Statistical Analysis Plan

Study AG10-301 (Part B)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Acoramidis (AG10) in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)

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Summary of Changes

Date	Version	Description
6/30/2021	1.0	First Version
11/17/2021	2.0	• Day of treatment used for derivation of baseline analysis visit • Added listing of important protocol deviations leading to exclusion from per-protocol population and updated the language in the section 5. • Added detail on how to calculate proportion of study IMP taken and clarification on how end of treatment date will be defined in section 10. • Added potential sensitivity analysis if stratification at randomization differs from groupings by laboratory values by more than 10% • Added Table 4 to summarize data handling approach to intercurrent events for primary analyses in section 11.1.1 • Added sensitivity analyses (missing 6MWT) for primary analyses in section 11.1.2.1 • Clarified derivation of baseline 6MWT distance walked in section 11.2.1 • Added clarification to the key secondary analyses, added imputation rule of missing values after death in section 11.2.1 • Added Table 5 to summarize data handling approach for intercurrent events for key secondary analyses in section 11.2.1. • Increased the number of imputed datasets for key secondary efficacy analyses • Added new sensitivity analyses for the key secondary analyses in section 11.2.3.4 • Added details to section 11.3.5 regarding serum TTR analysis • Added details to section 11.4.1 regarding Troponin I (TnI)analysis • Added analysis by eGFR groups to section 12. • Added details on summarization of data in section 12.2. • Updated previous table 4 to table 6. • Add imputation rule for lab results begins with "<" or ">". • Added exposure-adjusted (patient-years) adverse event rate analysis • Added Kaplan Meier plot for TEAEs leading to fatal outcome • Clarified COVID-19 specific reporting in section 12.3 • Added three-way interaction to subgroup analyses model Appendix 1.1 updated to match the text update within the document.
08/03/2022	3.0	• Added the definition of follow-up rules for the ACM events and CVH in section 3. • Added clarity to the definition of the baseline assessments in section 3.3. • Moved 'Missing Date Handling' rules in section 3.5 to Appendix 1.5

	• Added the additional component of change in NT-proBNP in the primary endpoint in section 11.1.1.to align with protocol amendment 6.0. Updated the analysis detail to accommodate the additional component. • Added rule to combine the strata if the sample size is extremely low in each stratum in section 11.1.1. • Added the detail of Win-Ratio method in section 11.1.1. • Added sensitivity analysis of the primary endpoint for different NT-proBNP thresholds in section 11.1.2. • Promoted 'Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 30' and 'All-Cause Mortality by Month 30' to key secondary endpoints in section 11.2.3 and section 11.2.4 to align with the multiplicity adjustment in SAP Version 2.0. • Updated the analysis detail for the key secondary endpoints in section 11.2.5 and section 11.2.6 to accommodate the changes. • Changed the imputation of missing during CV-related AE to during CV-related hospitalization in section 11.2.5 • Moved the primary endpoint of protocol amendment 5.0 to the other secondary endpoints section in section 11.3.1. • Moved the Win Odds method under other secondary endpoint for hierarchical combination of ACM and CVH to take ties into account in the analysis in section 11.3.2. • Promoted the exploratory endpoint of change from baseline in NT-proBNP to other secondary endpoints section in section 11.3.6. • Added Serum TTR to PK-PD analysis as it's the third PD marker in addition to FPE and WB stabilization in section 11.4.3. • Updated Appendix 1.1 to reflect the changes of analysis methods. • Updated Appendix 1.2 to add change in NT-proBNP as third component and move 6MWT to fourth component in F-S test.

1. LIST OF ABBREVIATIONS

6MWT	Six-Minute Walk Test
ACM	All-Cause Mortality
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATTR	TTR Amyloidosis
ATTR-CM	ATTR Cardiomyopathy
ATTRm-CM	Mutant ATTR-CM
ATTRwt-CM	Wild-Type ATTR-CM
BID	Twice Daily
BMI	Body Mass Index
CEC	Clinical Events Committee
CFB	Change From Baseline
CHF	Congestive Heart Failure
CI	Confident Interval
CIR	Copy Increments in Reference
CIF	Cumulative Incidence Function
CMAD	Cardiac Mechanical Assist Device
CMH	Cochran-Mantel-Haenszel
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV	Cardiovascular
CVH	CV-Related Hospitalization
[redacted]	[redacted]
DMC	Data Monitoring Committee
ECG	Electrocardiogram, Electrocardiographic
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOCI	Event of Clinical Interest
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5 Dimensions 5-Levels Health Outcomes Assessment
FPE	Fluorescent Probe Exclusion
F-S	Finkelstein-Schoenfeld
HF	Heart Failure
ICD	Implantable Cardioverter-Defibrillator
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat

IWRS	Interactive Web Response System
J2R	Jump to Reference
KM	Kaplan Meier
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	KCCQ-Overall Score
LV	Left Ventricular
MAR	Missing At Random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not At Random
NT-proBNP	N-Terminal Pro-Brain-Type Natriuretic Peptide
NYHA	New York Heart Association
OLE	Open Label Extension
PD	Pharmacodynamic
pg	Picogram
PK	Pharmacokinetic
PopPK	Population Pharmacokinetic
PP	Per-Protocol
[redacted]	[redacted]
PT	Preferred Term
QoL	Quality of Life
QTcB	Corrected QT interval, Bazatt's formula
QTcF	Corrected QT interval, Fridericia's formula
RFU	Relative Fluorescence Units
RIND	Reversible Ischemic Neurological Deficit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQs	Standardized MedDRA Queries
SOC	System Organ Class
T4	Thyroxine
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack
TnI	Troponin I
TTR	Transthyretin
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WB	Western Blot
WHO	World Health Organization

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2. INTRODUCTION

The AG10-301 ATTRibute-CM Trial (A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of the Efficacy and Safety of Acoramidis in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy) examines an investigational drug, acoramidis, in the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM). This document describes study objectives, data analysis methods, and data summaries for Part B of this clinical study protocol (CSP). Screening and randomization will be followed by a total of 30 months of blinded, placebo-controlled treatment.

Analysis approaches detailed within this document take precedence if different from the analyses and summaries presented in the protocol.

2.1 Objectives of Part B of the Study

2.1.1 Primary

To determine the efficacy of acoramidis in the treatment of subjects with symptomatic ATTR-CM by evaluating the difference between the acoramidis and placebo groups in the combined endpoint of All-Cause Mortality, the cumulative frequency of cardiovascular (CV)-related hospitalization, change from baseline in the NT-proBNP, and change from baseline in the Six-Minute Walk Test (6MWT).

2.1.2 Key Secondary

- To evaluate the effects of acoramidis on 6MWT.
- To evaluate the effects of acoramidis on health-related Quality of Life (QoL) as measured by a heart failure (HF)-specific instrument (KCCQ) in subjects with symptomatic ATTR-CM.
- To assess the pharmacodynamic (PD) effects of acoramidis by assessing circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization.
- To assess the effect of acoramidis on all-cause mortality.

2.1.3 Other Secondary

- To determine the efficacy of acoramidis treatment as measured by the individual components of the primary endpoint and hierarchical combinations thereof.
- To determine the efficacy of acoramidis in reducing CV mortality in subjects with symptomatic ATTR-CM.
- To evaluate the safety and tolerability of acoramidis administered for 30 months in subjects with symptomatic ATTR-CM.
- To assess the pharmacodynamic (PD) effects of acoramidis as assessed by established ex vivo assays of TTR stabilization.

2.1.4 Exploratory

- To evaluate the effects of acoramidis on circulating biomarkers of microvascular ischemia in subjects with symptomatic ATTR-CM.

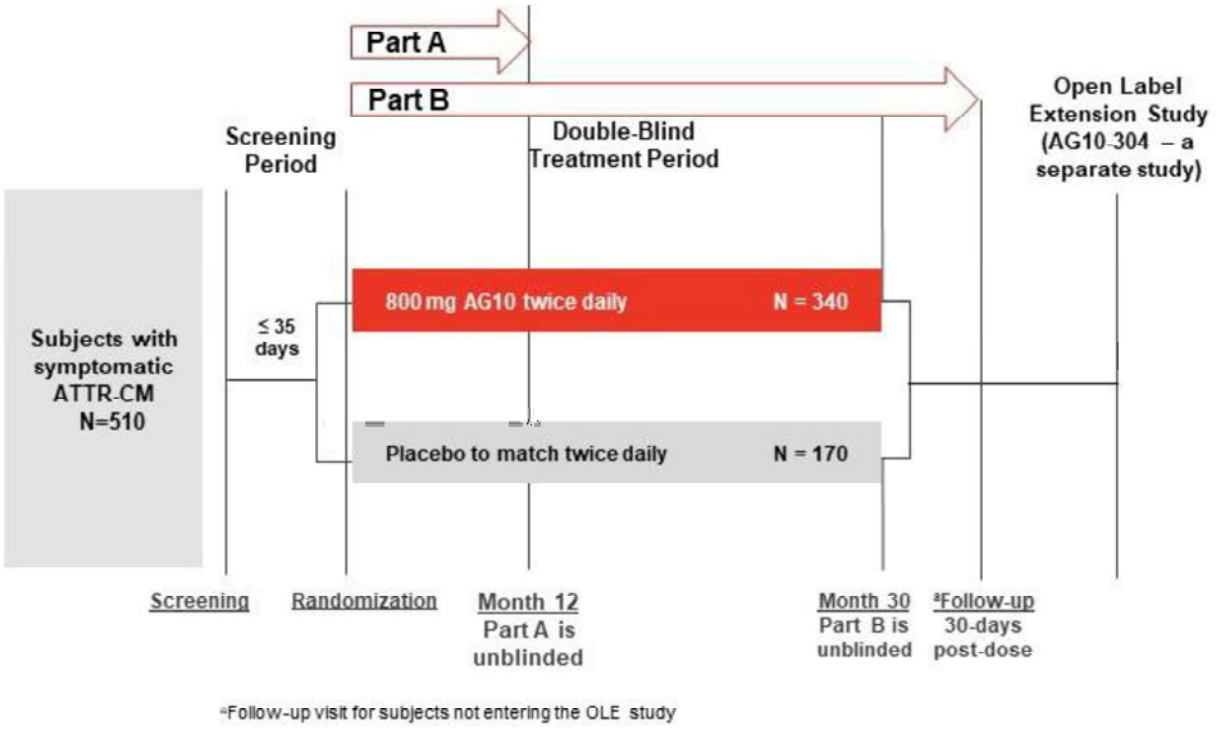
- To characterize the pharmacokinetics (PK) of acoramidis (and its predominant metabolite) when acoramidis-HCI 800 mg is administered orally twice daily (BID) in subjects with symptomatic ATTR-CM.
- To describe the population PK (PopPK) of acoramidis in subjects with ATTR-CM.
- To describe the PD properties and the PK-PD relationship of acoramidis as assessed by circulating prealbumin (TTR) concentration as an in vivo biomarker of stabilization and by established ex vivo assays of TTR stabilization, and correlation with acoramidis PK (PK-PD substudy).
- To evaluate the effects of acoramidis on health related QoL as measured by EuroQoL Health Outcomes Assessment tool (EQ-5D-5L) in subjects with symptomatic ATTR-CM.
- To assess the ability of acoramidis to bind and stabilize a diverse array of pathogenic and likely pathogenic variant TTR tetrameric species, representing amino acid substitutions located throughout the sequence of TTR that are responsible for a spectrum of clinical presentations, from sera and/or plasma of subjects with ATTR-CM (Additional assays).

2.2 Study Design

This prospective, Phase 3, randomized, multicenter, parallel-group study will evaluate the efficacy and safety of acoramidis in symptomatic subjects compared to placebo, administered on a background of stable heart failure therapy. Screening and randomization will be followed by a total of 30 months of blinded, placebo-controlled treatment. At the end of 12 months of treatment (Part A) efficacy of acoramidis will be assessed through analyses of the functional (6MWT) and health-related QoL (as measured by HF-specific instrument KCCQ) endpoints. At the end of 30 months of treatment (Part B) efficacy of acoramidis will be further assessed through analysis of All-Cause Mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWT.

This Statistical Analysis Plan (SAP) addresses Part B of the study. Part A has a separate document specifying its planned analyses. The study schematic for the ATTRibute-CM trial is shown in Figure 1. See Section 2.2 for criteria for conclusion of Part B of the study.

Figure 1 Study Schematic: ATTRibute-CM Trial



Approximately 510 eligible subjects will be randomized in a 2:1 ratio to acoramidis 800 mg or matching placebo administered orally BID. Part B of the study will conclude after the last subject enrolled has concluded the last visit of the study or is not expected to complete that visit (e.g. subject has died or withdrawn from the study). After that milestone, all data collected in the study database will be used for the analysis of Part B efficacy and safety outcomes to be presented in the Part B Clinical Study Report (CSR).

Subjects who complete the Month 30 visit will have a visit 30 days (± 7 days) after the last dose of investigational medicinal product (IMP). Subjects who complete the 30-months of double-blinded study treatment and the Month 30 visit assessments, may be eligible to enroll into the OLE study (AG10-304) with its own protocol and a separate SAP. Subjects who choose to enroll in the OLE Study (AG10-304) the same day as completing the Month 30 visit in AG10-301 will not be required to have the 30-day follow-up visit (in Study AG10-301).

Blinding to treatment allocation will be maintained for the subjects, Investigators, Clinical Events Committee (CEC), and Sponsor designated site monitoring personnel throughout the study until the final subject has completed the expected Month 30 or follow-up visit. Upon Part A unblinding, the Part A team conducting the analysis will not be involved in conduct or analysis of Part B prior to the Part B unblinding. The Part B statistical team conducting the analysis will not be involved in unblinded analysis of Part A. The operational processes and procedures that will be executed in conjunction with the Part B analysis to preserve confidentiality and blinding of the entire trial will be governed by a "Data Access Management Plan" finalized before Part A unblinding.

