Protocol Number:	Eidos AG10-301
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Protocol Title:	*A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM Trial)*
Indication:	*Transthyretin Amyloid Cardiomyopathy*
Phase:	3
Investigational Medicinal Product:	Acoramidis (AG10)
Sponsor:	Eidos Therapeutics, Inc. 1800 Owens Street, Suite C-1200 San Francisco, CA 94158
Key Sponsor Contacts:	[redacted] [redacted] Alternate Sponsor Contact: [redacted]
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INVESTIGATOR'S STATEMENT

I agree to conduct the study (Study AG10-301) in accordance with the protocol and with all applicable government regulations and Good Clinical Practice (GCP) guidance.

Principal Investigator's Signature	Date (DD/MMM/YYYY)

Principal Investigator's Name

CLINICAL STUDY SYNOPSIS

Study Number: AG10-301

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

Study Centers: Approximately 130 centers worldwide

Development Phase: 3

Objectives and Endpoints:

Objectives	Endpoints
Key Primary	
Part A • To determine the efficacy of acoramidis (AG10) in the treatment of subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) by evaluating the difference between the acoramidis and placebo groups in the change from baseline in the Six-Minute Walk test (6MWT)	**Part A** • Change from baseline to Month 12 of treatment in distance walked during the 6MWT
Part B • 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 NT-proBNP, and change from baseline in 6MWT	**Part B** • 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 over a 30-month fixed treatment duration
Key Secondary	
Part A • To evaluate the effects of acoramidis on quality of life (QoL) in subjects with symptomatic ATTR-CM	**Part A** • Change from baseline to Month 12 of treatment in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)
Part B • To evaluate the effects of acoramidis on 6MWT • To evaluate the effects of acoramidis on health-related 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	**Part B** • Change from baseline to Month 30 of treatment in distance walked during the 6MWT • Change from baseline to Month 30 of treatment in KCCQ-OS • Change from baseline to Month 30 in serum TTR (prealbumin) level (an in vivo measure of TTR stabilization) • All-Cause Mortality by Month 30 including death due to any cause, heart transplant, or CMAD

Secondary	
Part A • To assess safety and tolerability of acoramidis in subjects with symptomatic ATTR-CM	**Part A** • Safety parameters to be assessed: treatment-emergent serious adverse events (SAEs) and adverse events (AEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern
• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by o circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and o established ex vivo assays of TTR stabilization	• Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 12 • TTR stabilization as measured in established ex-vivo assays (fluorescent probe exclusion [FPE] and Western blot) at Month 12 in the PK-PD substudy
Secondary	
Part B: • To determine the efficacy of acoramidis treatment as measured by the individual components of the primary endpoint and hierarchical combinations thereof	**Part B**: • A hierarchical combination of All-Cause mortality and cumulative frequency of CV-related hospitalization over a 30-month fixed treatment duration • A hierarchical combination of All-Cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWT over a 30-month fixed treatment duration • Change in NT-proBNP from baseline to Month 30 of treatment • Cumulative frequency of CV-related hospitalization by Month 30
• To determine the efficacy of acoramidis in reducing CV mortality in subjects with symptomatic ATTR-CM	• CV mortality by Month 30
• To evaluate the safety and tolerability of acoramidis administered for 30 months in subjects with symptomatic ATTR-CM	• Safety parameters: treatment-emergent SAEs and AEs, AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern

• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by ○ circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and ○ established ex vivo assays of TTR stabilization	• Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 30 • TTR stabilization measured in established ex-vivo assays (FPE and Western blot) in the PK-PD substudy
Exploratory	
Part A • To evaluate the effects of acoramidis on circulating biomarker of myocardial wall stress in subjects with symptomatic ATTR-CM	**Part A** • Change from baseline in NT-proBNP
Part A and B: • To evaluate the effects of acoramidis on circulating biomarker of microvascular ischemia in subjects with symptomatic ATTR-CM	**Part A and B:** • Change from baseline in Troponin I (TnI)
• To characterize PK of acoramidis (and its predominant metabolite) when acoramidis-HCl 800 mg is administered orally twice daily (BID) in subjects with symptomatic ATTR-CM	• PK measures of acoramidis and its predominant metabolite after oral administration of acoramidis-HCl 800 mg BID in subjects with symptomatic ATTR-CM for steady state (every 3 months), in a subgroup of subjects followed at centers participating in the PK-PD substudy
• To describe the population PK (PopPK) of acoramidis in subjects with ATTR-CM	• PopPK analysis of acoramidis in the PK-PD substudy
• To describe the PD properties and the pharmacokinetic (PK)-PD relationship of acoramidis as assessed by circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and by established ex vivo assays of TTR stabilization, and correlated with acoramidis PK	• Describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM in the 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	• Change from baseline in the EQ-5D-5L
• 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 comparing acoramidis activity across a panel of TTR variants.

