs. • **Section 11.1**: ○ Added molecular weight for acoramidis acylglucuronide. ○ Box and whisker plots will be presented overall and by gene mutation type • **Section 11.2**: ○ Specified that summary tables are overall and by gene mutation type. ○ Added details for the summary of the FPE QC samples. ○ Added tables for the summary of the WB QC samples. ○ Added new table for descriptive summary for FPE percent target engagement. ○ Added mean plots (mean ± SD) for FPE percent target engagement. ○ Added new table for descriptive summary for WB percent stabilization (actual and change from baseline). ○ Added mean plots (mean ± SD) for WB percent stabilization. ○ Box and whisker plots will present prealbumin levels and not percent change from baseline in prealbumin levels ○ Added new table for descriptive summary for prealbumin levels (actual, change from baseline and percent change from baseline). ○ Added mean plot (mean ± SD) for prealbumin levels. • **Section 11.3**: ○ Added that figures will be provided overall and by mutant type ○ Added Spearman correlation for the overall and by gene mutation type at each visit up to Month 30. • **Section 12.0**: Added list of parameters included in tables and listings. • **Section 16.0:** (version 11-May-2021): ○ Sections 7.0, 8.0, 9.0 and 10.0 added minor clarifications.
15-Mar-2023	• Updated Table 1: Schedule of Assessments to reflect protocol amendment 4 • Adjusted Table 2: Analysis Visit Window • Added imputation rule for incomplete date of last dose of IMP • Updated approval contact information

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Statistical Analysis Plan

Protocol Title:	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
Protocol Version No./Date:	Amendment 4 / 09Sep2022
CRF Version No./Date:	11.0 / 24JUN2025
SAP Version No./Date:	5.0 / 05SEP2025

Approvals

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

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Signature /Date:	Signed by: Chris Chen Signer Name: Chris Chen Signing Reason: I approve this document Signing Time: 9/8/2025 | 4:20 PM PDT E64A4F6317D1432F885CD749F173C9F6 9/8/2025 | 4:20 PM PDT
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1.0 List of Abbreviatons

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
BLQ	Below limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CTMS	Clinical Trials Management System
CV%	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ET	Early Termination
FPE	Fluorescent Probe Exclusion
HCl	Hydrochloride
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
n	Number of Subjects
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PD	Pharmacodynamic
PN	Preferred Name
PT	Preferred Term
QTcB	QT corrected interval with Bazett's formula
QTcF	QT corrected interval with Fridericia's formula
RFU	Relative Fluorescence Unit
SAE	Serious Adverse Event

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SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SEM	Standard Error of The Mean
SI	International System of Units
SOC	System Organ Class
STDM	Standard Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
TTR	Transthyretin
ULN	Upper Limit of Normal
WB	Western blot
WHODrug	World Health Organization Drug Dictionary

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2.0 Introduction

The purpose of the statistical analysis plan (SAP) is to provide a detailed description of the principal features of the analysis described in the protocol and to include detailed procedures for executing the statistical analysis of the primary, secondary, and exploratory endpoints and other data collected under Eidos Therapeutics, Inc. Study AG10-202. Acoramidis hydrochloride (HCl), and Investigational Medicinal Product (IMP) are used interchangeably in this document. In Study AG10-202 Study Protocol Amendment 3, AG10 is used to refer to acoramidis and AG10 HCl is used to refer to acoramidis HCl.

This document describes study objectives, analysis sets, outcome measures, the timing of statistical analyses, data analysis methods, and data summaries for this protocol. Analysis approaches detailed within this document supersede the analyses and summaries presented in the protocol.

This plan is a living document that will be created during the trial start-up and will be finalized prior to database lock. This SAP will require sign off from the PRA Biometrics Project Manager, the Biostatistician and the Sponsor.

2.1 Objectives of Study

The primary objective of this study is to evaluate the long-term safety and tolerability of IMP administered to adult subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) who completed the AG10-201 study.

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of IMP administered orally twice daily in subjects with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of IMP as assessed by established assays of transthyretin (TTR) stabilization, including Fluorescent Probe Exclusion (FPE) assay and Western blot (WB), and to describe the PK-PD relationship of IMP in adult subjects with symptomatic ATTR-CM.

The exploratory objective of this study is:

- to describe the long-term effects of IMP on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.

2.2 Study Design

This study is a prospective, multicenter, Phase 2, long-term, open-label study in up to 55 male and/or female subjects with symptomatic ATTR-CM, ≥18 years of age, who have completed participation in Study AG10-201. This prospective multicenter, open-label study will evaluate the long-term safety, tolerability, PK and PD of IMP administered to eligible subjects with stable heart failure therapy. An open-label design is considered to be the most appropriate study design for meeting this objective**.**

The study will continue at the Sponsor's discretion, or until registration of the product for the treatment of symptomatic ATTR-CM.

Eligible subjects will begin dosing acoramidis HCl 800 mg administered twice daily. Information on Adverse Events (AEs) and concomitant medications will be collected throughout the study. The safety of the study will be monitored by an independent acoramidis HCl program-wide Data Monitoring Committee (DMC).

The schedule of assessments is provided in Table 1.

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Table 1: Schedule of Assessments