2.3 Study Population and Stratification

Approximately 510 males and females ≥18 and ≤90 years of age (at time of randomization) with chronic, stable, symptomatic (NYHA Class I-III) ATTR-CM will be randomized in a 2:1 ratio (340 subjects to active treatment, 170 to matching placebo) in the study. Randomization will be stratified according to whether subjects have ATTRm-CM or ATTRwt-CM with a targeted minimum of 20% of subjects with ATTRm-CM. Randomization will also be stratified according to NT-proBNP level (≤3000 vs >3000 pg/mL) and renal function defined by eGFR (≥45 vs <45 mL/min/1.73 m^2) at screening. For statistical analyses, the stratification factor levels used during randomization in the Interactive Web Response System (IWRS) will be utilized. If the overall mis-stratification proportion is greater than 10% of subjects, a sensitivity analysis on the primary and key secondary endpoints using actual stratification factors will be performed.

2.4 Sample Size Determination

The primary analysis population will include subjects with baseline eGFR ≥ 30 mL/min/1.73 m^2 (i.e., subjects with baseline eGFR < 30 mL/min/1.73 m^2 will be excluded from the primary analysis population). It is estimated that approximately 10% of subjects will have baseline eGFR < 30 mL/min/1.73 m^2. Sample size calculations are based on two-sided alphas = 0.01 for Part A and 0.04 for Part B.

The power for Part B was originally estimated based on the primary endpoint of a hierarchical combination of All-Cause Mortality and CV-related hospitalizations over a 30-month treatment period. The test statistic for the combined endpoint is Finkelstein and Schoenfeld's (Finkelstein 1999) adaptation of the generalized Gehan Wilcoxon test (and will be referred to as the Finkelstein-Schoenfeld (F-S) test). Simulations based on estimates of mortality and CV-related hospitalization from ATTR-ACT result in greater than 90% power with two-sided alpha = 0.04 with total N = 460 (= 0.9*510, i.e., after excluding 10% of subjects with baseline eGFR < 30 mL/min/1.73 m^2) for the Finkelstein-Schoenfeld test to reject the null hypothesis that neither All-Cause Mortality nor CV-related hospitalization is different between acoramidis and placebo. Simulations assumed an All-Cause Mortality rate of 40% for placebo with a hazard ratio of 0.7, mean number of CV-related hospitalizations by Month 30 of 1.15 and 0.75 in the placebo and acoramidis groups, respectively.

The primary endpoint is a hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWT.

The number of subjects who will initiate, and when they will initiate tafamidis after Month 12 is unknown and is not possible to estimate with any precision. Simulations to assess power for the four-component hierarchical endpoint (All-Cause Mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWT) were conducted under various scenarios taking into consideration potential tafamidis use and potentially missing data. The estimated power across the various scenarios remains above 80%.

2.5 Blinding

As noted in Section 2.2, a Data Access Management Plan will be documented prior to the unblinding of Part A of the study. Briefly, the Part B team will be blinded to treatment through

Part B data base lock. They will not participate in any unblinded analyses including subject-level information on treatment assignment, PK and PD or review of Part A.

2.6 Interim Analyses

No interim analysis is planned for this study. Part A analyses will occur following the last subject completing the Month 12 visit.

An independent Data Monitoring Committee (DMC) will provide independent reviews of data relevant to the safety, efficacy, outcomes and conduct of the ongoing trial. The DMC will operate in agreement with its charter, which was drafted in accordance with the March 2006 Food and Drug Administration Guidance document on the Establishment and Operation of Clinical Trial Data Monitoring Committees.

3. GENERAL ANALYSIS CONSIDERATIONS

This report will utilize subject data through their end of study participation. This includes scheduled, unscheduled, early termination visit dates, data from public records (for mortality) and telephone contacts.

All continuous variables will be summarized as means (standard deviations), medians (25th and 75th percentiles), minimum and maximum. The number and percentage of subjects in each category will be presented for categorical variables.

- Unless otherwise specified, all hypothesis tests will be two-sided.
- Alpha recycling rule (α_B): α_B will be 0.05 for the primary and key secondary endpoints if the p-value for the alpha-controlled sequentially-tested endpoints in Part A (change from baseline (CFB) in 6MWT, CFB in KCCQ score and CFB in TTR at 12 months) is <0.01, allowing us to re-use the 0.01 alpha for Part B. This is effectively a fallback procedure (Wiens 2005). α_B will be 0.04 otherwise. Any further mention of the controlled type 1 error in this document will be denoted by α_B.
- All CFB values are calculated as the respective (post baseline value – baseline value) for the measure of interest.
- Analysis approaches for primary and secondary efficacy endpoints are detailed in Section 11 while analyses for safety are outlined in Section 12. Formal statistical tests of the primary and select secondary efficacy analyses will be controlled at an alpha level of α_B sequentially as specified in Section 11. For other variables of interest uncontrolled for type 1 error, statistical comparisons will use a two-sided significance test evaluated at alpha level of 0.05.
- All analyses for primary, secondary and exploratory endpoints will adjust for the randomization stratification factors unless specified otherwise.

  Survival status response collected through the end of the study will be used for mortality in the efficacy analyses. For any analyses on All-Cause Mortality, receiving a heart transplant or a cardiac mechanical assist device (CMAD) will be treated as death. Survival status response collected on the corresponding eCRF page will be used. If the survival status is "Unknown" on the eCRF page, subjects will be censored at the date they are last known alive or the upper bound of the Month 30 visit analysis window, whichever is earlier.
- For efficacy analyses, CV-related hospitalizations are those that were adjudicated as CV related and non-elective by the CEC including Events of clinical interest (EOCI). The adjudicated CV-related hospitalizations occurring up to when the survival status eCRF page is filled out will be included in the analysis. For subjects who complete the 30-month study, CV-related hospitalization frequency is calculated for the period of (assessment date from survival status eCRF page - first dose of IMP date +1). For subjects who prematurely discontinue from the IMP or discontinue/withdraw from the study, CV- related hospitalization frequency is calculated relative to (30 days after last dose date - first dose of IMP date +1).
- Event rates per 100 patient-years by each of the treatment groups through 30 months will be calculated for the following endpoints: All-Cause Mortality, CV death, CV-related hospitalization and composite of All-Cause Mortality or first CV-related hospitalization.

- Kaplan Meier (KM) curves and cumulative incidence function (CIF) by treatment groups will be plotted for All-Cause Mortality, CV death, time to first CV-related hospitalization and time to All-Cause Mortality or first CV-related hospitalization. The number of subjects at risk, number of events and number of censored observations through 30 months will be summarized using the "Method=Life" option in PROC LIFETEST.
- All the descriptive summaries for the endpoints will also be repeated for the following concomitant tafamidis grouping:
  - acoramidis only: subjects who received any acoramidis and did not receive any tafamidis
  - placebo only: subjects who received only placebo and did not receive any tafamidis,
  - acoramidis+tafamidis: subjects who received any acoramidis and any tafamidis
  - placebo+tafamidis: subjects who received placebo and any tafamidis.

Analyses will be performed using SAS software version 9.4 or higher [redacted].

3.1 Analysis Populations

Analysis Population and Analysis Set are used interchangeably in this document.

3.1.1 Intention-to-Treat (ITT) Analysis Population

The ITT population (ITT) is defined as all randomized subjects who have received at least one dose of IMP and have at least one post baseline efficacy evaluation. Subjects in this population will be analyzed according to their assigned randomized treatment.

3.1.2 Modified Intention-to-Treat (mITT) Analysis Population

The modified ITT population (mITT) will be the primary analysis population for efficacy endpoints. The mITT population includes subjects who meet the definition of ITT and have a baseline eGFR $\geq$ 30 mL/min/1.73 m^2. Subjects in this population will be analyzed according to their assigned randomized treatment.

3.1.3 Per-Protocol (PP) Analysis Population

The per-protocol population will be a subset of the mITT population based on a pre-identified list of important protocol deviations. The list of subjects with such deviations from the protocol will be identified prior to unblinding Part A and Part B of the study. The PP population analysis will be considered as supportive of the mITT analyses for the primary efficacy and key secondary endpoints. Subjects will be analyzed according to their assigned randomized treatment. If the PP analyses set makes up a large fraction (>90%) of the mITT then the PP analysis will not be conducted.

3.1.4 Safety Analysis Population

For safety, the analysis population will include all randomized subjects who received at least one dose of IMP. Safety analyses will be presented by actual treatment received.

3.2 Study Day Derivation

The day of the study is the day relative to randomization date. The study day is defined as the (assessment/event date – randomization date) if the assessment/event date is prior to the randomization date and as (assessment/event date – randomization date) + 1 if the assessment/event date is on/after the date of randomization. Using this derivation, the day of randomization will be considered study day 1. There is no study day 0. Negative days indicate assessments prior to randomization. Positive days indicate assessments on or after randomization. A month is defined as 30.4375 days and a year is defined as 365.25 days. Study day will be used for all efficacy and other analyses unless stated otherwise.

The day of treatment is the day relative to first dose of IMP. The treatment day is defined as the (assessment/event date – first IMP dose date) if the assessment/event date is prior to the first IMP dose date. If the assessment/event date is on/after the date of the first IMP dose date, then the treatment day relative to first dose of IMP is defined as (assessment/event date – first IMP dose date) + 1. Using this derivation, the day of the first IMP dose date will be considered treatment day 1. There is no treatment day 0. Negative days indicate assessments/events prior to the first IMP dose date. Positive days indicate assessments/events on or after the first IMP dose date. A month is defined as 30.4375 days and a year is defined as 365.25 days. Treatment day will be used for safety summaries where identified.

3.3 Visit Windows for Analysis

Visit windows for presentation of results will be derived from date of the assessment (or visit date if assessment date was not collected or is missing) relative to the randomization date unless otherwise specified. Visit windows will be contiguous and are presented in Table 1, Table 2 and Table 3 based on assessment specific scheduled visits. Visit windows for assessments except KCCQ, 6MWT distance, and EQ-5D-5L are presented in Table 1. KCCQ is not assessed at Day 28 and will utilize the visit windows as shown in Table 2. 6MWT distance and EQ-5D-5L are not assessed at Day 28 and Month 3 so they have different window thresholds exhibited in Table 3.

Table 1 Analysis Visit Windows for Assessments except KCCQ, EQ-5D-5L, and 6MWT Distance

Double-Blind Treatment Period			
		Analysis Window Study Day	
Visit	Target Study Day	Low	High
Baseline	≤ 1*	≤1*	1*
Day 28	28	2*	59
Month 3	91	60	136
Month 6	183	137	228
Month 9	274	229	319
Month 12	365	320	410
Month 15	457	411	502
Month 18	548	503	593
Month 21	639	594	684
Month 24	731	685	776
Month 27	822	777	867
Month 30	913	868	958

*: The day of treatment is used, unless if the first IMP dose is taken on a later date of the protocol scheduled Day 1 visit, for which both time and date of the first IMP dose will be used as the window threshold.

Table 2 Analysis Visit Windows for KCCQ

Double-Blind Treatment Period			
		Analysis Window Study Day	
Visit	Target Study Day	Low	High
Baseline	≤ 1*	≤ 1*	1*
Month 3	91	2*	136
Month 6	183	137	228
Month 9	274	229	319
Month 12	365	320	410
Month 18	548	411	594
Month 24	731	595	867
Month 30	913	868	958

*: The day of treatment is used, unless if the first IMP dose is taken on a later date of the protocol scheduled Day 1 visit, for which both time and date of the first IMP dose will be used as the window threshold.

Table 3 Analysis Visit Windows for 6MWT Distance and EQ-5D-5L

Double-Blind Treatment Period *Day 1 = Randomization date			
		Analysis Window Study Day	
Visit	Target Study Day	Low	High
Baseline	≤ 1*	≤ 1*	1*
Month 6	183	2*	228
Month 9	274	229	319
Month 12	365	320	410
Month 18	548	411	594
Month 24	731	595	867
Month 30	913	868	958

*: The day of treatment is used, unless if the first IMP dose is taken on a later date of the protocol scheduled Day 1 visit, for which both time and date of the first IMP dose will be used as the window threshold.

Results presented by visit will use the visit record data closest to the scheduled (target) visit day. If two visits occur equidistant from the scheduled (target) visit day, the most recent visit record date (i.e., later of the 2 visits) will be used.
Shift tables from baseline to worst post-baseline will utilize all records for a subject, even if there are multiple visits within a derived visit window. Listings will present data from all visits attended.

Unless otherwise specified, baseline values are defined as the last measurement obtained on or prior to the date of the first IMP dose on the protocol scheduled Day 1 visit assessment, or prior to

the first IMP dose if taken on a later date. For subjects randomized and not treated, the baseline value will be the last measurement prior to randomization. When there is a missing baseline assessment, it will not be imputed, thus, subjects are excluded from any CFB analyses for which they have a missing baseline value.

3.4 Data Included in Part B Analyses

All data included in the study database will be used for Part B analyses.

3.5 Handling of Dropouts and Missing data

Imputation of missing values for efficacy analyses is detailed in Section 11. The robustness of the primary and key secondary efficacy analyses to missing data assumptions will be explored as detailed in Section 11. Missing dates for Adverse Events and Prior or Concomitant Medication will be handled as described in Appendix 1.5.

4. SUBJECT DISPOSITION

The number of subjects screened (i.e., signed informed consent) and the number of subjects randomized will be reported overall. Reasons for screen failures will be summarized.

The number and percentage of randomized subjects that received IMP, discontinued IMP early, failed to complete the study and the reason for discontinuation of IMP and from the study will be presented by treatment group and overall.

Any subjects randomized but not treated with any IMP will be presented in a separate listing.

5. PROTOCOL DEVIATIONS

A listing of subjects with important protocol deviations will be provided. A listing of prespecified subset of important protocol deviation leading to exclusion from PP population will be identified prior to database freeze for Part A and prior to database lock for Part B and reported. Subjects excluded from Part A PP population will not necessarily be excluded from Part B unless they also meet Part B subset of important protocol deviations.

6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Variables to be presented as reported at baseline are detailed in the remainder of Section 6. These variables will be summarized for the mITT and safety populations.