Study Design and Investigational Plan

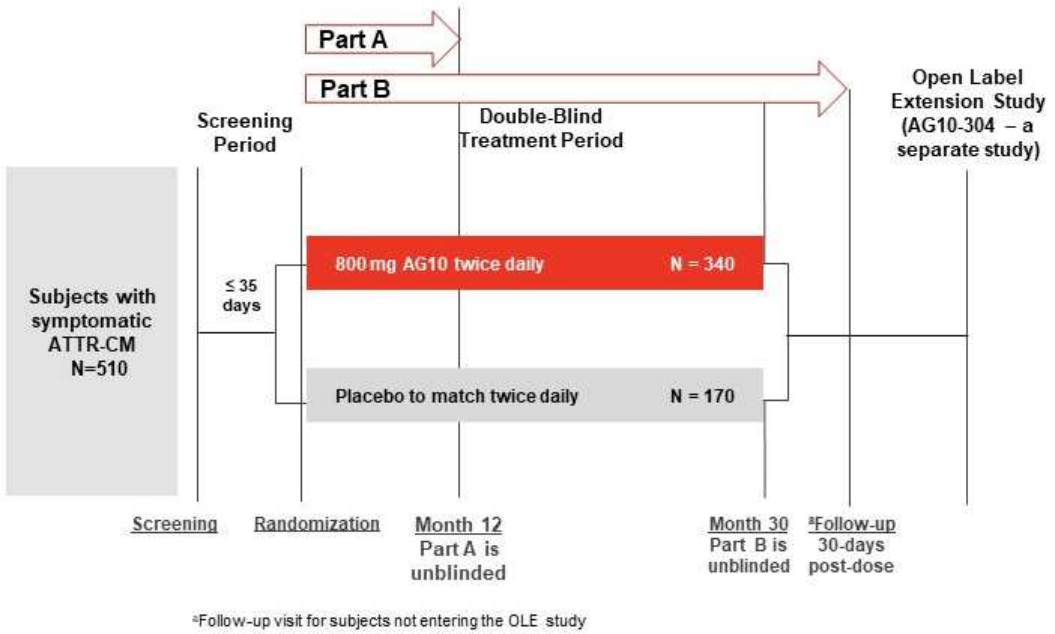
This prospective, Phase 3, randomized, multicenter, parallel-group study will evaluate the efficacy and safety of acoramidis in symptomatic subjects compared to placebo, administered on a background of stable heart failure therapy. Screening and randomization will be followed by a total of 30 months 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.

Subjects are not allowed to be treated with any ATTR-CM specific therapy during the first 12 months of the study. If a subject chooses treatment with ATTR-CM specific therapy, they will be asked to complete an early termination visit prior to discontinuation/withdrawal.

If, during participation in the study, tafamidis becomes available for the indication of ATTR-CM and subjects have access to it, subjects will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy. Currently, tafamidis is approved for the treatment of ATTR-CM in some regions. Subjects initiating therapy with tafamidis indicated for ATTR-CM must have completed the Month 12 visit. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, that subject should have an unscheduled visit with study assessments prior to initiation of the concomitant therapy. No other approved or investigational treatments, or therapies used off-label or as nonprescription supplements for the treatment of ATTR-CM will be permitted at any time during the study.

If a subject chooses to discontinue investigational medicinal product (IMP), discontinue or withdraw from the trial at any time, they will be asked to complete an early termination visit and associated procedures. If a subject chooses to initiate treatment with another therapy, including tafamidis in the first 12 months of the study, they will be asked to complete an ET visit and associated procedures prior to discontinuation/withdrawal. Subjects will continue monthly telephone contact up to Month 30. All participating subjects will be asked to consent to determination of vital status (alive, death, heart transplant, receiving cardiac mechanical assist device [CMAD]) at 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 through public records may not be withdrawn.

All subjects who complete 30 months of blinded study therapy and the final assessments of the double-blind treatment period (Month 30 visit) may be eligible to participate in an Open Label Extension (OLE) study (Study AG10-304, a separate protocol) of long-term acoramidis treatment.



Eligible subjects will be randomized in a 2:1 ratio to acoramidis HCl 800 mg or matching placebo administered orally BID. Subjects will be stratified at randomization based on whether they have wild-type ATTR-CM (ATTRwt-CM) or mutant ATTR-CM (ATTRm-CM) with a target of 20% of subjects with ATTRm-CM. Subjects 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. Samples for plasma PK and serum/plasma PD will be collected in the PK-PD substudy.

Information on AEs and concomitant medications will be collected throughout the study. The safety and conduct of the study will be monitored by an independent Data Monitoring Committee (DMC).

Number of Subjects: Approximately 510 subjects (340 subjects randomized to acoramidis and 170 subjects randomized to matching placebo)

Inclusion Criteria

To be eligible to participate in the study, subjects must meet all the following criteria:

1. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
2. Male or female ≥ 18 to ≤ 90 years of age at time of randomization.
3. Have an established diagnosis of ATTR-CM with either wild-type TTR or a variant TTR genotype (confirmed by genotyping) based on either:

   1. endomyocardial biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry; or

   2. positive technetium-99m (^{99m}Tc)-pyrophosphate (PYP) or -bisphosphonate (DPD or HMDP/HDP) scan, combined with accepted laboratory criteria excluding a diagnosis of AL amyloidosis (based on both immunofixation electrophoresis (IFE) of serum and urine, and serum free light chain (sFLC) analysis).