	Day 1	Day 14 (±3 days)	Day 45 (±7 days)	To Month 54: Visits Every 3 Months (±7 days) to Month 54[a, b, c]	After Month 54: Telephone Contact Every 3 Months (±7 days)[d]	After Month 54: Visits Every 6 Months (±7 days)[a, c]	ET Visit[e]	Follow-up Visit 30 days after date of last dose (±7 days)[f]	Unsched-uled Visit[g]
Written Informed Consent	X								
Inclusion/ Exclusion Criteria Review	X								
Medical History	X								
Physical Exam[h]	X	X	X	X		X	X	X	X
Vital Signs	X	X	X	X		X	X	X	X
Resting transthoracic echocardiogram[a]	X[a]			X[a]		X[a]	X[a]		X[a]
12-lead resting ECG[a]	X	X	X	X[a]		X[a]	X	X	X
PD assays[c]	X	X	X	X[c]		X[c]			
PK sample collection[c]	X	X	X	X[c]		X[c]			
Prealbumin collection[c]	X	X	X	X[c]		X[c]			
Study drug dosing during visit	X	X	X	X		X			
Clinical laboratory assessments	X	X	X	X		X	X	X	X
Pregnancy test[i]	X	X	X	X		X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Dispense IMP	X		X	X		X			
Collect Unused IMP			X	X		X	X		X
Adverse events	X	X	X	X	X	X	X	X	X

a. Resting 12-lead electrocardiogram and echocardiogram at Day 1, every 3 months until Month 12 then annually. Perform echocardiogram at ET Visit unless obtained in prior 6 months and at Unscheduled Visit only if clinically indicated.
b. Visits every 3 months from Day 1 visit until Month 54.
c. Samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 (predose only) and every 3 months after Month 15 up to Month 54. After the Month 54 clinic visit, samples will be collected every 6 months.
d. After Month 54, telephone contact will occur every 3 months after on-site clinic visits and include AE collection, concomitant medication use assessment, and IMP compliance assessment.
e. If a patient discontinues study participation, the patient will be asked to return to the study center for the ET Visit as soon as possible and to return any unused IMP.
f. When a patient discontinues study participation, the patient will be asked to return to the study center for the Follow-up Visit. The Follow-up Visit should be performed 30 days after date of last dose.
g. For assessment or follow up of an adverse event, only procedures that are indicated as needed by the investigator should be performed (eg, physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test).

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h. Complete Physical Exam including body weight at all visits.
i. Females of Child-Bearing Potential only. Urine pregnancy test at all visits.

2.3 Study Population

The study will enroll up to 55 males and/or females ≥18 years of age with chronic, stable, symptomatic ATTR-CM will be enrolled and begin dosing with acoramidis HCl 800 mg twice daily. See sections 8.3.1 and 8.3.2 of the study protocol for Inclusion and Exclusion criteria.

2.4 Study Dosage and Administration

IMP doses chosen for this study are based on results from nonclinical PK studies, data from the first-in-human single ascending dose and multiple ascending dose study, and data from a Phase 2 study (AG10-201). Further detail on dose selection can be found in the Investigator's Brochure (IB).

Dosing should occur twice daily, once in the morning and once in the evening.

Subjects will be dosed with acoramidis HCl 800 mg administered twice daily. Downward adjustment of dose or interruption of IMP is discouraged but permitted if necessary, in the event of intolerance to IMP. Subsequent upward adjustment of IMP back to the target dose should be attempted whenever possible. If it is believed that an AE may be drug-related, and depending on its severity, the IMP may be reduced from 800 mg twice daily to 400 mg twice daily.

2.5 Sample Size Determination

The planned number of subjects is determined by the number of eligible and interested subjects that have completed the Study AG10-201 and therefore is not expected to be greater than 55 subjects.

2.6 Blinding

This is an open-label study.

2.7 Interim Analysis

There will be a data snapshot to generate an interim clinical study report to support planned regulatory activities.

3.0 General Analysis Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS) version 9.4.

Unless otherwise specified, descriptive data summaries will be tabulated for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place. Counts of zero will not display a percentage.

All continuous variables will be summarized using mean, standard deviation (SD), median, minimum, maximum, 25th percentile, 75th percentile and number of subjects with observations. Unless otherwise specified, the mean, median, 25th percentile and 75th percentile will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

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3.1 Analysis Sets

Safety Analysis Set

The safety analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period. The safety analysis set will be used to summarize all safety data.

PK Analysis Set

The PK analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one quantifiable post-baseline concentration. The PK analysis set will be used to summarize all PK data in Study AG10-202.

PD Analysis Set

The PD analysis set will consist of all subjects receiving at least one dose of IMP during the Study AG10-202 treatment period and having at least one post-baseline PD assessment. The PD analysis set will be used to summarize all PD data in Study AG10-202.

3.2 Study Day Derivations

Study Day 1

Study Day 1 is defined as the first day of IMP administration in Study AG10-202.

Study Day

Study day is defined as the number of days from Study Day 1. Before Study Day 1, Study Day = (Date of Interest – Date of Study Day 1). Therefore, the day prior to Study Day 1 is -1.

On or After Study Day 1, Study Day = (Date of Interest – Date of Study Day 1) + 1.

A month is defined as 30.4375 days and a year is defined as 365.25 days.

First IMP Dose

For all subjects, the first IMP dose date is defined as the date of first dose in Study AG10-202. Date of first dose is recorded on the Exposure-First Dose Case Report Form (CRF).

Baseline and Change from Baseline

Baseline values are defined as the last pre-dose value obtained on or before the date of the first IMP dose in Study AG10-202.

Change from Baseline = (post-Baseline value – Baseline value).

Completion of study

Subject completion of the study is defined as an answer of “Yes” to the question “Did the subject complete the study (including Follow-Up)?” on the form of End of Study in the CRF.

Completion of treatment

Subject completion of treatment is defined as an answer of “Completed” to the question “End of Treatment Status” on the form of End of Treatment in the CRF.

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3.3 Visit Window for Analysis

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows. The actual visit date is allowed to fall within a specified interval of the target day.

In general, if more than one actual visit (including unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

Analysis window are as follows:

Table 2: Analysis Visit Windows

Visit	Target Study Day	Analysis Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	≤1	1
Day 14	15	2	31
Day 45	46	32	69
Month 3	92	70	138
Month 6	184	139	230
Month 9	275	231	321
Month 12	366	322	412
Month 15	458	413	504
Month 18	549	505	595
Month 21	640	596	686
Month 24	732	687	778
Month 27	823	779	869
Month 30	914	870	960
Month 33	1005	961	1051
Month 36	1097	1052	1143
Month 39	1188	1144	1234
Month 42	1279	1235	1325
Month 45	1371	1326	1417
Month 48	1462	1418	1508
Month 51	1553	1509	1599
Month 54	1645	1600	1736
Month 60	1827	1737	1919
Month 66	2010	1920	2102
Month 72	2193	2103	2285
Month 78	2376	2286	2468
Month 84	2559	2469	≥2469

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3.4 Handling of Dropouts and Missing Data

Subjects who discontinue from the study will not be replaced.