6.1 Demographic Variables

Demographic characteristics collected are:

- Age in years (quantitative and qualitative) variable:
  a) Continuous variable
  b) <78, and ≥78 years
  c) <65, and ≥65 years
- Gender (Male, Female)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)

6.2 Baseline Characteristics

Baseline characteristics collected and to be summarized are:

- Baseline height (cm)
- Baseline weight (kg)
- Baseline Body Mass Index (BMI) (kg/m^2)
- ATTR-CM type (ATTRm-CM vs ATTRwt-CM)
- Stratification factors (from IWRS based on data at screening):
  a) ATTR-CM type (ATTRm-CM vs ATTRwt-CM)
  b) Baseline NT-proBNP level (≤3000 vs >3000 pg/mL)
  c) Baseline eGFR (≥45 vs <45 mL/min/1.73 m^2)
- eGFR group (≥30 vs <30 mL/min/1.73 m^2) as calculated at baseline using the Modification of Diet in Renal Disease (MDRD) equation using the central laboratory data from [redacted] This will be presented for Safety Population only as this is part of the criteria for mITT population.

7. MEDICAL AND SURGICAL HISTORY

Medical and surgical history will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at the time of Part B database lock. Medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT). These summaries will be produced for the safety population.

8. ATTR-CM DIAGNOSIS AND HISTORY

ATTR-CM diagnosis and history variables to be reported at baseline include:

- Genetic status and if mutant, genotype
- Zygosity
- Clinical basis for diagnosis and if non-invasive, type of assessment
- History of atrial fibrillation and type
- History of thromboembolic event or stroke/ Transient Ischemic Attack (TIA)/ Reversible Ischemic Neurological Deficit (RIND)
- Permanent pacemaker placed
- Implantable cardioverter-defibrillator (ICD) placed
- Presence of amyloid polyneuropathy and if present, stage
- Diagnosis of renal disease
- Prior carpal tunnel release surgery
- Prior spinal stenosis surgery
- History of heart failure
- History of prior congestive heart failure (CHF) hospitalizations

- Clinical evidence of heart failure
- Heart failure symptoms that required or require ongoing treatment with a diuretic
- LV wall (interventricular septum or LV posterior wall) thickness
- Other relevant cardiovascular history
  - Active coronary artery disease
  - Prior valve surgery
  - Prior pericarditis, pericardial surgery or pericardiocentesis
  - Prior aortic surgery
  - Other prior arterial intervention (e.g., femoral-popliteal bypass or stent)

9. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded according to the AG10-301 Coding Conventions using the World Health Organization Drug Dictionary (WHODrug). Prior medications are those medications with a start date prior to the first day of IMP. For those that never received IMP, prior medications are those received prior to randomization. Concomitant medications are those taken on or after the day of first dose of IMP, including those started prior to IMP and continued past initiation of IMP. If no IMP is administered, concomitant mediations are those taken on or after the date of randomization. Note that medications that started prior to randomization and continued or stopped after randomization will be summarized as both prior and concomitant medications. Additionally, subjects initiating tafamidis and the time to initiation of tafamidis will be summarized separately.

Prior and concomitant medication use will be separately summarized by Anatomical Therapeutic Classification (ATC) medication class (Level 4) and preferred name (i.e. generic medication name). A subject reporting the same medication more than once will be counted once when calculating the number and percentage of subjects who received that medication.

These summaries will be produced for the safety population.

9.1 Permitted Concomitant Tafamidis ≥12 Months

Number of subjects in acoramidis and placebo arms that initiate concomitant tafamidis, duration of exposure and their time to starting this concomitant medication will be summarized descriptively as raw rates and by using KM estimates and plots. The baseline characteristics for subjects with introduction of tafamidis will be generated to understand any inherent differences in the subjects that initiate this concomitant medication. A subject level listing will also be provided.

10. EXTENT OF EXPOSURE TO IMP

The extent of IMP exposure and subject compliance will be assessed by several measures: the proportion of subjects receiving at least one dose, the proportion of tablets taken out of the scheduled number (i.e. ignoring dose reductions), and the number of months of exposure. Number of tablets taken is calculated as the number of tablets dispensed minus the number of tablets returned. In case any dispensed bottle is not returned by database lock, it is assumed for the purpose of last dose of IMP date that the subject has taken the drug per protocol up to the earlier date of the (1) last dose (if available on “End of Treatment” eCRF) or (2) the date that bottle is

expected to be emptied assuming the subject has taken the drug (two tablets) twice daily or (3) end of study date (as collected on the "End of Study" eCRF) .

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 adjusted exposure will be defined as: (last dose of IMP date – first dose of IMP date – number of days reported on eCRF as no medication was taken +1) / 30.4375. Number of days where no medication was taken can be calculated by counting days wherever dose is not available or is missed based on the Drug Accountability eCRF page and/or the Exposure-Missed Doses eCRF page.

Proportion of tablets taken of those scheduled will be calculated using the below formula. If there are unreturned bottles, the assumption is that the patient took the treatment per protocol during the period of when the bottle is not returned. Algorithm for Part B last dose of IMP date is defined earlier within this section.

$$\text{Proportion} = \frac{Number\ of\ tablets\ dispensed - returned\ up\ to\ Part\ B\ End\ of\ Treatment\ (EOT)}{Number\ of\ tablets\ supposed\ to\ be\ taked\ up\ to\ Part\ B\ EOT}$$

11. EFFICACY EVALUATIONS

11.1 Primary Efficacy Endpoint

The primary endpoint for Part B is the hierarchical combination of All-Cause Mortality, cumulative frequency of CV-related hospitalization as adjudicated by the clinical events committee (CEC), change from baseline (CFB) in NT-proBNP, and CFB in 6MWT over the 30-month duration.

Receiving a heart transplant or a cardiac mechanical assist device (CMAD) will be treated as death. For efficacy analyses, CV-related hospitalizations are those that were adjudicated as such by the CEC. A threshold of 500 pg/mL will be added in the comparison of CFB in NT-proBNP for each pair.

11.1.1 Primary Efficacy Analysis

The estimand for the primary endpoint can be summarized in the following attributes:

A) Population: Subjects with symptomatic ATTR-CM and baseline eGFR ≥ 30 mL/min/1.73m^2.
B) Variable: A hierarchical combination of All-Cause Mortality, cumulative frequency of CV-related hospitalization, CFB in NT-proBNP and CFB in 6MWT at the last available visit where both subjects have non-missing assessments.
C) Intercurrent event: The treatment policy approach will apply for the primary efficacy analysis. Measurements of the components of the primary efficacy endpoint will be used as available regardless of whether or not subjects discontinue IMP or initiate concomitant tafamidis. Please refer to Table 4 for the data handling approach of intercurrent events identified for the third and fourth components (CFB in NT-proBNP and 6MWT) in the primary estimand.
D) Population level summary: Sum of ranked scores (calculated within each randomization strata) by study treatment at Month 30.

No missing data will be imputed for the primary analysis based on the F-S test.

Details of the data handling method for CFB in NT-proBNP and 6MWT in the primary estimand is summarized below.

Table 4 Intercurrent Events and Handling Rules for Primary Analysis

		Primary Analysis
Intercurrent Events	Death	No imputation for missing NT-proBNP and 6MWT. ACM included as the first component of the primary hierarchical composite endpoint
	CVH	No imputation for missing NT-proBNP and 6MWT. CVH included as the second component of the primary hierarchical composite endpoint
	Discontinuation of IMP	No imputation for missing NT-proBNP and 6MWT. All NT-proBNP and 6MWT data collected will be used.
	Tafamidis Use after M12	No imputation for missing NT-proBNP and 6MWT. All NT-proBNP and 6MWT data collected will be used.
	Other protocol deviations	
Missing data due to any other reasons		No imputation for missing NT-proBNP and 6MWT.

The primary efficacy analysis will use the F-S test (Finkelstein 1999) applied to a hierarchical combination of All-Cause Mortality, cumulative frequency of CV-related hospitalization, CFB in NT-proBNP, and CFB in 6MWT at the last available visit where both subjects have non-missing assessments over the 30-month duration for this analysis.

The test is based on the principle that each subject is compared to every other subject within each stratum in a pair-wise manner. The analytical approach utilizes ACM as the first hierarchical step followed by frequency of CV-related hospitalization, NT-ProBNP, and 6MWT (Figure 2).

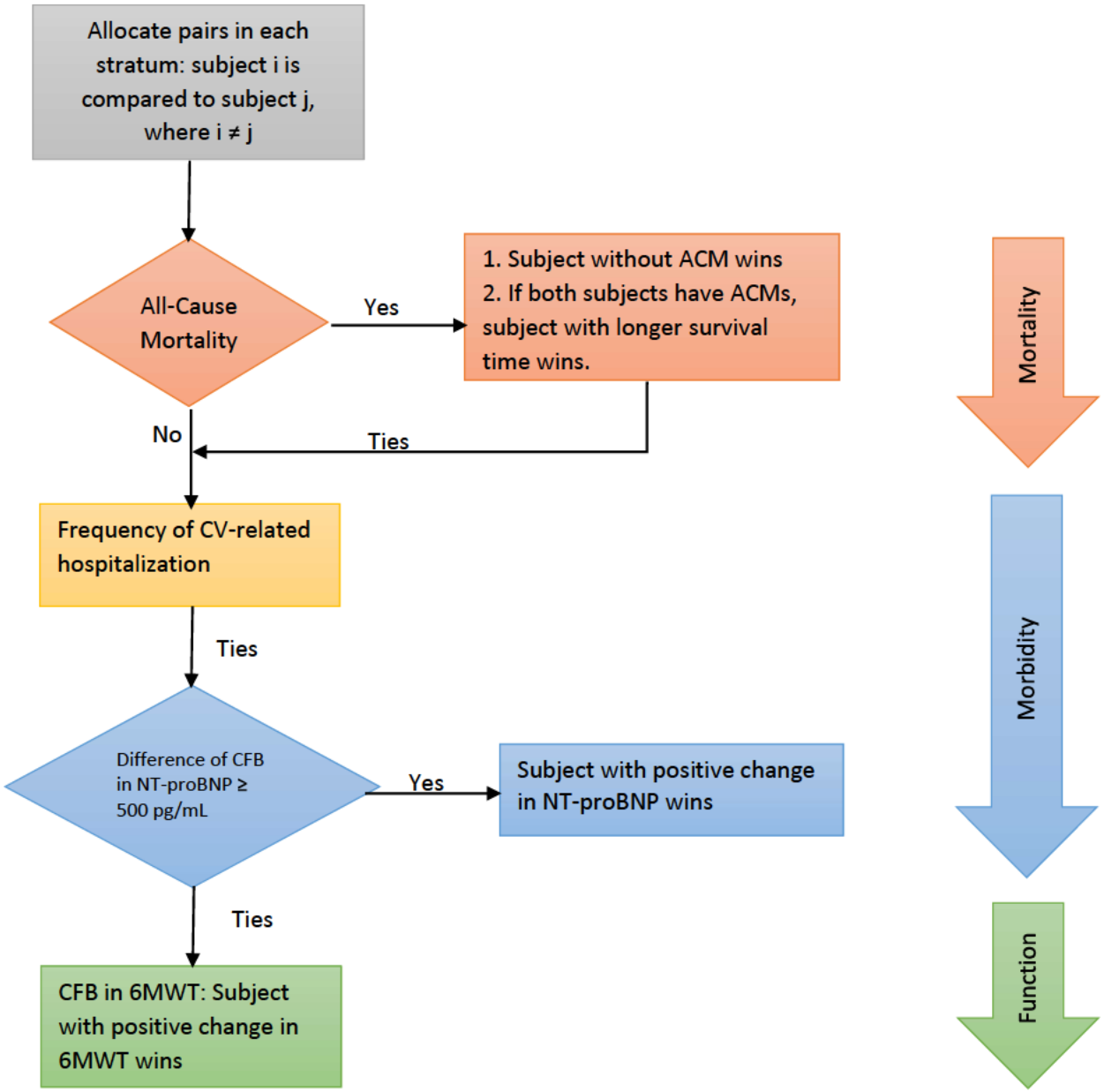
Vital status data (dead, alive, heart transplant, receiving CMAD) will be obtained for subjects who discontinue from the IMP and/or study procedures prior to Month 30 either via direct contact or through public records, regardless of discontinuation or withdrawal status. Unless precluded by governing law or regulation, consent for determination of vital status may not be withdrawn (Section 3.4 of the CSP).

The endpoint component of CV-related hospitalization includes both CV-related hospitalizations and EOCI. CV-related hospitalization is defined as a non-elective admission to an acute care setting for CV-related morbidity that results in ≥24 hours stay (or a date change if the time of admission/discharge is not available). EOCI are defined as medical visits (e.g., emergency department/ward, urgent care clinic, day clinic, etc.) of <24 hours where diagnosis and interventions indicate that the purpose of the visit was for intravenous diuretic therapy for management of decompensated heart failure.

The pairwise comparison of CFB in NT-proBNP will be performed for the last available pair of subjects. Difference of CFB in NT-proBNP between two subjects needs to be ≥ 500 pg/mL or else remains a tie and go to next component. For example: If CFB in NT-proBNP for subject A is 900 pg/mL and is 300 pg/mL for subject B, then subject B wins. If CFB in NT-proBNP for subject A is 500 pg/mL and is 300 pg/mL for subject B, then the comparison remains a tie and goes to the next component.

CFB in 6MWT will be compared between both subjects through 30 months using the last available pairs.

Figure 2 Finkelstein-Schoenfeld Scoring Algorithm



1. Positive change in NT-proBNP can be a smaller increase or a larger decrease from baseline in paired comparison.
2. Positive change in 6MWT can be a smaller decrease or a larger increase from baseline in paired comparison.
3. The paired comparison for NT-proBNP and 6MWT will use last available non-missing pair for both subjects.
4. A score will be assigned to the subject i within each pair with the following rules: win (+1), tie (0), loss (-1).