   Subjects with concurrent monoclonal gammopathy of undetermined significance (MGUS) may require confirmation of the diagnosis of ATTR-CM by tissue biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry.
4. Have
   a. a history of heart failure evidenced by at least one prior hospitalization for heart failure **or**
   b. clinical evidence of heart failure without prior heart failure hospitalization manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, or peripheral edema) **or**
   c. heart failure symptoms that required or require ongoing treatment with a diuretic.
5. Have NYHA Class I-III symptoms due to ATTR-CM.
6. Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception beginning with randomization and continuing for 30 days after the last dose of IMP. A male subject who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a double-barrier method of birth control.
7. Subjects taking cardiovascular medical therapy, with the exception of diuretic dosing, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to Screening.
8. Have completed ≥ 150 m on the 6MWT on at least 2 tests > 24 hours to ≤ 3 weeks apart and prior to randomization. The distance walked must be within 15% on two tests.

   If one of the first two tests is not ≥ 150 m or the first two tests are not within 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. If the third test is still not ≥ 150 m or within 15% of one of the first two tests, the subject will not be eligible for participation.
9. Must have NT-proBNP levels ≥ 300 pg/mL at Screening.
10. Must have LV wall (interventricular septum or LV posterior wall) thickness ≥ 12 mm as measured by transthoracic echocardiogram (ECHO) or cardiac magnetic resonance (CMR) documented in medical history within 10 years of Screening or at Screening ECHO or CMR.

Exclusion Criteria

Subjects who meet any of the following criteria at the Screening visit will not be eligible to participate in the study:

1. Acute myocardial infarction, acute coronary syndrome or coronary revascularization within 90 days prior to Screening.
2. Stroke or transient ischemic attack (TIA) within 90 days prior to Screening.
3. Has hemodynamic instability at Screening or Randomization that, in the judgment of the Investigator, would pose too great a risk for participation in the study.
4. Is likely to undergo heart transplantation within a year of Screening.
5. Has confirmed diagnosis of light-chain (AL) amyloidosis.

6. Has abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) or total bilirubin > 3 × ULN.
7. Has NT-proBNP levels ≥ 8500 pg/mL at Screening.
8. Has estimated glomerular filtration rate (eGFR) by modification of diet for renal disease (MDRD) formula < 15 mL/min/1.73 m^2 at Screening.
9. Known hypersensitivity to IMP (acoramidis or placebo), its metabolites, or formulation excipients.
10. Treatment for ATTR-CM with tafamidis, with marketed drug products lacking a labeled indication for ATTR-CM (e.g., diflunisal, doxycycline), or with natural products or derivatives used as unproven therapies for ATTR-CM (e.g., green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol) within 14 days prior to dosing; treatment with patisiran, inotersen, or other gene silencing agent: within 90 days for patisiran, 180 days for inotersen, and 5 half-lives for any other gene silencing agent, prior to dosing. If, during participation in the study, subjects gain access to tafamidis, they will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy.
11. Requires treatment with calcium channel blockers with conduction system effects (e.g., verapamil, diltiazem). The use of dihydropyridine calcium channel blockers is allowed. The use of digitalis will only be allowed if required for management of atrial fibrillation with rapid ventricular response.
12. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before IMP is administered. A negative urine pregnancy test at Screening and at Randomization are required for female subjects of childbearing potential.
13. In the judgment of the Investigator or Medical Monitor, has any clinically important ongoing medical condition or laboratory abnormality or condition that might jeopardize the subject's safety, increase their risk from participation, or interfere with the study.
14. Participation in another investigational clinical trial within 30 days prior to dosing with potential residual effects that might confound the results of this study. Participation in observational and/or registry studies should be discussed with the Medical Monitor.
15. Has any condition that, in the opinion of the Investigator or Medical Monitor, would preclude compliance with the study protocol such as a history of substance abuse, alcoholism or a psychiatric condition.

Test Product, Dosage, and Mode of Administration:

Day 1 through end of Double-blind Treatment: 800 mg acoramidis hydrochloride (HCl) or matching placebo, BID, by mouth

Duration of Study and Treatment: Up to approximately 32 months, including up to 35 days for Screening, 30 months for treatment (for both Parts A and B), and up to 1 month follow-up after the last dose of IMP (for subjects who complete the 30 months double-blind period and do not enroll in an OLE). 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).

Statistical Methodology

All statistical summaries may be performed using SAS Version 9.2 [redacted] or higher. Additional software may be used to produce graphics. PK parameters will be computed using Phoenix WinNonlin.