An AE will be considered treatment-emergent if the entered data (e.g., the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria.

Imputation of AE (for determination of treatment-emergent adverse event [TEAE] only) and **concomitant medication** start and stop dates:

- **Start Date:** If only ‘day’ is missing, and the month and year are not the same as the month and year of first dose, then impute day with the first of the month. Otherwise, if the month and year are the same as the first dose date, use the first dose date. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month and day with month and day of the first dose date (assuming same ‘year’). If ‘day’ and ‘month’ are missing and ‘year’ is not missing and is not the same year as first dose date, then impute with 1st of January. If the start date is completely missing, it will be set to the first dose date.
- **Stop Date:** If only ‘day’ is missing, impute day with last day of the month. If ‘day’ and ‘month’ are missing, and ‘year’ is not missing, then impute month with the 31st of December’ (or date of study discontinuation/completion if earlier than 31st of December and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. Stop date will not be imputed for ongoing AEs.

Imputation of incomplete date of last dose of IMP: if a subject discontinued the treatment but the date of last dose is incomplete, the date of completion/discontinuation from the End of Study CRF page will be used.

4.0 Subject Disposition

Subject disposition will be presented including numbers and percentages of subjects: treated in the study; who completed the study; who discontinued from the study; who completed treatment, and who discontinued treatment prematurely. Reasons for discontinuation of IMP and of the study will be summarized.

5.0 Protocol Deviations

Important protocol deviations data have been entered into the PRA Clinical Trials Management System (CTMS) and the SimpleTrials system. The Sponsor will conduct on-going reviews of the deviation data from CTMS and SimpleTrials system and the resulting set of protocol deviations throughout the study, adjusting the deviation criteria as seems appropriate. Data from the PRA CTMS was imported into the SimpleTrials CTMS data for reporting. In the SimpleTrials CTMS, Important protocol deviations are entered as ‘Major’; other protocol deviations (not important) are entered as ‘Minor’.

A listing of the important protocol deviations will be provided. No Per Protocol analysis will be performed.

6.0 Demographics and Baseline Characteristics

Demographic data are imported from the Study AG10-201 database. Demographic and Baseline Characteristics (sex, ethnicity, race, gene mutation status, subject’s variant type (for subjects with a gene mutation status of mutant), age [years], age group (<65, ≥65 to <75 or ≥75 [years], <65, ≥65 [years] and <78, ≥78 [years]) and weight [kg], will be summarized using the descriptive statistics for subjects in the Safety Analysis Set. Qualitative (categorical) variables (age group, sex, ethnicity, race) will be summarized using frequencies while quantitative (continuous) variables (age and weight) will be summarized using mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum. Demographic and baseline data will also be listed for subjects in the Safety Analysis Set.

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7.0 Medical History

Medical history for this study will include imported medical history and AEs initially reported in the AG10-201 study, as well as medical history that occurred after the close of Study AG10-201 and before enrollment in Study AG10-202.

Medical history and AEs reported in Study AG10-201 were imported into the Study AG10-202 database as medical history and was coded by Medical Dictionary for Regulatory Activities ([MedDRA] version 21.0). Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database and coded by MedDRA version 24.1 as applicable at time of analysis and will be presented in a summary table and with a subject listing.

8.0 Prior and Concomitant Medications/Procedures

Prior and concomitant medications reported in the Study AG10-201 study are included (imported) in the Study AG10-202 database and considered prior medications in the AG10-202 study. Sites were instructed to enter any new medications (started after the end of the Study AG10-201) in the concomitant medication form of the CRF. For reporting of Study AG10-202, prior medications will be any medication with a start date before the date of the first IMP dose as defined above.

Concomitant medications are defined as any medications ongoing at the start of treatment or with a start date on or after the first dose. Consequently, medications ongoing at the start of treatment will be reported as both prior and concomitant medications.

Prior and concomitant medications initially reported in AG10-202 will be coded according to the AG10-202 Coding Conventions using the World Health Organization Drug Dictionary (WHODrug) i.e. using the WHODrug dictionary version 2022SEP01 Prior and concomitant medications reported in the Study AG10-201 and imported in the Study AG10-202 database are coded with WHODrug dictionary version 2018MAR01. The prior and concomitant medication analyses will be performed using the Safety Analysis Set.

Summaries and listings of prior and concomitant medications by Preferred Name (PN) and each Anatomic Therapeutic Classification (ATC) levels (1 to 4) will be provided and by PN and ATC levels 1 to 2. In the summaries, subjects taking more than one medication in the same PN will be counted once for the number of subjects taking the medication of that PN.

Summaries and listings of prior and concomitant diuretics and cardiovascular medications will be presented by ATC levels 1 to 4 and PN as well as for ATC levels 1 to 2 and PN. Diuretics medications are medications classified under the ATC Level 2 of Diuretics and Cardiovascular medications are medications classified under the ATC Level 1 of Cardiovascular System.

9.0 Extent of Exposure to Study Drug

The extent of exposure will be presented as duration (months). The number of months of exposure will be defined as: (last dose of IMP date – first dose of IMP date +1) / 30.4375, regardless of intermittent discontinuations or dose reductions. Non-integer values will be rounded to one decimal place.

The number of months of actual exposure will be defined as: (last dose of IMP date – first dose of IMP date – number of days where no medication was taken +1) / 30.4375. The number of days when no medication was taken will be derived from the ‘Exposure-Missed Doses’ eCRF page. The number of days with no medications is derived as the number of missed doses divided by 2. The IMP is taken twice per day and one missed dose (AM or PM) corresponds to half a day.

As context for the extent of exposure, the proportion of subjects receiving at least one dose and the proportion of tablets taken out of the expected number of tablets to be taken. The strength of the tablets

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dispensed during the study is 200 mg (kits starting by '3') and 400 mg (kits starting by '4' or '5'). The subjects are expected to take a total of 4 tablets daily (strength 400 mg) or a total of 8 tablets daily (strength 200mg).