The pairwise comparisons as identified in Figure 2 are done within each stratum prior to calculating the sum of scores on which the test statistic is based. The three stratification factors resulting in a total of 8 strata (2X2X2) are identified below:

- ATTRm-CM or ATTRwt-CM *(with a targeted minimum of 20% of subjects with ATTRm-CM)*,
- NT-proBNP level (≤3000 vs >3000 pg/mL),
- Renal function defined by eGFR (≥45 vs <45 mL/min/1.73 m^2) at Screening

If there are ≤5 patients in any of the strata, the strata including ATTRm-CM will be combined and resulting in a total of 5 strata.

The primary hypothesis is:

> *H_0 (null hypothesis): All of the four components of All-Cause Mortality, cumulative frequency of CV-related hospitalization, change in NT-proBNP, and change in 6MWT distance are the same between placebo and acoramidis treatment groups*
>
> *Ha (alternative hypothesis): At least one component of All-Cause Mortality, cumulative frequency of CV-related hospitalization, change in NT-proBNP, and change in 6MWT distance is different between the placebo and acoramidis treatment groups*
>
> The primary hypothesis will be formally tested (two-tailed) using α_B (Section 3).

A table illustrating various scoring scenarios is included in Appendix 1.2 Finkelstein-Schoenfeld Scoring Algorithm.

The p-value from F-S test will be presented. Win-Ratio (Pocock 2012) and its confidence intervals will be calculated to aid in interpretation of the results for primary efficacy analysis from the F-S scoring algorithm.

The stratified non-matched Win-Ratio method will allocate all treated and placebo pairs within each stratum in the same hierarchical structure from F-S test. The win ratio (R_W) will be calculated by adding all wins from treatment group and dividing it by all wins from placebo group. The standard error of log (R_W) will be derived as: SE (log (R_W)) = log (R_W)/Z-score from F-S test. An approximate 95% CI of win ratio then can be estimated from confidence interval of log (R_W).

11.1.2 Sensitivity Analyses of the Primary Endpoint

11.1.2.1 F-S Test with Different Thresholds for the Difference in CFB in NT-proBNP

To evaluate the impact of the preset threshold of the difference between subjects in CFB in NT-proBNP comparison, the F-S test described in Section 11.1.1 will be repeated for mITT population using different thresholds that set to 250 pg/mL, 750 pg/mL and 1000 pg/mL.

11.1.2.2 Imputation for Missing Data in CFB NT-proBNP and CFB 6MWT

To evaluate sensitivity of the primary analysis result to the presence of missing CFB in NT-proBNP and CFB in 6MWT data at 30 months, the missing values at 30 months will be imputed. The choice of imputation method will depend on the reason for missing data.

Note that All-Cause Mortality is included as first component of the primary hierarchical composite endpoint, any missing data after ACM event will not be imputed. All data available post tafamidis use will be used as collected. The below imputation methods will be used for the subjects without ACM events and with missing measurements of 6MWT or NT-proBNP at 30 months:

- If the subject did not discontinue the IMP early and had missing measurements due to CV-related AE, then the missing measurements will be imputed by resampling from the bottom 25% in the same arm at a given visit.
- Any missing measurements due to early discontinuation of IMP will be imputed under MNAR using the Jump to Reference (J2R) method summarized in Section 11.2.1 below.
- All other missing 30-month measurements due to protocol deviations or any other reasons will be imputed under MAR.

The F-S method in primary analysis will be repeated on these imputed CFB NT-proBNP and CFB 6MWT datasets respectively, one at a time.

11.1.2.3 Multiple Imputation Methods for CV-related hospitalization

A two-stage multiple imputation process that follows the procedure for monotone missing data (Rubin 1987) will be used to assess the sensitivity of primary analyses for any missing CV-related hospitalizations due to early study discontinuation. Missing CV-related hospitalization will not be imputed after ACM event. Subjects who die in an interval will be excluded from the imputation model estimation. The imputation models will be estimated for each IMP group in two phases as below:

Models for CV-related hospitalization rates are estimated for each time interval (months 1-10 (period1), months 11-20 (period2), and months 21-30 (period3)). Within each short time interval (10 months), a negative binomial regression model will be assumed for hospitalization counts.

- No imputation is required for a subject who dies during the interval. All other subjects still in the study at the beginning of the interval are included in the model estimation. The reduced exposure of dropouts during the intervals is represented by an exposure multiplier (between 0-10) of the monthly hospitalization rate (McCullagh 1989).
- The monthly hospitalization rate during the first period is a function of the baseline NT-proBNP level, TTR genotype and renal function (eGFR).
- The monthly hospitalization rate during the second period is a function of the baseline covariates and the hospitalization counts during the first period. The monthly hospitalization rate during the third period is a function of the baseline covariates, and the hospitalization counts during the first and second periods.

The null hypothesis will then be tested using the complete-data as imputed above in step 1 using the same analytic method as for primary analyses (F-S test), any missing measurements for NT-proBNP and 6MWT will not be imputed. The results will finally be combined using Rubin's rule (Rubin 1987).

11.1.3 Supplementary Analyses of the Primary Endpoint

Supplementary analyses of the primary endpoint will be conducted to address concomitant tafamidis, which is allowed after Month 12.

11.1.3.1 Hypothetical Strategy

In this supplementary estimand, the hypothetical strategy will be applied to the intercurrent event of concomitant tafamidis instead, addressing the treatment effect in a hypothetical setting where concomitant tafamidis was not available to subjects.

The F-S test as used for primary efficacy analyses will be repeated in the mITT population using observations without any concomitant tafamidis. For subjects who had any concomitant tafamidis, the observations after initiation of tafamidis will not be used in this analysis.

11.1.3.2 Principal Stratum Strategy

In this supplementary estimand, the principal stratum strategy will be applied to the intercurrent event of concomitant tafamidis.

The F-S test as used for primary efficacy analyses will be repeated using the principal stratum strategy in which subjects from mITT population who initiate tafamidis are excluded (i.e., acoramidis only vs placebo only). The tafamidis grouping is defined in Section 3.

11.1.4 Supportive Analyses in the Per-Protocol Population

The PP population analyses will be considered as supportive of the mITT analyses for the primary efficacy and key secondary endpoints. Only the main analyses of these endpoints will be performed (i.e., not any of the sensitivity/supplementary analyses). Subjects will be analyzed according to their randomized treatment.

11.2 Key Secondary Endpoints

The key secondary endpoint(s) of Part B are:

1. Change from baseline to Month 30 in the distance walked during the 6MWT
2. Change from baseline to Month 30 of the KCCQ Overall Score (KCCQ-OS)
3. Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 30
4. All-cause mortality by Month 30, including heart transplant and CMAD

To maintain the α_B for the key secondary endpoints, they will be formally tested per the multiplicity adjustment rule in Section 11.5.

The estimand for the key secondary endpoints can be summarized in the following attributes:

A) Population: Subjects with symptomatic ATTR-CM and baseline eGFR $\geq$ 30 mL/min/1.73m^2.
B) Variable: CFB in 6MWT, CFB in KCCQ-OS, CFB in TTR (prealbumin) level, ACM including heart transplant and CMAD to Month 30
C) Intercurrent event: The treatment policy approach will apply. For subjects who initiate tafamidis post 12 months, die or those who discontinue study treatment earlier than 30 months, their last available post baseline 6MWT distance/KCCQ-OS will be used in analyses as available.

D) Population level summary: Difference in mean change from baseline in distance walked during 6MWT, difference in mean change from baseline in KCCQ-OS score, difference in mean change from baseline in TTR (prealbumin) level, difference in ACM including heart transplant and CMAD between acoramidis and placebo groups at Month 30.

No other missing data will be imputed for the key secondary endpoints.

11.2.1 Change from Baseline to Month 30 in Distance Walked During 6MWT

Change from baseline to Month 30 in distance walked during the 6MWT is one of the key secondary efficacy endpoints for Part B.

For the subjects randomized, the baseline 6MWT is the average of the total distance walked by subject for the two qualifying 6MWTs that meet the protocol-defined criteria on or prior to the date of randomization. In case there are more than one pair of qualifying 6MWTs, the pair of two qualifying 6MWTs with most similar distance (percentage between each other relative to the larger distance walked and then absolute difference in distance if tied on percentage) walked will be utilized to calculate the baseline value. If such a pair (meeting all protocol-defined criteria) cannot be determined programmatically, then: 1) if there are only two 6MWTs within 35 days prior to randomization, these 6MWTs will be used to calculate the baseline; 2) if there are more than one pair of 6MWTs within 35 days prior to randomization, the pair with the most similar distance will be used; 3) If <2 6MWT results are available within 35 days of randomization, apply rules 1)-2) using all 6MWT data prior to randomization; 4) if only one 6MWT is available after step 3), the result of that test will be used as the baseline value.

Subjects who prematurely discontinue the study will have the 6MWT administered at the time of discontinuation.

Observed 6MWT distance values will be utilized if available at Month 30 regardless of intercurrent events such as IMP discontinuation, tafamidis initiation, and other protocol deviations. Missing data due to reasons other than IMP discontinuation and death will be handled by mixed model repeated measures (MMRM) without imputation. For missing data following death, the imputation would be performed by sampling with replacement (within treatment arm) from the bottom 5% of observed (non-missing) change from baseline values in each arm at a given visit.

For missing data following IMP discontinuation before the Month 30 visit and while subjects are alive, the key secondary analysis will utilize the Jump to Reference (J2R) multiple imputation (MI) approach suggested by Carpenter et al. (Carpenter 2013). This method treats intermediate missing values separately from monotone missing values. A missing value is said to be intermediate if a later response is observed for that subject. The J2R approach imputes intermediate missing values under a randomized-arm missing at random (MAR) assumption. Missing values in the acoramidis arm for visits after IMP discontinuation will be imputed under the assumption of missing not at random (MNAR), utilizing the J2R approach. The J2R imputation will not be used to complete missing data due to death.

In the J2R approach, the distribution of missing values in 6MWT distance in the acoramidis arm for visits once the subject discontinues IMP is set to the distribution of the "reference" group. In other words, missing values for the subjects due to IMP discontinuation in the acoramidis group "jump" to the distribution expected in the reference group. In this discussion, the reference group is the group of subjects randomized to placebo. Missing data post IMP in the reference group are imputed under randomized-arm MAR.

The generic algorithm utilized by Carpenter et al (Carpenter 2013) and references for SAS code to implement the J2R analysis is presented in Appendix 1.3. The model of interest will be based on a MMRM analysis. At least one thousand one hundred imputed datasets will be created. The number of imputed datasets may be increased above 1100 as needed to improve model performance. Analysis will be performed on the imputed datasets and the results will be combined using Rubin's rule (Rubin 1987).

The key secondary efficacy endpoint of change from baseline in distance walked during the 6MWT for the imputed datasets will be analyzed using a MMRM with an unstructured covariance matrix. Should the model not converge with an unstructured covariance approach, autoregressive (1), compound symmetry and independent covariance structures will be utilized and the approach with the best Akaike's information criterion will be selected for the analysis. Repeated measures will be change from baseline in 6MWT distance collected by visit. The model will include terms for randomization stratification factors (wild vs. mutant genotype, NT-proBNP group, and eGFR group), treatment group, time (i.e., visit), and treatment group by time interaction as fixed effects, and baseline 6MWT as a covariate. Time will be treated as a categorical variable (i.e., as visit). However, if more than 10% of the completed subject visits at Month 30 are outside the protocol specified visit window (-7 days), time will be modeled as a continuous measure (i.e., as days).

Least square means will be displayed for each post-baseline study visit to summarize treatment effects over time.

Details of the data handling method before MMRM is applied in the key secondary analysis is summarized in below Table 5.

Table 5 Intercurrent Events and Handling Rules for Key Secondary Analysis

		Primary
Intercurrent Events	Death	Missing value will be imputed by sampling with replacement from the bottom 5% of observed CFB values in the corresponding arm at a given visit.
	CVH	No imputation for missing value
	Discontinuation of IMP	J2R Multiple Imputation
	Tafamidis Use	All data collected will be used regardless; No imputation for missing value
	Other protocol deviations	
Missing data due to other reasons		No imputation for missing value

Summaries of observed 6MWT distance, change from baseline, and percent change from baseline will be tabulated by visit

Sample SAS code for the MMRM analysis is presented in Appendix 1.4.

11.2.2 Change from Baseline to Month 30 of treatment in the (KCCQ-OS)

The KCCQ is a 23-item questionnaire (divided into seven domains) developed to measure health status and health-related quality of life in subjects with heart failure. Items include heart failure symptoms, impact on physical and social functions, and how their heart failure impacts their QoL. The KCCQ will be administered on Day 1, and again every 3 months through month12 and then every 6 months through Month 30. Subjects who prematurely discontinue the study will have the KCCQ administered at the time of discontinuation.

The KCCQ-OS values will be calculated from the answers on the "Kansas City Cardiomyopathy Questionnaire" eCRF according to the Scoring Instructions provided by Outcomes Instruments, LLC (revision 3/27/01). The scoring algorithm adjusts for missing answers to questions by calculating means of questions actually answered. The algorithm also specifies the minimum number of responses required to calculate each summary score.

Analyses of the KCCQ-OS will utilize the same analytical approach as that used for change from baseline in 6MWT at Month 30. Least square means will be displayed for each post-baseline study visit to summarize treatment effects over time.

Summary statistics of the overall score, the seven domain scores, the Total Symptom Score and the Clinical Summary Score will be presented by treatment group and visit.

11.2.3 Change from baseline in TTR (prealbumin) (an in vivo measure of TTR stabilization) at Month 30

Levels of serum TTR will be assessed by a central laboratory. Change from baseline in serum TTR levels (an in vivo measure of TTR stabilization) to Month 30 will be analyzed similarly to the change from baseline in 6MWT at Month 30.

In addition, levels of serum TTR, change from baseline and percent change from baseline in serum TTR level will also be summarized by visit and ATTRwt-CM and ATTRm-CM genotype groups. Additionally, Box and whisker plots will be presented for serum TTR and percent change from baseline in serum TTR overall and by gene mutation genotype.

The proportion of subjects whose TTR level is below 20 mg/dl and within the range of (20 mg/dl, 40 mg/dl) and greater than 40 mg/dL will also be presented by visit.