The analysis set for safety analyses will be the Safety Analysis Set: all subjects dosed. Unless otherwise specified, baseline values are defined as the last measurement obtained before the first dose of IMP. For efficacy for both Parts A and B, the primary analysis population will exclude subjects with baseline eGFR < 30 mL/min/1.73m^2. Additional details will be described in the statistical analysis plan (SAP).

Sample Size: 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.

Part A: The primary endpoint of Part A is the change from baseline in the distance achieved in the 6MWT following 12 months of double-blind study treatment.

The sample size calculation for the primary endpoint in Part A is based on the following assumptions: two-sided alpha = 0.01, power = 0.9, normally distributed data per group, equal within group standard deviations. Based on the ATTR-ACT study (Maurer 2018), it is estimated that the between group mean change from baseline is

30 meters with an estimated within group standard deviation of 70 meters. Under these assumptions, with a t-test, a total sample size of approximately 365 subjects will provide 90% power to reject the null hypothesis of no mean difference between groups. To allow for the possibility that approximately 20% of subjects may not complete the Month 12 6MWT, and that approximately 10% of subjects will have baseline eGFR < 30 mL/min/1.73 m^2 the adjusted sample size is approximately 510 subjects (340 allocated to acoramidis and 170 allocated to placebo).

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 test). Simulations based on estimates of mortality and CV-related hospitalizations 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 hospitalizations 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 over a 30-month fixed treatment duration.

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%.

Efficacy Analyses

The alpha for Part A is 0.01 and 0.04 for Part B.

Part A: The primary analysis will be the change from baseline to Month 12 in the distance walked during the 6MWT. The key secondary endpoint will be the change from baseline to Month 12 on the KCCQ-OS.

The primary efficacy endpoint will be analyzed using a mixed model repeated measures (MMRM). The model will include terms for randomization stratification factors, treatment, time, treatment by time interaction. An unstructured variance-covariance model will be used. The key secondary endpoint will be analyzed similarly.

The secondary endpoint of change from baseline in TTR level will also be analyzed similarly at Month 12. To control alpha, KCCQ-OS and change from baseline in TTR level will be formally tested sequentially in this order at significance level of 0.01 if the primary endpoint is statistically significant at the 0.01 level.

An additional secondary endpoint will be measurements of TTR stabilization at Month 12.

Part B: The primary analysis will use a hierarchical combination of the Finkelstein-Schoenfeld method applied to All-cause mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWT at the last available visit over the 30-month fixed treatment duration.

The key secondary endpoints adjusted for alpha are:

- Change from baseline to Month 30 in the distance walked during the 6MWT
- Change from baseline to Month 30 on the KCCQ-OS
- Change from baseline to Month 30 in serum TTR level
- All-Cause Mortality by Month 30, including death due to any cause, heart transplant, or CMAD

To control alpha at the 0.04 level, the key secondary endpoints will be formally tested sequentially in the order shown above if the primary endpoint is statistically significant at the 0.04 level.

Additional secondary endpoints (not adjusted for alpha) include:

- A hierarchical combination of All-cause mortality and cumulative frequency of CV-related hospitalization over a 30-month fixed treatment duration
- A hierarchical combination of All-Cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWT over a 30-month fixed treatment duration
- Change in NT-proBNP from baseline to Month 30 of treatment
- Cumulative frequency of CV-related hospitalization by Month 30
- CV mortality by Month 30
- TTR stabilization measured in established ex-vivo assays (FPE and Western blot) in the PK-PD substudy

Safety Analyses:

In Part A, safety and tolerability data, excluding adjudicated CV-related hospitalizations, will be summarized for the entire study cohort after data freeze that will occur after the last subject for analysis has completed 12 months of double-blind study treatment.

Following the conclusion of Part B, all safety data will be analyzed and summarized.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The incidence of each treatment-emergent AE will be summarized by system organ class, preferred term and treatment assignment. Multiple AEs mapped to the same preferred term will be counted once per subject. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary with generic term and Anatomical Therapeutic Chemical (ATC) code and summarized by ATC code, WHO generic name, and treatment. Safety laboratory findings, vital signs, and 12-lead ECGs will be summarized descriptively and listed by treatment assignment and visit. Values and changes from baseline at scheduled time points will be summarized. Laboratory data will be listed and values and changes from baseline at each visit will be summarized. An additional listing of treatment-emergent laboratory abnormalities will be provided.

Blinding for Part A and Part B

Analysis for Part A will be performed by a team within an independent data reporting center who will be unblinded after the last enrolled subject in Part A has completed 12 months of treatment. Subject level CV-related hospitalizations data will not be available to the Sponsor Part A team; however, the aggregated overall summary without treatment group information may be available to the Sponsor Part A team.

A separate Part B team within the independent data reporting center will remain blinded to Part A subject level data prior to and following unblinding of Part A.