If one or multiple kits have not been returned, the following assumption will be followed:

- If a subject discontinued from the study and their last dispensed kits were not returned, it will be assumed that the subject took their IMP as planned per the study (i.e. 800 mg twice daily) up to their last dose date.
- Otherwise, if a kit was not returned at the following visit, it is assumed that all IMP was taken from that kit.
- Lastly, for the interim snapshot, if the kits were not returned and no visit was performed after the kits were dispensed (ongoing subjects), it will be assumed that the subject took their IMP as planned per the study (i.e. 800 mg twice daily) up to the data cut-off date.

The subject number, date(s) when IMP was dispensed, number of tablets dispensed in each bottle, date of return of each bottle of IMP and number of tablets in each bottle returned will be presented for each subject in listings.

10.0 Safety Evaluations

The Safety Analysis Set will be used for all safety analyses.

Safety parameters to be assessed include: TEAEs, treatment-emergent serious adverse events (SAEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal electrocardiogram (ECG) parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern.

10.1 Adverse Events

Only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables. Serious TEAEs and Treatment-Emergent Serious Adverse Events are used interchangeably in this document.

10.1.1 All Treatment-Emergent Adverse Events

For the purposes of data collection for this study, any untoward event that is reported from the time that the subject signs the Informed Consent Form (ICF) until 30 days after the last dose of IMP is to be considered an AE. An AE will be considered a TEAE if it was not present before the first dose of IMP for the Study AG10-202 study or if it was present before the first dose of IMP but increased in severity during the treatment period. Only TEAEs will be included in the summary tables.

An AE that occurs more than 30 days after the last dose of IMP will not be counted as a TEAE. For interim reporting, the last dose of IMP for the determination of treatment emergence will be assigned as the date of the data extract for ongoing subjects. For subjects that have discontinued IMP, the date of last dose will be as recorded on the End of Treatment CRF. For subjects that died during the reporting period, if a date of last dose is not reported, the date of death will be used for the date of last dose.

A summary of the following will be presented: all TEAEs; treatment-related TEAEs; TEAEs with outcome of death; Serious TEAEs; treatment-related Serious TEAEs; non-serious TEAEs; TEAEs leading to discontinuation of IMP, and TEAEs leading to discontinuation of study.

Tabular summaries with numbers and percentages of subjects that have the following TEAEs will be provided by System Organ Class (SOC) and Preferred Term (PT).

- All TEAEs;
- TEAEs by maximum severity;

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- Treatment-related TEAEs;
- Non-serious TEAEs;
- TEAEs leading to discontinuation of IMP;
- TEAEs leading to discontinuation of study.

The summary of TEAEs will also be repeated by SOC only and by PT only. The most frequent TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

At each level of summarization (e.g., all TEAEs, SOC, and PT), subjects will be counted only once. For tables categorized by severity, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event for that SOC or PT. Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing values for severity will be considered as 'Severe' and missing value for relationship to IMP will be considered as 'Related' in the summary.

TEAEs leading to discontinuation of IMP are those with an action taken with IMP on the AE CRF page of 'Drug Withdrawn'.

TEAEs leading to discontinuation of the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

By-subject listings will be provided for the following: All TEAEs, non-TEAEs, TEAEs leading to discontinuation of study drug and TEAEs leading to discontinuation of study.

The duration of AEs in days will be derived as the AE end date (including imputation date for incomplete AE end date) – AE onset date (imputed date for incomplete AE onset date) +1.

10.1.2 Treatment-Related Adverse Events

Treatment-related TEAEs include AEs from AE CRF page where relationship to IMP is checked as 'Related'. Missing value for relationship to treatment will be considered as 'Related' in the summary.

Subject incidence of the treatment-related TEAEs will be tabulated by SOC and PT and associated listing will be provided. The summary of treatment-related TEAEs will also be repeated by SOC only and by PT only. The most frequent treatment-related TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

Subject incidence of the treatment-related serious TEAEs will be tabulated by SOC and PT and associated listing will be provided.

10.1.3 Treatment-Emergent Serious Adverse Events

The number and percentage of subjects and the number of SAEs reported for the following categories of SAEs will be presented.

- SAEs;
- SAEs with an outcome of death;
- Treatment-related SAEs;
- SAEs leading to discontinuation of IMP;
- SAEs leading to discontinuation of study.

In addition, subject incidence of the treatment-emergent SAEs will be tabulated by SOC and PT for the above categories. Subjects will be counted only once within each SOC or PT.

The summary of serious TEAEs will also be repeated by SOC only and by PT only. The most frequent

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serious TEAEs (reported by at least 5% of the subjects) will be summarized by PT.

By-subject listings will be also provided for the each of the above categories.

10.1.4 Adverse Events Leading to Discontinuation of Study Drug and/or the Study

AEs leading to discontinuation of IMP are those with an action taken with regard to IMP of 'Drug Withdrawn'. AEs leading to discontinuation from the study are those on the AE CRF page with "YES" for the question "Did the adverse event cause the subject to be discontinued from the study?"

Subject incidence of the TEAEs leading to discontinuation of IMP will be tabulated by SOC and PT and associated listing will be provided.

Subject incidence of the TEAEs leading to discontinuation of study will be tabulated by SOC and PT and associated listing will be provided.

10.1.5 Adverse Events with an Outcome of Death

An AE with an outcome of fatal reported will be considered as AE with an outcome of death.

Subject incidence of the TEAEs with an outcome of death will be tabulated by SOC and PT and an associated listing will be provided.

10.1.6 Exposure-Adjusted Incidence Rate Adverse Events

Exposure-adjusted incidence rate will be derived for TEAEs, serious TEAEs and treatment-related TEAEs, overall and at each SOC and PT levels.