The mean of TTR will be plotted over visit using both absolute value of serum TTR and change from baseline in serum TTR for subjects whose baseline TTR level is below 20 mg/dl and subjects whose baseline TTR level is within the range of [20 mg/dl to 40 mg/dl], separately.

11.2.4 All-Cause Mortality by Month 30

Any death, receiving a heart transplant or a cardiac mechanical assist device (CMAD) recorded up to the 30-month duration will be summarized and analyzed as a time to event endpoint in mITT. The number and percentage of subjects with All-Cause Mortality events will be summarized by treatment group and the subset of death, receiving a heart transplant or a CMAD will also be provided.

The time to All-Cause Mortality will be analyzed using a stratified Cox proportional hazards model that includes treatment as an explanatory factor along with baseline 6MWT. P-values and confidence intervals for the HR will be based on the Wald statistic (Appendix 1.4).

Prior to running the Cox proportional hazards model, the overall validity of proportional hazards assumption will be examined by graphical methods and model, such as:

- Log (-log) plots; if the assumption holds the curves should be approximately parallel to each other.
- Include treatment*log (time) as a factor in the model and test the interaction factor at the 0.05 significance; non significance (p>0.05) of this factor would suggest proportionality.

In case the stratified Cox model does not converge, then a regular Cox proportional hazards model will be used with stratification factors, treatment, and baseline 6MWT as explanatory variables.

In addition, stratified log-rank test will be performed.

Treatment differences in the proportion of subjects with All-Cause Mortality will be tested at Month 30 with the stratified Cochran-Mantel-Haenszel (CMH) test.

Sample SAS code(s) are included in Appendix 1.4

11.2.5 Sensitivity Analyses of the Key Secondary Endpoint(s)

Sensitivity analyses will be conducted for the key secondary endpoints to examine the impact of missing data on interpretation of results. Four approaches to sensitivity analysis will be used: 1) Copy increments in reference (CIR); 2) MMRM without imputation; 3) Tipping point analysis; 4) MMRM with imputation of missing values occurring during a CV-related hospitalization.

All participating subjects will be asked to consent to determination of vital status (alive, death, heart transplant, receiving CMAD) at Month 30. Sensitivity analyses will not be performed for All-Cause Mortality.

11.2.5.1 Copy Increments in Reference (CIR)

This approach utilizes the generic algorithm of Carpenter et al. (Carpenter 2013) as used for the key secondary analysis but uses a different assumption as to the trajectory of responses after the intercurrent event of discontinuation of IMP. After cessation of IMP, missing 6MWT distance and KCCQ score values of subjects in the acoramidis group track that of the mean profile of the placebo group, starting from the last value observed for each subject.

11.2.5.2 MMRM without imputation

The CFB 6MWT and KCCQ-OS at Month 30 efficacy endpoints will be analyzed using the MMRM from the key secondary analysis without imputation of missing values.

11.2.5.3 Tipping Point Analysis

If the key secondary analysis has a p-value $\geq \alpha_B$ for the effect of treatment, two sets of tipping point analyses will be conducted on the imputation of missing data due to discontinuation of IMP or due to death separately. For each set of the following tipping point analysis, the approaches descripted in the key secondary efficacy analysis will be applied except for the imputation method for the specific intercurrent event being examined.

Discontinuation of IMP

As the assumption of a conservative, immediate J2R in change in 6MWT distance and KCCQ-OS at IMP discontinuation is progressively lessened, this analysis will determine if and at which point the p-value becomes $< \alpha_B$. The methodology of Carpenter et al. (Carpenter 2013) used in the key secondary analysis will be utilized. After imputation is completed, a fixed non-stochastic amount (the delta) is added onto the imputed observations.

The magnitude of the treatment difference estimated with the J2R approach for each post-baseline visit (denoted by Δ_t, t = 6, 9, 12, 18, 24, 30) from the key secondary analysis will serve as the basis for delta adjustment. Subjects in the acoramidis arm with imputed values at visit t (t = 6, 9, 12, 18, 24, 30) will have value δ_t added to the imputed value. The values of δ_t will progressively increase from 0% (i.e., J2R, no change), in 10% increments up to 125% of Δ_t.

A total of at least 1100 imputed datasets will be generated. Then, analysis will be performed on imputed datasets and the results will be combined using Rubin's rule (Rubin 1987).

In a similar manner, if the key secondary analysis has a p-value $\leq \alpha_B$ for the effect of treatment, the tipping point analysis will be conducted with value δ_t subtracted from the imputed values in the acoramidis arm.

Death

Tipping point analysis will also be carried out on imputation strategy for missing data due to death. If the p-value from the key secondary analysis has a p-value $\geq \alpha_B$, the key secondary analysis will

be repeated with missing data following death being imputed by sampling with replacement (within treatment arm) from the bottom 10% up to all (in 5% increments) of the observed (non-missing) change from baseline values in each arm at a given visit. A total of at least 1100 imputed datasets will be generated.

11.2.5.4 Imputation of missing values occurring during a CV-related hospitalization

In addition to the data handling approaches in the key secondary analysis, imputation of missing data due to CV-related hospitalization will be added by replacing missing values occurring during a CVH with observations sampled with replacement (within treatment arm) from the bottom 25% of the observed (non-missing) change from baseline values in each arm at a given visit. Missing data is considered during CVH if the targeted visit day coincides with the subject's CVH(s) stay and there's no other non-missing assessment within the same analysis visit window.

11.2.6 Supplementary Analyses of the Key Secondary Endpoint(s)

Supplementary analyses of the key secondary endpoint(s) will be conducted to address concomitant tafamidis permitted after 12 months.

The key secondary efficacy analyses will be repeated in mITT set using both hypothetical strategy and principal stratum strategy, as defined in Section 11.1.3.1 and Section 11.1.3.2.

11.2.6.1 Time Dependent Covariate Cox proportional hazards model for All-Cause Mortality

To examine the introduction of tafamidis to the study treatments, cox proportional hazards model for the All-Cause Mortality with the randomized study treatment (acoramidis and placebo) will be performed, however, now with the addition of the time dependent covariate for introduction of tafamidis.

11.2.6.2 Analyses on ITT Population

The analyses planned for All-Cause Mortality will be repeated on the ITT population.

11.3 Other Secondary Endpoints

Additional secondary endpoints, not adjusted for alpha are:

11.3.1 Hierarchical combination of All-Cause Mortality, CV-related hospitalization and CFB in 6MWT over a 30-month period

The F-S method will be used as done for the primary efficacy endpoint to analyze the hierarchical combination endpoint of All-Cause Mortality, cumulative frequency of CV-related hospitalization, and CFB in 6MWT over the 30-month duration of the trial.
The analyses will be conducted in mITT population.

11.3.2 Hierarchical combination of All-Cause Mortality and CV-related hospitalization over a 30-month period

The F-S method will be used as done for the primary efficacy endpoint to analyze the hierarchical combination endpoint of All-Cause Mortality, and cumulative frequency of CV-related hospitalization over the 30-month duration of the trial.

To evaluate the robustness of F-S test due to ties in pairwise comparison, Win Odds (Brunner, 2021) and confidence interval will be provided to take ties into account in the analysis.

The analyses will be conducted in mITT population.

11.3.3 Cardiovascular mortality by Month 30

Any all-cause mortality adjudicated by the CEC as due to a cardiovascular or undetermined cause up to the 30-month duration will be summarized and analyzed as a time to event endpoint. For cardiovascular mortality, subjects who died for non-cardiovascular reasons will be designated as censored at the time of death. The same analytic methods as for All-Cause Mortality will be used.

11.3.4 Cumulative frequency of cardiovascular-related hospitalization by Month 30

Cumulative frequency of CEC adjudicated CV-related hospitalization will be analyzed using negative binomial regression analysis with treatment, the three stratification factors and an offset term equal to log of each subject's study duration included in the model. If the number of subjects with zero CV-related hospitalization is high, a zero inflated negative binomial model will be performed to provide further assurance of the results.

Stratified Cochran-Mantel-Haenszel (CMH) row means scores tests will be used to analyze the frequency of CEC adjudicated cardiovascular-related hospitalizations by treatment.

Sample SAS code is included in Appendix 1.4

Additionally, CV-related hospitalization will be summarized by adjudicated attributed categories.

11.3.5 TTR Stabilization Measured in Established Ex-Vivo Assays (Fluorescent Probe Exclusion (FPE) and Western Blot (WB)) in the PK-PD substudy

In the PK-PD sub-study, ex vivo TTR stabilization will be assessed through Fluorescent Probe Exclusion (FPE) percent stabilization and Western Blot (WB) percent stabilization. Only subjects with sufficient data to calculate TTR stabilization will be included in the following analyses.

FPE is a competitive binding assay measuring occupancy of TTR's thyroxine (T4) binding site. For each sample, FPE reading is measured in triplicate 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 × triplicate = 78 data points). FPE data will be tabulated for time: Y=60 mins for all visits. FPE percent stabilization, at Day X will be derived as follows (using the mean of the triplicates):

$$\frac{100 \times \left[\left(FPE_{Day\ 1@60min} - FPE_{Day\ 1@pre-probe}\right) - \left(FPE_{Day\ X@60min} - FPE_{Day\ X@pre-probe}\right)\right]}{\left(FPE_{Day\ 1@60min} - FPE_{Day\ 1@pre-probe}\right)}$$

where Day 1 represents the last sample prior to first dose of study drug.

The WB is a measure of a bound ligand's ability to prevent the accelerated dissociation of tetrameric TTR under acidic denaturing conditions. WB data will be tabulated for all visits. WB percent stabilization at Day X will be derived as follows:

$$100\ x\ \frac{\text{mean}_{72\ hour\ acidification,duplicates,Day\ X}}{\text{mean}_{0\ hour\ acidification,duplicates,Day\ X}}$$

Summary statistics of FPE and WB percent stabilization at each visit will be presented. Treatment differences in the FPE and WB percent stabilization at each visit will be presented in graphs for wild/mutant genotype TTR. The distribution of TTR stabilization (FPE and WB) at each visit will be displayed using box and whisker plots. At each visit, the proportion of subjects meeting ≥75%, ≥90%, ≥99% will be summarized by treatment groups for wild/mutant TTR and overall. The FPE rate constant will be presented for each visit for each subject (Equation for deriving Rate Constant is shown in Section 11.4.3).

Treatment differences in the proportion of subjects meeting ≥90% percent stabilization will be summarized by visit and will be tested at Month 30 nominally (without alpha control) with the CMH statistic (2-sided, alpha = 0.05) adjusting for wild/mutant genotype TTR, NT-proBNP group, and eGFR group. In addition, the proportion of subjects who maintain ≥ 90% stabilization at Month 30 after achieving ≥90% stabilization at Day 28 will be summarized descriptively by treatment group.

Summary statistics of TTR stabilization will be presented for ATTRwt-CM and ATTRm-CM genotype groups. Summaries of quality control samples will be reported for FPE and Western Blot analyses.

11.3.6 Change from baseline in N-terminal pro-Brain-type Natriuretic Peptide (NT-proBNP)

The change from baseline in NT-proBNP to the Month 30 visit will be examined. The analytic method utilized in the analysis of the key secondary endpoint(s) will be repeated for NT-proBNP. If the normality assumption is violated, the log-transformed NT-proBNP will be used in the MMRM model. The estimated geometric means for the ratio of NT-proBNP to baseline levels and their 95% confidence intervals will also be provided based on the MMRM model.

11.3.7 Supplementary Analyses for Other Secondary Endpoints

11.3.7.1 Hypothetical Strategy

Supplementary analyses for other secondary endpoint(s) will be done to address concomitant tafamidis permitted after 12 months. The analytic method used for their primary analyses will be repeated, within the mITT set, using the hypothetical strategy as defined in Section 11.1.3.1.

11.3.7.2 Principal Stratum Strategy

Supplementary analyses for other secondary endpoint(s) to address concomitant tafamidis permitted after 12 months will also be done using the primary analyses methods along with principal stratum strategy as defined in Section 11.1.3.2 within the mITT set.

11.3.7.3 Time Dependent Covariate Cox proportional hazards model for the cardiovascular mortality or first CV-related hospitalization

To examine the introduction of tafamidis to the study treatments, cox proportional hazards model for the cardiovascular mortality or the first CV-related hospitalization with the randomized study treatment (acoramidis and placebo) will be performed, however, now with the addition of the time dependent covariate for introduction of tafamidis.

11.3.7.4 Analyses on ITT Population

The analyses planned for cardiovascular mortality (Section 11.3.3) will be repeated on the ITT population.

11.4 Exploratory Endpoints

11.4.1 Change from baseline in Troponin I (TnI)

TnI may be summarized descriptively and will be analyzed separately for each assay used. For subjects whose TnI results were obtained with the same assay for all time points starting with baseline, descriptive summaries of observed value and change from baseline may be provided. The proportion of subjects with Troponin I values not detectable (below the lower limit of quantification), and summary statistics for assays above that threshold will be presented.

11.4.2 Change from baseline in the EuroQol Health Outcomes Assessment tool (EQ-5D-5L)

The EQ-5D-5L is a brief, self-administered generic health status instrument that takes about 5 minutes to complete and per protocol should be conducted after completion of the KCCQ. The instrument includes two parts. In the first part, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having five levels of function (1-no problem, 2-slight problem, 3-moderate problem, 4-severe problem, and 5-extreme problem). The second part is a respondent's self-rating of current health status on a Visual Analog Scale (VAS) with endpoints labeled "best imaginable health state" (score of 100) and "worst imaginable health state" (score of 0). The scores from the 5 dimensions may be used to calculate a single index value, also known as a utility score. Complete details of administration and scoring are provided in the Study Procedures Manual.