Blinding to individual subject treatment allocation will be maintained for the subjects, Investigators, Clinical Events Committee (CEC), and Sponsor designated site monitoring personnel throughout the study to completion. The operational details of maintaining the blind and data access will be described and the process will be governed by a Data Access Management Plan.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
AL	Light-chain
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATTR	TTR amyloidosis
ATTR-CM	ATTR cardiomyopathy
ATTRm	Mutant ATTR
ATTRm-CM	Familial ATTR-CM
ATTR-PN	ATTR polyneuropathy
ATTRwt	Wild-type ATTR
ATTRwt-CM	Wild-type ATTR-CM
BID	Twice daily
BUN	Blood urea nitrogen
CABG	Coronary artery bypass surgery
CBC	Complete blood count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CK	Creatine kinase
CK-MB	Creatine kinase-MB fraction
CMAD	Cardiac mechanical assist device
CMR	Cardiac magnetic resonance
CRF	Case report form
CRT	Cardiac resynchronization therapy
CTFG	Clinical Trials Facilitation and Coordination Group
CV	Cardiovascular
DCC	Diagnostic Confirmation Committee
DMC	Data Monitoring Committee
DPD	3,3-diphosphono-1,2-propanodicarboxylic acid
ECG	Electrocardiogram, electrocardiographic
ECHO	Echocardiogram
ECMO	Extra-corporeal membrane oxygenation
EDC	Electronic Data Capture

eGFR	Estimated glomerular filtration rate
EOCI	Events of clinical interest
EQ-5D-5L	EuroQol 5-dimensions 5-levels Health Outcomes Assessment
EQ VAS	EuroQol-Visual Analogue Scale
ET	Early termination
FAC	Familial ATTR-CM
FAP	Familial amyloid polyneuropathy
FDA	Food and Drug Administration
FPE	Fluorescent Probe Exclusion
FSH	Follicle-stimulating hormone
FT4	Free Thyroxine
GCP	Good Clinical Practice
HCl	Hydrochloride
HDP	Hydroxylmethylene diphosphonate
HMDP	Hydroxylmethylene diphosphonate
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
IABP	Intra-Aortic Balloon Pump
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFE	Immunofixation electrophoresis
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Score
LV	Left ventricular
MAD	Multiple Ascending Dose
MDRD	Modification of diet for renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of undetermined significance
mITT	Modified ITT
MMRM	Mixed model repeated measures

NT-proBNP	N-terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
OLE	Open Label Extension
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PE	Physical examination
PK	Pharmacokinetic
PopPK	Population Pharmacokinetic
PP	Per-protocol
PYP	Pyrophosphate
QoL	Quality of Life
RBP	Retinol-binding protein
REB	Research Ethics Board
sFLC	Serum free light chain
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SSA	Senile Systemic Amyloidosis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TIA	Transient ischemic attack
TnI	Troponin I
TTR	Transthyretin
TSH	Thyroid-stimulating hormone
TUDCA	Tauroursodeoxycholic acid
ULN	Upper Limit of Normal
WBC	White blood cell
WHO	World Health Organization
^{99m}Tc	Technetium-99m
6MWT	Six-Minute Walk Test

1. INTRODUCTION

1.1. Background

Acoramidis is a potent and selective stabilizer of transthyretin (TTR) that is being developed by Eidos Therapeutics, Inc. for the treatment of TTR amyloidosis (ATTR), a progressive, fatal disease in which deposition of amyloid derived from either mutant or wild-type TTR causes severe organ damage and dysfunction.

Clinically, ATTR presents as either a cardiomyopathy (ATTR-CM), an infiltrative, restrictive cardiomyopathy characterized by progressive left and right heart failure, or as a peripheral polyneuropathy (ATTR-PN), a length-dependent neurodegenerative disease affecting sensorimotor and autonomic functions.

Familial ATTR-CM (ATTRm-CM), or FAC, and familial ATTR-PN or familial amyloid polyneuropathy (FAP), are driven by pathogenic point mutations in the TTR gene; over 140 such mutations have been described. In addition, older individuals may develop ATTR derived from wild-type TTR (ATTRwt, formerly called Senile Systemic Amyloidosis [SSA]). In ATTRwt, the major organ involved is the heart (ATTRwt-CM), although carpal tunnel syndrome and tendon involvement are also common.

Destabilization, misfolding, and aggregation of TTR lead to deposition of TTR amyloid and tissue damage. Several small molecules have been shown to bind to and stabilize TTR, potentially preventing the initiating event in amyloidogenesis. Eidos' therapeutic hypothesis is that a highly effective TTR stabilizer will halt or slow ATTR disease progression in ATTR-CM (both mutant ATTR [ATTRm] and ATTRwt) and ATTR-PN.

Acoramidis is a potent, highly selective, small molecule TTR stabilizer. It has demonstrated ability to stabilize TTR in vivo following oral dosing to nonhuman mammals, in healthy volunteers and in patients with ATTR-CM.

1.2. Clinical Benefit-Risk Assessment of Acoramidis

ATTR-CM is a serious, progressive, and life-threatening disease associated with either wild-type TTR or, in the familial form of the disease, with pathogenic mutations in the TTR gene. While such loss-of-function mutations may accelerate the development and progression of ATTR-CM, age-related dissociation of the destabilized, native tetrameric form of the protein is the initiating pathophysiological event. The degree to which individual mutations promote destabilization of the tetramer is associated with a higher degree of penetrance, an earlier onset of symptoms, and/or a more aggressive and rapidly progressive clinical course.