At each level of the summary, the subject-years of exposure is the sum of the duration from the first dose of IMP to the start date of the first event of interest (for the subjects with an event of interest) plus the duration from the first dose of IMP to the last dose of IMP + 30 days or data cut-off date (for subjects with no event of interest) divided by 365.25. The incidence rate is the number of subjects with the event of interest divided by subject-years multiplied by 100.

10.2 Clinical Laboratory Tests

Descriptive summaries of observed values and changes from baseline will be provided for numerical laboratory assessments by visit based on International System of Units (SI). If a result begins with a "<", then the result will be imputed by the numeric part divided by the square root of 2. If a result begins with a ">", then the result will be imputed by the numeric. The categorical laboratory results will be summarized by frequency and percentage and by visit.

Laboratory values will also be tabulated in shift tables from baseline where available. For the shift tables, laboratory results will be categorized by the central laboratory (when normal ranges have been defined) as high (higher than the upper limit of the normal range), normal (within the normal range) or low (lower than the lower limit of the normal range). Unavailable results (samples not collected, visit not done, discontinuation) will also be summarized and included in the total count. The percentages will be based on the number of subjects at baseline within each category, (for example, for a given parameter, regardless of the visit, the percentage of subjects with low post-baseline results and low baseline results will be based on the number of subjects with low baseline results). Shift from baseline to worst post-baseline will also be summarized, if a subjects has both a low and high post-baseline results, the subjects will be summarized under High category.

Where applicable, figures of mean laboratory values and of individual subject's laboratory parameters (spaghetti plots) by visit will be presented.

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The number and proportion of subjects with liver test elevations will be presented. Liver test elevations are assessed by using post-Baseline results for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin based on the definitions presented in Table 3.

Table 3: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN - < 3 x ULN ALT or AST ≥ 3 x to < 5 x ULN ALT or AST ≥ 5 x to < 10 x ULN ALT or AST ≥ 10 x to < 20 x ULN ALT or AST ≥ 20 x ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

The number and percentage of subjects with concurrent (defined as measurements on the same day) ALT or AST ≥ 3 times upper limit of normal (ULN) and total bilirubin > 2 times ULN will also be presented.

In addition, tables for the numeric laboratory parameters presenting the normal ranges in both reported units and SI units will be provided.

Laboratory parameters with abnormal results as identified by the central lab will be listed. Subject listings will also be provided for all laboratory tests.

10.3 Vital Signs

Descriptive summaries of observed values and changes from baseline will be provided for vital signs by visit.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for vital signs parameters.

10.4 Physical Examination

Physical examination will be provided in listings only**.**

10.5 Electrocardiogram

Descriptive summaries of observed values and changes from baseline will be provided for ECGs (PR interval, QRS duration, QT interval, QT corrected interval with Bazett's formula [QTcB] and with Fridericia's formula [QTcF]) by visit.

Number and percentage of subjects for each the following categories (based on the International Council for Harmonisation [ICH] E14 guidance) will be tabulated by visit:

- QT interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcB interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- QTcF interval greater than each of the following thresholds: 450 msec, 480 msec and 500 msec;
- Increase in change from baseline in QT interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- Increase in change from baseline in QTcB interval greater than 10 msec, 30 msec, 60 msec and

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90 msec;

- Increase in change from baseline in QTcF interval greater than 10 msec, 30 msec, 60 msec and 90 msec;
- PR interval greater than 200 msec and change from baseline in PR interval > 25%;
- QRS interval greater than 120 msec and change from baseline in QRS interval > 25%.

Figures of mean and individual (spaghetti plots) parameters will be presented by visit for all ECG parameters.

Subject listings will also be provided for all ECG results.

10.6 COVID-19 Related Analysis

Any deviations from the protocol related to Coronavirus disease 2019 (COVID-19) control measures will be summarized and a listing will be generated.

Listings may be provided for subjects with the following: visits altered by or missed due to COVID-19 control measures; visits missed due to COVID-19 Infection Related Adverse Event; subjects with study discontinuations due to COVID-19 control measures; subjects with IMP discontinuation due to COVID-19 control measures; subjects with missed IMP doses related to COVID-19 control measures, and subjects with COVID-19adverse events. COVID-19 AEs will be identified using Standardised MedDRA Query on COVID-19 with a narrow scope.

11.0 Pharmacokinetics and Pharmacodynamics

11.1 Pharmacokinetics

Pre-dose blood samples for the determination of plasma acoramidis and acoramidis acylglucuronide will be collected on Days 1, 14, and 45, and months 3, 6 and 15 and then every 3 months after Month 15. Only pre-dose samples are planned for collection. Samples that are collected post-dose will not be included in these analyses.

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be performed by a designated bioanalytical laboratory, which will report the concentrations in ng/ml. The acoramidis molar concentration will be derived using the molecular weight of 292.31g/mol as freebase, and the acoramidis acylglucuronide concentration will be derived using the molecular weight of 468.43 g/mol as freebase

Plasma concentrations of acoramidis and acoramidis acylglucuronide will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), SD, coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, 25th percentile, 75th percentile and maximum will be calculated for all nominal concentration time points (visits).

The level of precision for each concentration will be presented as follows:

- Minimum and Maximum in same precision as in bioanalytical data;
- Mean, Median, 25th percentile and 75th percentile in one more level of precision than Minimum and Maximum;
- SD and SEM in one more level of precision than Mean;
- n will be presented as an integer;
- CV% will be presented to the nearest tenth.

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All below limit of quantification (BLQ) values will be presented as “BLQ” in the concentration listings and footnoted accordingly.

Box and whisker plots will be presented for PK group analysis with concentration (ng/mL) on the y-axis and visit on the x-axis. The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker. The box and whisker plots will be presented overall and by gene mutation type.

11.2 Pharmacodynamics

Pre-dose PD blood samples will be collected at Day 1, Day 14, Day 45, Months 3, 6 and 15 and then every 3 months after Month 15. The PD of acoramidis will be assessed by established assays of TTR stabilization, including FPE assay and WB, and to describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM.

Note: Observed values and change from baseline in circulating prealbumin levels will also be measured as a PD marker.