Data from the EQ-5D-5L will be examined in three ways:

1. Categorization of a subject's health status change from baseline by visit will be summarized descriptively as the proportion of subjects within a category. The approach of Devlin 2010 will be used. Health status change between time periods is classified into one of four categories based on the scores in each health state dimension over time:
    a. Their health state is better (i.e., better on at least one dimension and is no worse in any other dimension).
    b. Their health state is worse (i.e., worse in at least one dimension and no better in any other dimension).
    c. Their health state is exactly the same (i.e., same state on each dimension).
    d. The changes in heath are "mixed': better on one dimension, but worse on another.
2. Descriptive statistics for the VAS will be presented. The analysis utilized for the key secondary endpoint will be repeated for the change from baseline in the VAS response.
3. Descriptive statistics for the index score will be presented. The analysis utilized for the key secondary endpoint will be repeated for the change from baseline in the index score response.

For the VAS and the index score, the sensitivity analyses described for the key secondary endpoint (excluding the tipping point analysis) will be used to explore the sensitivity of conclusions to missing values.

11.4.3 PK-PD Analysis

The FPE rate constant will be tabulated for each subject in the PK-PD substudy with sufficient data for analysis for all visits.

The rate constant k is derived as follows: The mean values of the triplicate (duplicate when triplicate values are not available) of full 6hr FPE time course measurements Relative Fluorescence Units (RFU) are fitted with the following equation.

Fluorescence (RFU) = offset + $A(1 - e^{(-k*t)})$
where:

t is the time of fluorescence measurement, in minutes,
k is the rate constant, expressed in 1/minutes, determined by the fit,
A is the amplitude, expressed in RFU, determined by the fit, and
Offset is determined by the fit, expressed in RFU.

For PK-PD correlation analysis, the PD results (Serum TTR, FPE percent stabilization, FPE rate constant, and WB percent stabilization) will be plotted against PK measurements (plasma acoramidis concentration) overall and by genotype (ATTRwt-CM/ATTRm-CM). PK-PD correlation analysis will be done by wild/mutant genotype and overall. The FPE rate constant and the plasma acoramidis concentration will also be tabulated by subject by visit. In addition to the FPE rate constant, RFU will be evaluated by linear regression over the first hour for each subject.

11.4.4 PK Analysis

Plasma concentration of acoramidis will be summarized at each timepoint by treatment group for subjects in the PK-PD substudy with sufficient data for analysis. In addition, plasma acoramidis concentration will be listed for individual subjects for each timepoint. Concentration will be reported for steady state predose except for the Day 28 1 hour post-dose measurement.

11.4.5 Other Exploratory Endpoints

The analysis of the other exploratory endpoints will be performed outside of this statistical analysis and may be reported in a separate report.

11.5 Multiplicity Adjustment

To control α_B, the following efficacy endpoints will be formally tested sequentially in the order specified below:

- The primary efficacy endpoint
- Change from baseline to Month 30 in 6MWT
- Change from baseline to Month 30 in KCCQ-OS
- Change from baseline to Month 30 in serum TTR level
- All-Cause Mortality by Month 30 (stratified cox proportional hazard model)

In this hierarchical approach, except for the primary efficacy endpoint, an endpoint will only be formally tested if the previous endpoint is statistically significant at the α_B level (p-value is $< \alpha_B$). If an endpoint is not statistically significant at the α_B level (p-value is $\geq \alpha_B$), the statistical tests corresponding to all subsequent endpoints will be considered not statistically significant. Multiplicity adjustment will apply to primary efficacy endpoint and key secondary endpoints only. The multiplicity procedure will be applied to the mITT analysis set only.

12. SAFETY EVALUATIONS

One of the secondary objectives in Part B is to assess the safety and tolerability of acoramidis administered for 30 months in subjects with symptomatic ATTR-CM. Safety and tolerability of acoramidis will be assessed within the safety population unless stated otherwise. Safety parameters to be assessed include treatment-emergent adverse events (TEAEs) and serious TEAEs, TEAEs leading to IMP 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 clinical relevance. Safety analyses will be conducted in the safety analysis population by actual treatment received. A subject that takes at least one dose of acoramidis will be presented in the acoramidis actual treatment group.

Analysis by eGFR group (≥30 vs <30 mL/min/1.73 m^2) at screening will be conducted for summaries of TEAEs, clinical laboratory parameters, liver function tests, vital signs, and ECG.

12.1 Adverse Events

Adverse event (AE) data will be collected on the "Adverse Events" eCRF and coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 23.1 or newer). For the purpose of data collection for this study, any untoward event that is reported from the time that the subject signs the ICF until 30 days after the last dose of IMP is to be considered an AE.

An AE (classified by preferred term (PT)) that occurs during the treatment period will be considered a 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. Conservatively, if an AE occurs in the same date as the first IMP date, then it will be considered a TEAE. All AEs included in the adverse event summaries are treatment emergent.

A subject level summary table of TEAE characteristics by treatment will be presented. This table will include:

- Subjects who experienced at least one TEAE
- Serious TEAE: Subjects who had at least one treatment emergent serious adverse event (SAE) meeting a seriousness criterion (death, life threatening, requires or prolongs hospitalization, persistent or significant disability/incapacity, congenital anomaly or birth defect, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).
- TEAE with fatal outcome: Subjects who had a TEAE with an outcome of death
- TEAE resulting in permanent IMP discontinuation: Subjects who had at least one TEAE with an action taken regarding IMP discontinuation
- TEAE related to IMP: Subjects who had at least one TEAE indicated as related to IMP as assessed by the investigator
- Severe TEAE: Subjects who had at least one TEAE with a severity of severe

The incidence of each TEAE will also be summarized by system organ class (SOC), PT and treatment assignment. Additionally, the incidence of each TEAE will also be summarized by SOC, PT, severity, and treatment assignment. Multiple AEs mapped to the same PT will be counted once per subject though the number of events per PT may also be presented.
The incidence table of TEAE, serious TEAE and related TEAEs by PT or SOC, respectively, in descending order will also be provided. A similar summary of most frequent TEAEs by PT will be provided. Appropriate summaries will be repeated for serious TEAEs, IMP related TEAEs, TEAEs leading to discontinuation of IMP and TEAEs leading to fatal outcome. Additionally, exposure-adjusted (patient-years) event rate will be summarized for TEAE, Serious TEAE and related TEAEs by SOC, PT and treatment assignment.

A listing displaying TEAEs leading to fatal outcome will be generated. TEAEs and non-treatment emergent AEs will be provided in a listing.

Additionally, Kaplan Meier plot will be presented for TEAEs leading to fatal outcome.

12.2 Physical Exam, Vital Signs, ECG, Clinical Laboratory Parameters

Safety laboratory findings, vital signs, and 12-lead ECGs will be summarized (including figures) and listed by treatment group and visit. Values and changes from baseline at scheduled time points will be summarized.

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 represented in shift tables from baseline to worst post-baseline and from baseline to last post-baseline values. An additional listing of laboratory abnormalities will be provided.

The number and proportion of subjects with liver test elevations will be presented by treatment group. Liver test elevations are assessed by using post-baseline results for ALT, AST, ALP, and total bilirubin based on the definitions presented in the following table.

Table 6 Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN to < 3xULN ALT or AST ≥ 3x to < 5x ULN ALT or AST ≥ 5x to < 10x ULN ALT or AST ≥ 10x to < 20x ULN ALT or AST ≥ 20x 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 ULN and total bilirubin > 2 times ULN will also be presented.
Body measurement and vital signs to be reported include weight, height, BMI, resting systolic and diastolic blood pressure, resting heart rate, and respiratory rate.
Clinically relevant physical exam results as determined by the investigator will be identified by a positive response to the corresponding question (field PECLSIG) on the "Physical Examinations (Body Systems)" eCRF.

Data from the "ECG – Central reading" eCRF will be utilized to summarize clinically relevant changes from the baseline ECG as recorded in the interpretation of the ECG (field INTP_EGORRES) and the clinically relevant change from baseline (EGCLSIG) fields.

The following ECG parameters will be presented:

PR, QRS, QT, QTcB and QTcF summaries of observed values and change from baseline by treatment group and by timepoint/visit including Day 28 pre-dose and Day 28 post dose.

Proportion of subjects with observed QT, QTcB and QTcF greater than a given threshold (e.g., >450, >480 and >500 msec).

Proportion of subjects with change from baseline in QT, QTcB and QTcF over predetermined cut offs (>10, >30, >60, >90 msec) by treatment group and by timepoint/visit including Day 28 pre-dose and Day 28 post dose. These will also be presented as worst post-baseline values.

Proportion of subjects with QTcF >500 msec and change from baseline >60 msec by treatment group and by timepoint/visit including Day 28 pre-dose and Day 28 post dose. These will also be presented as worst post-baseline values.

Proportion of subjects with PR >200 msec and change from baseline >25% (of baseline observed value) by treatment group and by timepoint/visit including Day 28 pre-dose and Day 28 post dose. These will also be presented as worst post-baseline values.

Proportion of subjects with QRS duration >120 msec and change from baseline >25% (of baseline observed value) by treatment group and by timepoint/visit including Day 28 pre-dose and Day 28 post dose. These will also be presented as worst post-baseline values.

12.3 Covid-19 Related

Any important deviations from the protocol related to Covid-19 as reported will be summarized overall and by treatment.A listing will be generated including all protocol deviations related to COVID 19. COVID-19 impact on: visits, IMP and Study Completion, Six Minute Walk Test (6MWT) Assessments and Adverse Events of COVID-19 will be summarized overall and by treatment. Listings of all subjects recorded as impacted by COVID-19 (related to visit completion, early study or IMP discontinuation, inability to complete 6MWT, missed IMP doses, or any reported adverse events of COVID-19) will also be provided as appropriate. Standardized MedDRA Queries (SMQs) will be utilized to summarize COVID-19 events.

12.4 Database Sources

The ATTRibute-CM clinical database will be housed in RAVE EDC (Electronic Data Capture) hosted by [redacted] In addition, [redacted] will obtain the central laboratory data from [redacted] and [redacted] the central ECG data from ERT Clinical, PK and PD data from [redacted] and [redacted] and the CEC data from central adjudication vendor. The central laboratory, Clinical Trial Management System (CTMS), ECG and CEC data will be transferred to the [redacted] will obtain unblinded randomization data collected in the Interactive Web Response System (IWRS), from [redacted] after the Month 30 data are locked for analysis.

Hence, the data used for analysis will include but may not be limited to the below 9 main sources:

1. the Interactive Web Response System (IWRS),
2. the eCRF/RAVE EDC,
3. CTMS,
4. the central laboratory,
5. [redacted]
6. central ECG,
7. PK and
8. PD data and
9. the clinical events committee (CEC) database.

Data from the IWRS will be used to determine treatment assignment. The eCRF will be the source for site-level geographic information, all baseline and follow-up data, and will also contain the 6MWT and KCCQ data entered by the sites. CTMS will be used for site information. The central laboratory will provide all laboratory data including prealbumin. The ECG data will be provided by a separate laboratory. The CEC will provide adjudicated endpoints for primary analyses.

13. SUBGROUP ANALYSIS

Descriptive subgroup analyses will be conducted for randomization stratification factors for the primary endpoint, the components of the primary endpoint, and for the key secondary endpoints.

These factors include ATTRm-CM or ATTRwt-CM type, NT-proBNP level (≤3000 vs >3000 pg/mL) and renal function defined by eGFR (≥45 vs <45 mL/min/1.73 m^2) at screening.
In addition to the stratification variables, subgroup analyses will be conducted for age (< 78 and ≥ 78 years), country of enrollment (United States vs. rest of world) and NYHA class at baseline (I or II vs. III). Subgroup analyses for the primary endpoint will be done by using the F-S method same as for the primary efficacy analysis. For the key secondary endpoints, the subgroup analyses will be performed using the same analyses models as for those endpoints, with the addition of the subgroup factor, subgroup x treatment and subgroup x time and subgroup x time x treatment interaction terms.
In addition, summary statistics may be tabulated by subgroups for selected endpoints.

14. SUMMARY OF CHANGES FROM PROTOCOL

The following changes from Protocol Amendment 6 are reflected in the SAP version 3.0:

- Assessing circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization has been removed in Other Secondary Objectives. The objective has been promoted to Key Secondary Objectives.

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16. APPENDICES

Appendix 1.1. Statistical Analysis Summary

Efficacy Endpoints		**Analysis***	**PP Analysis**	**Sub-group Analysis**	**Sensitivity Analysis**	**Supplementary Analysis***
					Missing Data	**With concomitant tafamidis grouping****
Primary	Combination All-Cause Mortality, CV-Related Hospitalization (CVH), CFB in NT-proBNP and CFB in 6MWT over Month 30	F-S	X	X	1. F-S test with different threshold for NT-proBNP 2. Imputation for missing NT-proBNP 3. Imputation for missing 6MWT 4. Two-stage multiple Imputation approach for missing CVH, 6MWT and NT-proBNP not imputed.	F-S analysis repeated* using both Hypothetical strategy and Principal stratum strategy
Key Secondary	CFB to Month 30 in 6MWT distance	MMRM with an unstructured covariance matrix using J2R MI approach	X	X	1. CIR 2. MMRM 3. Tipping point (J2R) 4. Imputing for missing value during CVH	MMRM with an unstructured Covariance matrix using J2R MI approach repeated* using both Hypothetical strategy and Principal stratum strategy
	CFB to Month 30 in KCCQ		X	X		
	CFB in TTR at Month 30		X	X		
	All-Cause Mortality by Month 30	1. Cochran-Mantel-Haenszel 2. Cox proportional hazards model adjusted for stratification factors	X	X		1. Cochran-Mantel-Haenszel repeated* using both Hypothetical strategy and Principal stratum strategy 2. Cox model adj. for stratification factors repeated*

		3. Stratified log-rank test				using both Hypothetical strategy and Principal stratum strategy 3. Stratified log-rank using both Hypothetical strategy and Principal stratum strategy 4. Time dependent covariate Cox model 5. The primary analytic methods will also be repeated in ITT.
Other Secondary	Combination All-Cause Mortality, CVH and CFB in 6MWT over Month 30	F-S				1. F-S analysis repeated* using both Hypothetical strategy and Principal stratum strategy
	Combination All-Cause Mortality and CVH over Month 30	F-S			1. Win odds	1. F-S analysis repeated* using both Hypothetical strategy and Principal stratum strategy 2. Time dependent covariate Cox model for composite of ACM or first CVH