Dissociation of tetrameric TTR into intrinsically unstable monomeric TTR favors misfolding and aggregation into amyloidogenic precursors, which can form amyloid fibrils that are deposited in affected tissues and organs, leading to local cytotoxicity and both architectural and functional disruption. Small molecule stabilizers like acoramidis reduce the likelihood of tetramer dissociation and this mechanism provides the therapeutic rationale supporting their use in halting or slowing progression of the disease. The preclinical data and clinical safety data collected to

date have shown an acceptable safety profile and support the continued clinical assessment of acoramidis in patients with ATTR-CM.

Acoramidis has been well-tolerated in toxicology studies at what are predicted to be supra-therapeutic exposures. Results from Phase 1 and Phase 2 studies to date, have shown that administration of acoramidis has demonstrated good tolerability with no safety signals of potential clinical concern at proposed therapeutic exposures (Fox 2019, Judge 2019).

For current nonclinical and clinical data for acoramidis, please refer to the acoramidis Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Key Primary	
Part A: • To determine the efficacy of acoramidis (AG10) in the treatment of subjects with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) by evaluating the difference between the acoramidis and placebo groups in the change from baseline in the Six-Minute Walk test (6MWT)	**Part A**: • Change from baseline to Month 12 of treatment in distance walked during the 6MWT
Part B: • 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 NT-proBNP, and change from baseline in 6MWT	**Part B:** • 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 over a 30-month fixed treatment duration
Key Secondary	
Part A • To evaluate the effects of acoramidis on quality of life (QoL) in subjects with symptomatic ATTR-CM	**Part A** • Change from baseline to Month 12 of treatment in Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)
Part B • To evaluate the effects of acoramidis on 6MWT • To evaluate the effects of acoramidis on health-related QoL as measured by a heart failure (HF)-specific instrument (KCCQ) in subjects with symptomatic ATTR-CM	**Part B** • Change from baseline to Month 30 of treatment in distance walked during the 6MWT • Change from baseline to Month 30 of treatment in KCCQ-OS

• To assess the pharmacodynamic (PD) effects of acoramidis by assessing circulating prealbumin (transthyretin [TTR]) concentration as an in vivo biomarker of stabilization	• Change from baseline to Month 30 in serum TTR (prealbumin) level (an in vivo measure of TTR stabilization)
• To assess the effect of acoramidis on all-cause mortality	• All-Cause Mortality by Month 30 including death due to any cause, heart transplant, or CMAD
Secondary	
Part A • To assess safety and tolerability of acoramidis in subjects with symptomatic ATTR-CM	**Part A** • Safety parameters to be assessed: treatment-emergent serious adverse events (SAEs) and adverse events (AEs), AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern
• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by o circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and o established ex vivo assays of TTR stabilization	• Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 12 • TTR stabilization as measured in established ex-vivo assays (fluorescent probe exclusion [FPE] and Western blot) at Month 12 in the PK-PD substudy
Secondary	
Part B • To determine the efficacy of acoramidis treatment as measured by the individual components of the primary endpoint and hierarchical combinations thereof	**Part B** • A hierarchical combination of All-Cause mortality and cumulative frequency of CV-related hospitalization over a 30-month fixed treatment duration • A hierarchical combination of All-Cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWT over a 30-month fixed treatment duration • Change in NT-proBNP from baseline to Month 30 of treatment • Cumulative frequency of CV-related hospitalization by Month 30
• To determine the efficacy of acoramidis in reducing CV mortality in subjects with symptomatic ATTR-CM	• CV mortality by Month 30

• To evaluate the safety and tolerability of acoramidis administered for 30 months in subjects with symptomatic ATTR-CM	• Safety parameters: treatment-emergent SAEs and AEs, AEs leading to treatment discontinuation, abnormal physical exam findings of clinical relevance, abnormal vital signs of clinical relevance, abnormal ECG parameters of clinical relevance, and changes in clinical safety laboratory parameters of potential clinical concern
• To assess the pharmacodynamic (PD) effects of acoramidis as assessed by o circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and o established ex vivo assays of TTR stabilization	• Change from baseline in TTR (prealbumin) level (an in vivo measure of TTR stabilization) at Month 30 • TTR stabilization measured in established ex-vivo assays (FPE and Western blot) in the PK-PD substudy
Exploratory	
Part A • To evaluate the effects of acoramidis on circulating biomarker of myocardial wall stress in subjects with symptomatic ATTR-CM	**Part A** • Change from baseline in NT-proBNP
Part A and B: • To evaluate the effects of acoramidis on circulating biomarker of microvascular ischemia in subjects with symptomatic ATTR-CM	**Part A and B:** • Change from baseline in Troponin I (TnI)
• To characterize the PK of acoramidis (and its predominant metabolite) when acoramidis-HCl 800 mg is administered orally twice daily (BID) in subjects with symptomatic ATTR-CM	• PK measures of acoramidis and its predominant metabolite after oral administration of acoramidis-HCl 800 mg BID in subjects with symptomatic ATTR-CM for steady state (every 3 months), in a subgroup of subjects followed at centers participating in the PK-PD substudy
• To describe the population PK (PopPK) of acoramidis in subjects with ATTR-CM	• PopPK analysis of acoramidis in the PK-PD substudy