Fluorescent Probe Exclusion (FPE) Stabilization

For each sample, FPE reading is measured in duplicate for every 15 min up to 6 hours. The measurement points are pre-probe, 0 min, 15 min, 30 min….360 min (total 26 points × duplicate = 52 data points). Two QC samples (0 µM, 7.5 µM) are included in duplicate in each plate. For each 0 min – 360 min datapoint, the corresponding pre-probe value should be subtracted to derive “adjusted Relative Fluorescence Unit (RFU)”.

FPE Percent Target Engagement, at Day X will be derived as follows (using the mean of the duplicates):

$$100 \times \frac{(\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe }) - (\text{FPE Day X @60 min-FPE Day X @pre-probe})}{\text{FPE Day 1 @60 min - FPE Day 1 @pre-probe}}$$

FPE data will be tabulated for time: Y=60 mins for all visits. All timepoints will be used for FPE plots.

Western Blot (WB) Stabilization

WB Percent Stabilization at Day X will be derived as follows:

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates, Day\ X)}{mean\ of\ 0\ hour\ acidification\ duplicates,\ \ Day\ X}$$

WB data will be tabulated for all visits.

Number and percentage of subjects with FPE % target engagement ≥ 75%, ≥ 90%, ≥ 99% will be summarized overall and by gene mutation type for each visit. Descriptive summary of FPE % target engagement will be presented overall and by gene mutation type for each visit,

Number and percentage of subjects with WB % stabilization ≥ 75%, ≥ 90%, ≥ 99% will be summarized overall and by gene mutation type for each visit. Descriptive summary of WB % stabilization and its change from baseline will be presented overall and by gene mutation type for each visit,

A table of the FPE variations in QC readings (mean and CV% of the duplicates at 60 min minus the mean of the pre-probes duplicates) will be presented for 0 µM QC samples and 7.5 µM QC samples for each plate. Percent target engagement for each plate will be provided and is defined as follow:

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$$100 \times \frac{(\text{FPE 0 µM @60 min - FPE 0 µM @pre-probe}) - (\text{FPE 7.5 µM @60 min - FPE 7.5 µM @pre-probe})}{\text{FPE 0 µM @60 min - FPE 0 µM @pre-probe}}$$

Where 0 µM denotes the 0 µM QC samples and 7.5 µM denotes the 7.5 µM QC samples.

A table of the WB variations in QC readings (means and CV% of the duplicate for 0 hour acidification and 72 hour acidification) for each control (DMSO and 5 µM acoramidis) will be presented by gel. Percent stabilization for each gel will be summarized for each control type and is defined as follow.

$$100 \times \frac{(mean\ of\ 72\ hour\ acidification\ duplicates)}{mean\ of\ 0\ hour\ acidification\ duplicates}$$

Figures for FPE assay will include the complete time course of Fluorescence generation for each viable serum sample at each blood draw time point by subject.

FPE mean percent target engagement and WB mean percent stabilization will be presented (bar chart) by visit (Day 1, Day 14, Month 3, Month 6,etc.) overall and by gene mutation type. This will be presented with both standard error and standard deviation of the mean. At Day 1 FPE percent target engagement is by definition zero and doesn't need to be presented.

FPE mean percent target engagement ± SD and WB mean percent stabilization ± SD will be presented (mean plot) by visit. At Day 1 FPE percent target engagement is by definition zero and will be display as 0 on the plot.

In addition, box and whisker plots by gene mutation type will be presented for WB percent stabilization and FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6, … etc.). The box and whisker plot will indicate the median, the mean, 25-75% box, and 5-95% whisker.

Mean percent change from baseline in prealbumin levels by visit (Day 14, Day 45, etc.) will be presented (bar chart) overall and by gene mutation type. This will be presented with both standard error and standard deviation of the mean.

Mean prealbumin levels ± SD by visit will be presented (mean plot).

In addition, box and whisker plots overall and by gene mutation type will be presented for prealbumin level (mg/dL) by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

A summary of subjects who reached certain thresholds (10%, 25%, and 50%) of percent increase in prealbumin overall and by gene mutation type for each visit will be provided. In addition, descriptive summary of prealbumin levels, change from baseline in prealbumin levels and percent change from baseline in prealbumin levels will be presented overall and by gene mutation type for each visit,

A subject data listing will include WB percent stabilization by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.). Another subject data listing will include FPE percent target engagement by visit (Day 1, Day 14, Day 45, Month 3, Month 6,. etc.). Finally, a subject data listing will include prealbumin concentration and percent change from baseline by visit (Day 1, Day 14, Day 45, Month 3, Month 6, etc.).

11.3 Pharmacodynamics and Pharmacokinetics Relationship

Correlation plots will be provided overall and by mutant type as follows. Spearman correlation will be provided overall and by gene mutation type at each visits up to Month 30.

1. Acoramidis concentration vs. FPE percent target engagement
2. Acoramidis concentration vs. WB percent stabilization
3. Acoramidis concentration vs. Prealbumin percent change from baseline

12.0 Echocardiographic Parameters (Exploratory)

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Descriptive summaries of observed values and changes from baseline for echocardiographic parameters of LV mass, stroke volume index and global longitudinal strain will be provided. A listing of echocardiogram parameters (LV mass, stroke volume index and global longitudinal strain) will also be provided.

13.0 References

ICH E3 Structure and content of clinical study reports..

ICH E9 Statistical principles for clinical trials. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials.

ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. https://www.ema.europa.eu/en/ich-e14-clinical-evaluation-qtqtc-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic.

14.0 Summary of Changes from the protocol

The following changes from Protocol Amendment 3 are reflected in the SAP version 2.0:

- Baseline values are defined in the protocol Amendment 3 as the last value obtained on or before the date of the first dose from Study AG10-201. For SAP version 2.0, baseline is defined as the last value obtained on or before the first dose of Study AG10-202.
- There are no time-to-event analyses planned for clinical events as stated in protocol Amendment 3.
- Since this is a single arm study, data will not be reported by treatment group as stated in protocol Amendment 3.
- Safety parameters to be assessed include: TEAEs, treatment-emergent SAEs, AEs leading to treatment discontinuation, abnormal physical examination findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern. More details were added for clarity.
- Summary of clinical events will not be performed as data wasn't collected to support such an analysis.