	CV-related Mortality by Month 30	1. Cochran-Mantel-Haenszel 2. Cox proportional hazards model adjusted for stratification factors 3. Stratified log-rank test		1. Cochran-Mantel-Haenszel repeated* using both Hypothetical strategy and Principal stratum strategy 2. Cox model adj. for stratification factors repeated* using both Hypothetical strategy and Principal stratum strategy 3. Stratified log-rank using both Hypothetical strategy and Principal stratum strategy 4. Time dependent covariate Cox model 5. The primary analytic methods will also be repeated in ITT.
	CVH Frequency	1. Negative Binomial regression analysis with treatment, and an offset term (log of study duration) 2. CMH row mean scores 3. Zero-inflated Negative Binomial model		1. Negative Binomial regression with an offset term (log of study duration) repeated* using both Hypothetical strategy and Principal stratum strategy 2. CMH row mean scores repeated* using both Hypothetical strategy and Principal stratum strategy

	TTR Stabilization via FPE at Month 30 (PK-PD substudy)	Cochran-Mantel-Haenszel		Cochran-Mantel-Haenszel repeated* using both Hypothetical strategy and Principal stratum strategy
	TTR Stabilization via Western Blot at Month 30 (PK-PD substudy)	Cochran-Mantel-Haenszel		Cochran-Mantel-Haenszel repeated* using both Hypothetical strategy and Principal stratum strategy
	CFB to Month 30 in NT-proBNP	MMRM with an unstructured covariance matrix using J2R MI approach		MMRM with an unstructured Covariance matrix using J2R MI approach repeated* using both Hypothetical strategy and Principal stratum strategy

Note: Exploratory endpoints are not included in this overview.
* KM plots and CIF plots by treatment and by concomitant tafamidis grouping will be created for all components of endpoints and for time to All-Cause Mortality or first CVH.
**Concomitant tafamidis grouping is defined in Section 3:
• acoramidis only
• placebo only
• acoramidis+tafamidis
• placebo+tafamidis

Appendix 1.2 Finkelstein-Schoenfeld Scoring Algorithm (Primary Efficacy Endpoint)

Scenario	Subject: i/j	All-Cause Mortality/ Survival Times (from baseline)	CV-related hospitalization	CFB in NT-proBNP over 30-month (difference ≥500 pg/mL)	CFB in 6MWT over 30-month	Score
1	i	Dead	not in consideration	not in consideration	not in consideration	-1
	j	Alive	not in consideration	not in consideration	not in consideration	+1
2	i	Dead/Low	not in consideration	not in consideration	not in consideration	-1
	j	Dead/High	not in consideration	not in consideration	not in consideration	+1
3	i	Dead/Tied	High	not in consideration	not in consideration	-1
		Alive				
	j	Dead/Tied	Low	not in consideration	not in consideration	+1
		Alive				
4	i	Dead/Tied	Tied	negative change	not in consideration	-1
		Alive				
	j	Dead/Tied	Tied	positive change*	not in consideration	+1
		Alive				
5	i	Dead/Tied	Tied	Tied	negative change	-1
		Alive				
	j	Dead/Tied	Tied	Tied	positive change**	+1
		Alive				
6	i	Dead/Tied	Tied	Tied	Tied	0
		Alive				
	j	Dead/Tied	Tied	Tied	Tied	0
		Alive				

* Positive change in NT-proBNP can be a smaller increase or a larger decrease from baseline in paired comparison.
** Positive change in 6MWT can be a smaller decrease or a larger increase from baseline in paired comparison.

Subjects that are tied on "All-Cause Mortality" will be compared by frequency of CV-related hospitalization. If the 2 subjects have different follow-up times, the smaller of the 2 follow-up times will be used in comparing the frequency of CV-related hospitalization. Subjects that are tied on frequency of CV-related hospitalization will be compared by the CFB in NT-proBNP at last available non-missing pair with 500 pg/mL threshold. If the difference between two subjects is less than 500 pg/mL in CFB NT-proBNP or no non-missing pair exists, subjects will be compared by the CFB in 6MWT distance without threshold at the last visit both subjects have non-missing

assessments. For example, Subject A has last visit at Month 12 and Subject B has last visit at Month 24, non-missing assessments from Month 12 will be used for comparison.

Appendix 1.3 Generic algorithm from Carpenter et al. (2013)

1. Separately for each treatment arm, take all subjects' pre-deviation data and—assuming MAR—fit a multivariate normal distribution with unstructured mean (i.e., a separate mean for each of the 1+J baseline plus post randomization observation times) and unstructured variance–covariance matrix (i.e., a (1+J)×(1+J)covariance matrix) using a Bayesian approach with an improper prior for the mean and an uninformative Jeffreys prior for the variance–covariance matrix (Schafer, 1997, p. 155).
2. Separately for each treatment arm, draw a mean vector and variance–covariance matrix from the posterior distribution.
3. For each subject who deviates before the end of the study, use the draws from step 2 to build the joint distribution of that subject's pre- and postdeviation outcome data assuming J2R (CIR for sensitivity analysis).
4. For each subject who deviates before the end, use that subject's joint distribution in step 3 to construct the conditional distribution of post deviation given pre deviation outcome data. Sample the post deviation data from this conditional distribution, to create a "completed" data set.
5. Repeat steps 2–4 K times, resulting in K imputed data sets.
6. Fit the model of interest to each imputed data set, and combine the resulting parameter estimates and standard errors using Rubin's rules Rubin (1987) for final inference.

SAS macro code to complete the above imputations can be accessed at www.missingdata.org.uk.

Appendix 1.4 Sample SAS codes for key secondary and other endpoints.

Sample SAS code to fit the MMRM specified for the key secondary sensitivity analysis. The response variable Y is the change from baseline at the Month 30 visit.

The response variable Y is the change from baseline at the study visits.

```
PROC MIXED DATA=xxx

METHOD=REML;

CLASS pid trt visit genotype ntbnpgrp gfrgrp;

MODEL y= ybase trt visit genotype ntbnpgrp gfrgrp trt*visit / S;

REPEATED visit /SUBJECT= pid r type=UN;

LSMEANS trt*visit / PDIFF;

RUN;
```

Note: y = change from baseline, ybase = baseline value, trt = treatment, ntbnpgrp = NT-proBNP group, gfrgrp = eGFR group

Sample SAS code for the time to event analysis is given below.

```
PROC LIFETEST DATA=xxx PLOTS=(s) graphics;
TIME days*status(0);
STRATA trt;
RUN;


PROC PHREG DATA=xxx;
CLASS trt (ref=< >) genotype (ref= < >) renal_function (ref= < >) NT_proBNP (ref= < >);
MODEL days*status(0)=trt / ties=EXACT;
STRATA genotype renal_function NT_proBNP;
RUN
```

Sample SAS code for the Negative binomial regression:

```
PROC DATA=xxx;
ln_days=log(studydays);* log transformation to normalize duration of participation ;
RUN;

PROC GENMOD DATA=xxx;
CLASS TRT(REF="1") GENOTYPE(ref="1") NTBNP(ref="1") RENFUN (ref="1");
```

```
MODEL CVHNUM = TRT GENOTYPE NTBNP RENFUN / DIST=NEGBIN LINK=LOG
OFFSET=ln_days;

ESTIMATE 'RR' TRT 1 -1/EXP;
run;
```

Sample SAS code for the Cochran Mantel-Haenszel test:

```
PROC FREQ DATA=xx;
TABLES TRT*STATUS / CMH
RUN;
```

Appendix 1.5 Missing Date Handling

1. Missing Date Information for Adverse Events

The following imputation rules apply to cases in which the start date is incomplete (i.e., partly missing) for Adverse Events (AEs) stop date and end date are used interchangeably in this document. 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 AG10-301 study was taken?" is "No" on the AE eCRF page) and/or the imputed data meet the treatment-emergent criteria.

A. For AEs that occurred prior to the first dose (ie, the answer to "Did this AE start before the first dose for the AG10-301 study was taken?" on the Adverse Events eCRF page is "Yes"):

Missing Day and Month

- If the year is the same as the year of the date of informed consent, the day and month of the date of informed consent will be assigned to the missing fields.
- If the year is prior to the year of the date of informed consent, December 31 will be assigned to the missing fields.
- If the year is after the year of the date of informed consent, January 1 will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year are the same as the month and year of the date of informed consent, the date of informed consent will be assigned to the missing day.
- If either the year is before the year of the date of informed consent or if both years are the same but the month is before the month of the date of informed consent, the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of informed consent or if both years are the same but the month is after the month of the date of informed consent, the first day of the month will be assigned to the missing day.

If the stop date is complete and it is before the date of first dose of IMP and the imputed start date as above is after the stop date, the start date will be imputed by the stop date. If the stop date is complete and it is on or after the date of first dose of IMP and the imputed start date as above is after the stop date, the start date will be imputed by the date immediately before the date of first dose of IMP.

If the start date is completely missing, the date of informed consent will be used to impute the start date.

B. For AEs that occurred after the first dose (ie, the answer to "Did this AE start before the first dose for the AG10-301 study was taken?" on the Adverse Events eCRF page is "No"):

Missing Day and Month

- If the year is the same as the year of the date of the first dose of IMP, the day and month of the date of the first dose of IMP will be assigned to the missing fields.
- If the year is prior to the year of the date of the first dose of IMP, December 31 will be assigned to the missing fields.
- If the year is after the year of the date of the first dose of IMP, January 1 will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year are the same as the month and year of the date of the first dose of IMP, the date of the first dose of IMP will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of IMP or if both years are the same but the month is before the month of the date of the first dose of IMP, the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of IMP or if both years are the same but the month is after the month of the date of the first dose of IMP, the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is on or after the date of the first dose of IMP, the date of the first dose of IMP will be assigned to the missing start date.
- If the stop date is before the date of the first dose of IMP, the stop date will be assigned to the missing start date.

If the start date is completely missing and the stop date is partial, the following algorithm will be used to impute the start date.

- If there is enough information to determine that the stop date is after the date of the first dose of IMP, the date of the first dose of IMP will be assigned to the missing start date.
- If there is enough information to determine that the stop date is before the date of the first dose of IMP, the informed consent date will be assigned to the missing start date.

If the start date is completely missing and the stop date is either missing or lacks sufficient information to determine whether it is before or after date of first dose of IMP, the start date will be imputed as date of first dose of IMP.

2. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partly missing) start date will be imputed. Medications with missing end date will be treated as ongoing. Partially missing end date will not be imputed. The following rules will be applied to impute the missing or incomplete start date. If the end date is complete and the imputed start date is after the stop date, the start date will be imputed as the end date.

If all day, month, and year of the start date of medication are missing and end date is after the first dose date or ongoing, the medication will be considered as concomitant medication.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of IMP, the day and month of the date of the first dose will be assigned to the missing fields.

- If the year of the incomplete start date is prior to the year of the date of the first dose of IMP, December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of IMP, January 1 will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IMP, the day of the date of the first dose will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of IMP or if both years are the same but the month is before the month of the date of the first dose of IMP, the last day of the month will be assigned to the missing day.

  If either the year is after the year of the date of the first dose of IMP or if both years are the same but the month is after the month of the date of the first dose of IMP, the first day of the month will be assigned to the missing day.

Addendum to Statistical Analysis Plan

Study AG10-301 (Part B)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Acoramidis (AG10) in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)

SAP Addendum Version: 1.0 **Effective**: 30 June 2023

SAP Version: 3.0 **Effective**: 03 August 2022

Protocol Date: 16 June 2022 **Version:** Amendment 6.0

Sponsor: Eidos Therapeutics, Inc.

[redacted]

Date

Date

[redacted]

Date

Date

2 Jul 2023

Date

1. Section 3 General Analysis Considerations

- For the purpose of Month 30 efficacy analysis of ACM and CVH, it is defined as up to 907 days. This is based on operational scheduled Month 30 clinical visit on Day 900 (Randomization Date +899 Days) plus a 7-day window.
- Subjects without ACM event will be censored at the Min[Last known alive date, Day 907] for the ACM component in the primary analysis and survival analyses.
- For efficacy analysis of CV-related hospitalizations, the first dose of IMP date was used as reference date for calculation of CV-related hospitalization frequency. Modification is made to use the randomization date instead to be consistent with study day derivation for efficacy analysis. CV-related hospitalization frequency is calculated for the period of (the earlier date of (last dose date +30 days) or Day 907 or ACM date for subjects with ACM or Last known alive date - randomization date +1).
- The intent-to-treat population (ITT) is defined as all randomized subjects who have received at least one dose of IMP and have at least one post baseline efficacy evaluation including 6MWT, KCCQ, EQ-5D-5L, NT-proBNP, Troponin-I, serum TTR, ACM (survival status) and CVH.
- Revised target study days in Section 3.3 Visit Widows for Analysis to be better aligned with operational targeted clinical visit dates. No changes to lower bounds and upper bounds of corresponding analysis window.

Visit	Target Study Day
Baseline	≤ 1*
Day 28	28
Month 3	90
Month 6	180
Month 9	270
Month 12	360
Month 15	450
Month 18	540
Month 21	630
Month 24	720
Month 27	810
Month 30	900

*: The day of treatment is used, unless if the first IMP dose is taken on a later date of the protocol scheduled Day 1 visit, for which both time and date of the first IMP dose will be used as the window threshold.