• To describe the PD properties and the pharmacokinetic (PK)-PD relationship of acoramidis as assessed by circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and by established ex vivo assays of TTR stabilization, and correlated with acoramidis PK	• Describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM in the 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	• Change from baseline in the EQ-5D-5L
• 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 comparing acoramidis activity across a panel of TTR variants.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

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 (Terms KCCQ overall score and KCCQ overall summary score are interchangeably used in this document). 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.

Subjects are not allowed to be treated with any ATTR-CM specific therapy during the first 12 months of the study. If a subject chooses treatment with ATTR-CM specific therapy during the first 12 months of the study, they will be asked to complete an early termination visit prior to discontinuation/withdrawal.

If during participation in the study, tafamidis becomes available for the indication of ATTR-CM and subjects have access to it, subjects will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy. Currently, tafamidis is approved for the treatment of ATTR-CM in some regions. Subjects initiating therapy with tafamidis indicated for ATTR-CM must have completed the Month 12 visit. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, they should have an unscheduled visit with study assessments prior to initiation of the concomitant therapy. No other approved or investigational treatments or therapies used off-label or as nonprescription supplements for the treatment of ATTR-CM will be permitted at any time during the study.

If a subject chooses to discontinue investigational medicinal product (IMP), discontinue or withdraw from the trial at any time, they will be asked to complete an early termination visit and associated procedures. If a subject chooses to initiate treatment with another therapy, including tafamidis in the first 12 months of the study, they will be asked to complete an ET visit and associated procedures prior to discontinuation/withdrawal. Subjects will continue monthly phone contact up to Month 30. All participating subjects will be asked to consent to determination of vital status (alive, death, heart transplant, receiving cardiac mechanical assist device [CMAD]) at 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 through public records may not be withdrawn.

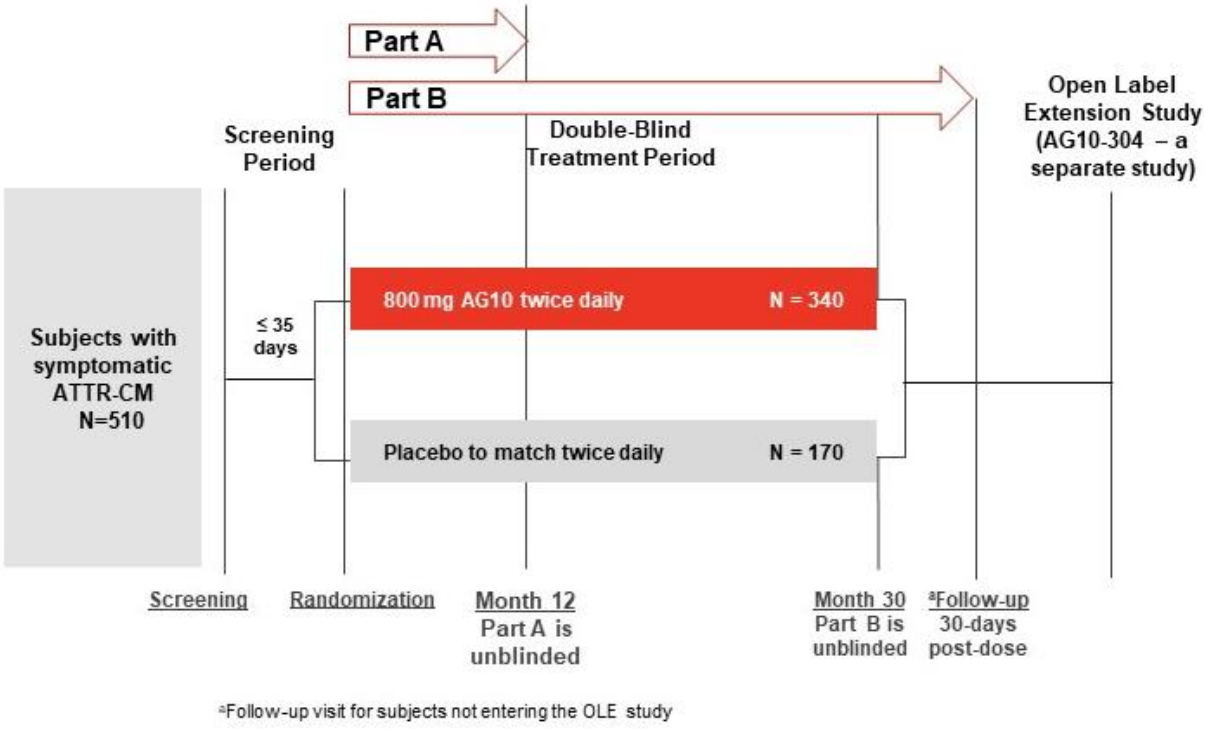
All subjects who complete 30 months of blinded study therapy and the final assessments of the double-blind treatment period (Month 30 visit) may be eligible to participate in an Open-Label extension (OLE) study (Study AG10-304, a separate protocol) of long-term acoramidis treatment.