15.0 Validation

The goal is to ensure that each Table; Figure, and Listing (TFL) delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

Data Handling and Transfer

Data will be entered and exported as SAS (version 9.4) datasets. Converted datasets will be created using SAS and following standard Clinical Data Interchange Standards Consortium Standard (CDISC) Data Tabulation Model ([SDTM], version 1.4, Implementation Guide version version 3.2) conventions. Analysis datasets will be created using SAS and following CDISC Analysis Data Model ([ADaM], version 2.1, Implementation Guide version 1.1) standards.

Medical history and AEs will be coded using the MedDRA, version 24.1 at the time of the analysis to assign a SOC and PT to each event. Prior and concomitant medications will be coded using the WHODrug 2022SEP01 Global B3 at the time of the analysis.

Additional details can be found in the PRA Data Management Plan for Study AG10-202.

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16.0 Summary of Changes

Date	Description
03-Jul-2019	Initial version

11-May-2021	Version 2.0
	• Document was reformatted for clarity.
	• Document was aligned with protocol amendment 3 and CRF version 5.0.
	• Updated the List of Abbreviations.
	• Updated AG10 to acoramidis.
	• Consistent use of IMP instead of study drug or study treatment.
	• Consistent use of subject to refer to individuals participating in the study instead of patient.
	• Added 25th and 75th percentile statistics to the summary statistics, wherever applicable.
	• Removed original section 7 (Study Endpoints, Variables and Covariate). This is now covered under each corresponding analysis method section.
	• Removed original section 12.7.3 (Clinical Events) as data was not collected and analysis is not applicable.
	• **Section 2.0:** Updated incorporating details of study purpose and scope.
	• **Section 2.2:** Study design was updated in alignment with study protocol amendment 3.
	• **Section 2.3:** Added a separate section for study population.
	• **Section 2.4:** Added a section for study dosage and administration with more details.
	• **Section 2.6:** Removed the randomization section and added this blinding section clarifying that AG10-202 is an open label study.
	• **Section 2.7**: Updated interim analysis section. There will be a data snapshot to generate an interim clinical study report in support planned regulatory activities.
	• **Section 3.3**: Section updated to specify the derivations of analysis windows for the reporting of the study results (previously nominal visits were to be used).
	• **Section 3.4**:
	  ○ Added this section to compile all imputation rules handling of dropouts and missing data.
	  ○ Added clarify to missing data imputation rule. An AE will be considered treatment-emergent if the entered data (e.g. the answer to “Did this AE start before the first dose for the AG10-202 study was taken?” on the AE CRF page) and/or the imputed data meet the treatment-emergent criteria.
	• **Section 4.0:** Added completed treatment to subject disposition analysis.
	• **Section 5.0**: Added details explaining that PRA and SimpleTrials CTMS hold the protocol deviations for the study.

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	• **Section 6.0**: Added (<78, ≥78 [years]) to age group.
	• **Section 7.0**:
	  ○ Added a separate section for medical history with more details for clarity.
	  ○ Indicated that Medical history and AEs reported after close of Study AG10-201 were entered into the Study AG10-202 database.
	  ○ Dictionary version was updated to the latest version used.
	• **Section 8.0**:
	  ○ Added summaries and listings of prior and concomitant diuretics and cardiovascular medications, which may be presented.
	  ○ Moved definition of prior and concomitant medications from Section 8.0 definition (initial version) to Section 8.0 Prior and Concomitant Medications/Procedures.
	• **Section 9.0**:
	  ○ Summary of doses missed was removed.
	  ○ Duration of exposure derivation was clarified.
	  ○ Number of tablets administrated summary replaced by proportion of tablets taken out of dispensed.
	• **Section 10.0:** List of safety parameters was updated and moved from previous Section 7.0..
	• **Section 10.1**: Stated that only treatment emergent Adverse Events, including treatment-emergent Serious Adverse Events, will be included in the summary tables.
	• **Section 10.1.1**:
	  ○ Added clarity to treatment emergent adverse event definitions.
	  ○ Added treatment-related Serious TEAEs and non-serious TEAEs to the overall TEAE summary.
	• **Section 10.1.2:** Added a separate section to outline analysis for treatment-related adverse events.
	• **Section 10.1.3:**
	  ○ Added overall SAE summaries for SAE, SAEs leading to IMP discontinuation and SAEs leading to discontinuation.
	  ○ Removed the breakdown into all different serious criteria.
	  ○ Added summaries by SOC and PT and additional listings for SAEs.
	• **Section 10.1.4:** Added a separate section to outline analysis for adverse events leading to discontinuation of study drug and/or the study.
	• **Section 10.1.5:** Added a separate section to outline analysis for adverse events with an outcome of death.
	• **Section 10.2**:
	  ○ Added shift tables, where available.

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Date	Description
	○ Added table and listing for liver test elevations. ○ Added mean and individual spaghetti plots. • **Section 10.3**: Added mean and individual spaghetti plots. • **Section 10.5**: ○ Added a separate section to outline all ECG related analysis. ○ Additional summaries tables added for potentially abnormal QT, QTcB, QTcF, PR and QRS intervals parameters. ○ Added mean and individual spaghetti plots. • **Section 10.6**: New section for COVID-19 related analysis. • **Section 11.1:** ○ Added details for the derivation of PK concentration to molar concentration. ○ Removed median concentrations with confidence intervals figure. ○ Removed the sentences of subject's inclusion or exclusion for PK analysis as data from all subjects in the PK analysis set will be included. • **Section 11.2**: ○ Clarified that prealbumin levels are a PD parameter. ○ Clarified that listings for the WB and FPE will be provided. ○ Clarified that listing for prealbumin and percent change in prealbumin levels will be provided. ○ Added summary of subjects with percent increase in prealbumin levels above certain thresholds. ○ Clarified figures presentation/contents. ○ Removed figures presenting RFU and by percent target engagement by AG10 concentration. ○ Removed figures presenting mean and 95% confidence intervals for FPE and WB percent stabilization. ○ Removed figure presenting mean and 95% confidence intervals for prealbumin. ○ Removed summary table of the overall percent stabilization for both WB and FPE. • **Section 11.3**: ○ Added a separate section to outline the PD/PK correlation plots. ○ Specify that percentage change from baseline prealbumin levels is used in the correlation plots instead of prealbumin levels. ○ Removed correlation plot between prealbumin and RFU. • **Section 12.0**: Added descriptive summaries of observed values and changes from baseline for echocardiographic parameters. • **Section 13.0**: Included ICH E3, E9 and E14 as references.