2. Section 11 Efficacy Evaluations

- For clarifications of footnote 1 and footnote 2 in Figure 2:
  - In pairwise comparison (FS-test, Win Ratio and Win odds) of NT-proBNP at a given visit, subject with smaller change from baseline value by a margin of 500 pg/mL wins, and if the difference in change from baseline values between the two subjects is less than 500 pg/mL, the comparison would be considered as a tie. In pairwise comparison of 6MWT at a given visit, subject with larger change from baseline value wins, and if the two subjects have the same change from baseline values, the comparison would be considered as a tie.
- In Section 11.1.1, in case Win Ratio equals to 1, the standard error of log (Rw) will be derived using asymptotic method (Dong 2018).
- In Section 11.2.1, missing value will be imputed by sampling with replacement from the bottom 5% of observed CFB values in the corresponding arm at a given visit due to intercurrent event of death. Bottom refers to the worst change from baseline.
- In Section 11.1.2.2 Imputation for Missing Data in CFB NT-proBNP and CFB 6MWT, if the subject did not discontinue the IMP early and had missing measurements due to CVH, then the missing measurements will be imputed by resampling from the bottom 25% in the same arm at a given visit. It should be CVH instead of CV-related AE. Bottom refers to the worst change from baseline.
- In Section 11.1.2.3 Multiple Imputation Methods for CV-related hospitalization, for the comparison of CVH in FS-Test, calculated rate after imputation between two subjects will be compared in this sensitivity analysis. Added Appendix 1.6 for imputation details.
- In Section 11.1.3, Section 11.2.6 and Section 11.3.7, supplementary analyses were proposed for primary endpoint, key secondary endpoints, and other secondary endpoints. While Tafamidis use is only allowed after 12 months, there are subjects who initiated Tafamidis after randomization and before 12 months. Even though these subjects are protocol deviations, these subjects will still be included for the efficacy analysis. Tafamidis use from randomization till ACM event date for subjects with ACM events or Min[Last known alive date, Day 907] for subjects without ACM events will be included in analysis.
- In section 11.2.5.4, for imputation of missing values occurring during a CV-related hospitalization, missing data is considered during CVH if the targeted visit day +/- 7 days window overlaps with the subject's CVH(s) stay and there's no other missing reason due to death or IMP discontinuation. In case the CVH discharge date is missing, only CVH start/admission date will be compared with the targeted visit day +/- 7 days window for overlapping.
- In Section 11.3.3 Cardiovascular mortality by Month 30, it is stated that any all-cause mortality adjudicated by the CEC as due to a cardiovascular or undetermined cause up to the 30-month duration will be summarized and analyzed as a time to event endpoint. For this analysis, receiving a heart transplant (HT) or a cardiac mechanical assist device (CMAD) will be treated as cardiovascular mortality. Same rule will also apply to Section 11.3.7.3 Time Dependent Covariate Cox proportional hazards model for the cardiovascular mortality or first CV-related hospitalization and Section 11.3.7.4 Analyses planned for cardiovascular mortality on ITT Population. Additionally, a summary of CV Death Type Classification per CEC adjudicated results will be provided.

- In Section 11.3.6, for analysis of change from baseline in N-terminal pro-Brain-type Natriuretic Peptide (NT-proBNP), if the normality assumption is violated, the log-transformed NT-proBNP will be used in the MMRM model. The estimated geometric means for the ratio of NT-proBNP to baseline levels and their 95% confidence intervals will also be provided based on the MMRM model.
- In Section 11 efficacy evaluation, added exploratory analyses of 6MWT, KCCQ, NT-proBNP, EQ-5D-5L. Results from the MMRM analysis at each individual time point other than month 30 will be included. Additional exploratory analyses of 6MWT, KCCQ, NT-proBNP will include results from the MMRM analysis at each individual time point by treatment group, ATTRm-CM or ATTRwt-CM type, NT-proBNP level (≤3000 vs >3000 pg/mL), renal function defined by eGFR (≥45 vs <45 mL/min/1.73 m^2) at screening, age (< 78 and > 78 years), country of enrollment (United States vs. rest of world) and NYHA class at baseline (I or II vs. III).
- HT and CMAD will be handled in the same way as death for intercurrent event handling.
- In Section 11.3.5, it's stated that FPE percent stabilization will be derived using the mean of the triplicates. FPE samples are assayed in triplicates; however, in cases where there is insufficient sample volume, data are collected in duplicate. In these cases, FPE data will be processed using the mean of the duplicates.
- In section 11.4.3, for some subjects at some visits, the estimate of FPE rate constant may not be available. In such cases, the corresponding rate constant estimates will not be included for the relevant analyses.

3. Section 12 Safety Evaluations

- For adverse event related analysis, missing values for severity will be considered as "Severe" and missing values for relationship to IMP will be considered as "Related" in the summary.

4. Section 13 Subgroup Analysis

- For subgroup analysis on primary efficacy endpoint, F-S test and Win-Ratio analysis will be implemented within each stratum in a similar way as for the primary efficacy analysis. In case stratified analysis is not feasible for F-S test and Win-Ratio analysis, unstratified analysis will be performed. If the subgroup variable itself is a stratification factor, it will be removed from the stratification variable list for the stratified analysis. Within the subgroup of ATTRm-CM, unstratified analyses will be implemented.
- For the key secondary efficacy endpoints of change from baseline to Month 30 in 6MWT, KCCQ and TTR, and the secondary endpoint of change from baseline to Month 30 in NT-proBNP, the subgroup analyses will be performed using the same MMRM models as for those endpoints, with the following additional model terms: the subgroup factor, subgroup x treatment, subgroup x time and subgroup x time x treatment interaction terms. If the subgroup variable is already included in the model as a covariate, the subgroup factor will not be repeated.
- For subgroup analysis on the key secondary efficacy endpoint of ACM by Month 30, the time to ACM will be analyzed using the same stratified Cox regression model as for the primary analysis, with the following additional model terms: the subgroup factor, subgroup

x treatment interaction term. If subgroup variable itself is a stratification factor, then it will be removed from the stratification variable list. In addition, stratified log-rank test and stratified CMH test will be performed within each subgroup in a similar way as in the primary analyses on the ACM endpoints. If the subgroup variable itself is a stratification factor, it will be removed from the stratification variable list for the stratified analysis.

- For subgroup analysis on the secondary efficacy endpoint of CVH frequency by Month 30, the same negative binomial regression model as that for the primary analysis will be used. The following additional terms will also be included into the model: the subgroup factor and subgroup x treatment interaction term. If the subgroup variable is already included in the model as a covariate, it will not be repeated. In addition, other planned primary analysis on the CVH endpoint will be repeated for each subgroup.

5. Appendix 1.4 Sample SAS codes for key secondary and other endpoints

- **Proc Lifetest**

Before:

```
PROC LIFETEST DATA=xxx PLOTS=(s) graphics;
TIME days*status(0);
STRATA trt;
 RUN;
```

Updated:

```
proc lifetest data=xxx;
time days*status(0);
strata genotype renal  function NT  proBNP /group=trtn;
ods output HomTests=HomTests(where=(test='Log-Rank') keep=test probchisq);
run;

/Subgroup Analysis - using renal_function as an example/
proc lifetest data=ttacm;
by renal_function;
time days*status(0);
strata genotype NT_proBNP/ group=trtn;
ods output HomTests=HomTests1(where=(test='Log-Rank') keep=test probchisq
renal_function);
run;
```

Note: "assuming status=0 corresponds to the censoring case".

- **Proc Phreg**

Before:

```
PROC PHREG DATA=xxx;
CLASS trt (ref=< >) genotype (ref= < >) renal_function (ref= < >) NT_proBNP (ref= < >);
MODEL days*status(0)=trt / ties=EXACT;
STRATA genotype renal_function NT_proBNP;
RUN
```

Updated:

```
PROC PHREG DATA=xxx;
CLASS trt (ref=< >) genotype (ref= < >) renal_function (ref= < >) NT_proBNP (ref= < >);
model days*status(0)=trtn bl6mwt / ties=exact;
strata genotype renal_function NT_proBNP;
hazardratio 'H1' trtn / cl=wald;
LSMEANS trtn / diff cl exp;
ODS OUTPUT HazardRatios = HazardRatios Diffs=diff;
RUN;
```

Note: "assuming status=0 corresponds to the censoring case".

- **Stratified CMH**

  Before:

```
PROC FREQ DATA=xx;
TABLES TRT*STATUS / CMH
RUN;
```

  After:

```
PROC FREQ DATA=xxx;
TABLES genotype*renal_function*NT_proBNP * trtn * status / cmh;
ods output CMH=cmh(where=(althypothesis='Row Mean Scores Differ ')
keep=althypothesis prob);
RUN;

/Subgroup Analysis – using renal_function as an example/
PROC FREQ DATA=xxx;
by renal_function;
TABLES genotype *NT_proBNP * trtn * status / cmh;
ods output CMH=cmh1(where=(althypothesis=' Row Mean Scores Differ ')
keep=althypothesis prob renal_function);
RUN;
```

6. Appendix 1.5 Missing Date Handling

- Use first IMP dose for calculating general concomitant medication (excluding Tafamidis) days and partial date imputation.
- Use randomization date for calculating Tafamidis days and partial date imputation.
- The partial Prior or Concomitant Medication end date imputation logic
  - If only day is missing, then assign it as the last day of the month.
  - If both day and month are missing, then assign 31DEC.
  - If fully missing, then not imputed.
  - The imputed end date should be on or after start date.
  - The imputed date cannot be later than subject death date.
- Rules to impute missing death date
  - Missing day part only: Max of [first day of the month from partial death date, last known alive date +1]
  - Complete missing: Last known alive date +1
- In case of any incomplete CVH/EOCI start date, imputation rules for missing adverse events date outlined in SAP Appendix 1.5 will be followed.
- Rules to impute partial treatment end date

End of Treatment (EOT) Date Completeness			**Imputation Rule for EOT**
Year	**Month**	**Date**	
Yes	**Yes**	**Yes**	NA
Yes	**Yes**	**No**	1. If death Date is available and is in the same or earlier than the eCRF EOT Month, impute the death date as the EOT date; 2. Else, if there are unreturned bottles, calculate the date the last unreturned bottles are expected to be emptied. a. If the calculated date is before the month of the partial EOT date, then use the first date of the month of the partial EOT date. b. If the calculated date is in the same month of the partial EOT date, then use the calculated date. c. If the calculated date is after the month of partial EOT date, then use the last date of the month of the partial EOT date. 3. Else, if End of Study (EOS) is available, impute the EOT date as MIN (EOS, last date of the eCRF EOT Month) 4. Else, impute the last date of the eCRF EOT Month
Yes	**No**	**No**	1. If death Date is available and is in the same or earlier than the eCRF EOT Year, impute the death date as the EOT date; 2. Else, if there are unreturned bottles, calculate the date the last unreturned bottles are expected to be emptied. a. If the calculated date is before the year of the partial EOT date, then use the first date of the year of the partial EOT date. b. If the calculated date is in the same year of the partial EOT date, then use the calculated date. c. If the calculated date is after the year of partial EOT date, then use the last date of the year of the partial EOT date.3. Else, if EOS is available, impute the EOT date as MIN (EOS, last date of the

			eCRF EOT Year) 4. Else, impute the last date of the eCRF EOT Year
No	**No**	**No**	1. If death Date is available, impute the death date as the EOT date; 2. Else, if there are unreturned bottles, impute the EOT date as the date the last unreturned bottles are expected to be emptied 3. Else, if EOS is available, impute the EOT date as EOS 4. Else, impute the EOT date with the last available visit date

7. Appendix 1.6 Clarification for Section 11.1.2.3 Multiple Imputation Methods for CV-related hospitalization

- A two-stage multiple imputation process will be performed to impute the missing CV-related hospitalization due to early study discontinuation. The study duration of 30 months will be partitioned into 3 intervals of 10 months each. These will be referred to as period 1, period 2, and period 3, representing months (0, 10], (10, 20] and >20, respectively. Imputation models will be estimated and applied separately for each treatment group. Hospitalizations are not imputed for subjects after ACM event. The imputation procedure consists of two distinct phases: 1) models for CV-related hospitalization rates are estimated for each time interval, and 2) these models are then used to impute the number of cardiovascular hospitalizations following censoring (dropout) amongst subjects who dropout in an interval.
- Early study discontinuation is the only source of missing hospitalization data, so there will be a monotone missing data pattern. Within each short time interval (10 months), a Negative Binomial regression model will be assumed for hospitalization counts. No imputation is required for a subject who dies during the interval. Because the model applies only to subjects who survive the interval, and subjects who die during the interval are likely to have differing hospitalization rates, subjects who die in an interval will be excluded from the imputation model estimation. All other subjects still in the study at the beginning of the interval are included in the model estimation. The reduced exposure of dropouts during the intervals is represented by an exposure multiplier (between 0-10) of the monthly hospitalization rate (McCullagh and Nelder, 1989). The monthly hospitalization rate during the first period is a function of the stratification factors. The monthly hospitalization rate during the second period is a function of the stratification factors and the hospitalization counts during the first period. The monthly hospitalization rate during the third period is a function of the stratification factors, and the hospitalization counts during the first and second periods.
- PROC GENMOD will be used to compute maximum likelihood estimates (MLE) of the parameters of the Negative Binomial regression model. It will also be used to compute the variance-covariance matrix for the estimates from each time period. If the number of subjects with zero CV-related hospitalization is high, a zero inflated Negative Binomial regression will be performed. A total of 1100 imputed data sets will be generated. To account for estimation error when forming the imputed data sets, 1100 independent sets of the Negative Binomial model parameters will be generated for each time period from a multivariate normal distribution with mean equal to the MLE, and with the variance-covariance matrix equal to the MLE variance-covariance matrix. The ith set of Negative Binomial model parameters from each time period are paired together, yielding 1100 sets of parameters for generating the 1100 imputed data sets. For each iteration, the individual subject Negative Binomial parameters (stopping parameter and success probability) will be generated using the Negative Binomial regression coefficient estimates for that iteration. The imputation process described here is applied with each set of Negative Binomial model parameters. Subjects without complete data are comprised of two types: those with no participation during the period, and those with partial participation during the period. For those with no participation, the prediction equation will be used to impute a hospitalization count for the entire period. For those with partial participation, the prediction model will be

applied to impute a hospitalization count appropriate for the remainder of the period after the subject dropped out. The imputed value will be added to the actual observed value for that subject from the part of the period prior to their dropping out. In case the imputed CVH count for a given period is larger than the maximum of the observed CVH counts among subjects with full follow-up during that period, the imputed count will be truncated as (1 + the maximal CVH count for the given period among subjects with full follow-up).

8. Reference

Dong G, Qiu J, Wang D, Vandemeulebroecke M. The stratified win ratio. J Biopharm Stat. 2018;28(4):778-796.