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Date	Description

	• **Section 14.0**:
	  ○ Updated current text to refer to protocol amendment 3.
	  ○ Added clarification of the safety parameters assessed.
	  ○ Clarify that the summary of clinical events will not be performed.
	• **Section 15.0**:
	  ○ Moved original section 11.0 Data Review under this Validation section.
	  ○ Updated versions for SDTM and ADaM.
	  ○ Updated versions for MedDRA and WHO dictionaries.
	  ○ Removed Data Screening paragraph as this is governed by Data Management Plan and is not within the scope of SAP.
	• **Section 16.0:** Added summary of changes.

18-Oct-2021	• **Section 1.0**: added abbreviation for SI
	• **Section 3.3:**
	  ○ Corrected visit windows (added Month 9 and Month 12).
	• **Section 5.0**:
	  ○ Clarified that protocol deviations reported in the PRA CTMS were imported into the SimpleTrials CTMS.
	• **Section 6.0**:
	  ○ Added summary for age group of <65, ≥65 years.
	• **Section 7.0**:
	  ○ Clarified that data imported from AG10-201 was coded using MedDRA version 21.0 and the medical history and AE reported after close of Study AG10-201 were coded by MedDRA version 23.1.
	• **Section 8.0**:
	  ○ Clarified that data imported from AG10-201 was coded using WHO Drug dictionary version 2018MAR01 and the medications reported after close of Study AG10-201 were coded by WHO Drug dictionary version 2020SEP01.

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Date	Description
	○ Clarified that the summary for prior/concomitant medications will include each of the ATC levels (1 to 4) and additional tables will be created for the summary with ATC levels 1, level 2 and PN. ○ Added details on how Cardiovascular medications and Diuretics medications are selected. • **Section 9.0**: ○ Clarified that days where no medication was taken is derived from the 'Exposure-Missed Doses' eCRF page. Clarified how missed days were derived as the IMP is taken twice daily. ○ Updated proportion of tablets taken out of dispensed by proportion of tablets taken out of number of tablets expected to be taken to have a measure of compliance ○ Provided details for kits not returned. ○ Provided details on the different strengths of tablets dispensed during the study. ○ Removed visit and number of bottled of IMP dispensed from the data listing as those field are not included in the listing. • **Section 10.1.1**: ○ Added summary of TEAE by SOC only and by PT only ○ Added summary for the most frequent TEAE by PT. • **Section 10.1.2**: ○ Added summary of treatment-related TEAE by SOC only and by PT only ○ Added summary for the most frequent treatment-related TEAE by PT. • **Section 10.1.3**: ○ Added summary of treatment-related serious TEAE in the overall table. ○ Added summary of serious TEAE by SOC only and by PT only ○ Added summary for the most frequent serious TEAE by PT. • **Section 10.1.6**: ○ New section to describe summary for exposure-related incidence rate. • **Section 10.2**: ○ Clarified that tables will present SI results. ○ Added rules for imputation for the results beginning with '>' or '<'. ○ Provided details for the percentages derivation for the shift tables and added definition for non-available category. ○ Added details for shift tables from baseline to worst post-baseline. ○ Added tables for the normal ranges in reported and SI units. • **Section 10.6**: ○ Removed COVID-19 vaccine AEs from the list of data listings.

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Date	Description
	○ Added details on selection for COVID-19 AEs. • **Section 11.1**: ○ Added molecular weight for acoramidis acylglucuronide. ○ Box and whisker plots will be presented overall and by gene mutation type • **Section 11.2**: ○ Specified that summary tables are overall and by gene mutation type. ○ Added details for the summary of the FPE QC samples. ○ Added tables for the summary of the WB QC samples. ○ Added new table for descriptive summary for FPE percent target engagement. ○ Added mean plots (mean ± SD) for FPE percent target engagement. ○ Added new table for descriptive summary for WB percent stabilization (actual and change from baseline). ○ Added mean plots (mean ± SD) for WB percent stabilization. ○ Box and whisker plots will present prealbumin levels and not percent change from baseline in prealbumin levels ○ Added new table for descriptive summary for prealbumin levels (actual, change from baseline and percent change from baseline). ○ Added mean plot (mean ± SD) for prealbumin levels. • **Section 11.3**: ○ Added that figures will be provided overall and by mutant type ○ Added Spearman correlation for the overall and by gene mutation type at each visit up to Month 30. • **Section 12.0**: Added list of parameters included in tables and listings. • **Section 16.0:** (version 11-May-2021): ○ Sections 7.0, 8.0, 9.0 and 10.0 added minor clarifications.
15-Mar-2023	• Updated Table 1: Schedule of Assessments to reflect protocol amendment 4 • Adjusted Table 2: Analysis Visit Window • Added imputation rule for incomplete date of last dose of IMP • Updated approval contact information
05-Sep-2025	• Updated CRF and SAP versions and dates • Updated approval contact information • Updated Schedule of Assessments to include “Collect Unused IMP” and “Adverse Event” • Updated Analysis Visit Windows to include “Month 78” and “Month 84”

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	• Removed Day 1 from the summary of mean percent change from baseline in prealbumin levels

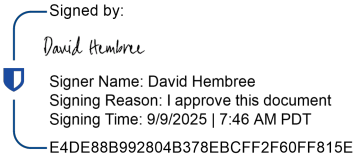
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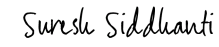
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