Information on AEs and concomitant medications will be collected throughout the study. The safety and conduct of the study will be monitored by an independent Data Monitoring Committee (DMC).

The Schedule of Assessments is provided in Appendix A. Detailed descriptions of study visits can be found in Section 3.8.

The study schematic is provided in Figure 1.

Figure 1: Study Schematic



3.2. Discussion of Study Design and Rationale

This prospective study is designed to evaluate the efficacy and safety of acoramidis in subjects with ATTR-CM, administered on a background of stable heart failure therapy. A randomized, double-blind, placebo-controlled design is considered to be the most appropriate study design to meet this objective. On the basis of information gained from previous clinical experience with acoramidis, the dose of acoramidis HCl 800 mg BID has been selected for this study to represent the optimal combination of potential efficacy, safety, and tolerability.

3.2.1. Subject 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. Subjects will be stratified at randomization based on whether they have ATTRwt-CM or ATTRm-CM with a target of 20% of subjects with ATTRm-CM. Subjects 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.

3.2.2. Duration of Treatment

Subjects will be treated with the IMP (acoramidis or placebo) for 30 months. IMP may be discontinued without discontinuing/withdrawing from the study (refer to Section 3.4 for details).

Part A and Part B will be reported separately. All subjects who complete 30 months of blinded study therapy and the final assessments of the double-blind treatment period may be eligible to participate in an Open Label Extension (OLE) study (Study AG10-304, a separate protocol) of long-term acoramidis treatment.

3.2.3. Selection of Study Population

Approximately 510 males and females ≥ 18 and ≤ 90 years of age with symptomatic ATTR-CM (NYHA Class I-III) will be randomized in a 2:1 ratio (340 subjects to acoramidis and 170 subjects to matching placebo) in the study.

3.3. Eligibility Criteria

3.3.1. Inclusion Criteria

To be eligible to participate in the study, subjects must meet all the following criteria:

1. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
2. Male or female ≥ 18 to ≤ 90 years of age at time of randomization.
3. Have an established diagnosis of ATTR-CM with either wild-type TTR or a variant TTR genotype (confirmed by genotyping) based on either:
    a. endomyocardial biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry; or
    b. positive technetium-99m (^{99m}Tc)-pyrophosphate (PYP) or -bisphosphonate (DPD or HMDP/HDP) scan, combined with accepted laboratory criteria excluding a diagnosis of AL amyloidosis (based on both immunofixation electrophoresis (IFE) of serum and urine, and serum free light chain (sFLC) analysis).

Subjects with concurrent monoclonal gammopathy of undetermined significance (MGUS) may require confirmation of the diagnosis of ATTR-CM by tissue biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry.

4. Have
    a. a history of heart failure evidenced by at least one prior hospitalization for heart failure **or**
    b. clinical evidence of heart failure without prior heart failure hospitalization manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g.,

elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, or peripheral edema) **or**

c. heart failure symptoms that required or require ongoing treatment with a diuretic.

5. Have NYHA Class I-III symptoms due to ATTR-CM.
6. Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception beginning with randomization and continuing for 30 days after the last dose of IMP. A male subject who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a double-barrier method of birth control (as described in Section 3.5).
7. Subjects taking cardiovascular medical therapy, with the exception of diuretic dosing, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to Screening.
8. Have completed ≥ 150 m on the 6MWT on at least 2 tests > 24 hours to ≤ 3 weeks apart and prior to randomization. The distance walked must be within 15% on two tests.
9. If one of the first two tests is not ≥ 150 m or the first two tests are not within 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. If the third test is still not ≥ 150 m or within 15% of one of the first two tests, the subject will not be eligible for participation.
10. Must have NT-proBNP levels ≥ 300 pg/mL at Screening.
11. Must have LV wall (interventricular septum or LV posterior wall) thickness ≥ 12 mm as measured by transthoracic echocardiogram (ECHO) or cardiac magnetic resonance (CMR) documented in medical history within 10 years of Screening or at Screening ECHO or CMR.

3.3.2. Exclusion Criteria

Subjects who meet any of the following criteria at the Screening visit will not be eligible to participate in the study:

12. Acute myocardial infarction, acute coronary syndrome or coronary revascularization within 90 days prior to Screening.
13. Stroke or transient ischemic attack (TIA) within 90 days prior to Screening.
14. Has hemodynamic instability at Screening or Randomization that, in the judgment of the Investigator, would pose too great a risk for participation in the study.
15. Is likely to undergo heart transplantation within a year of Screening.
16. Has confirmed diagnosis of light-chain (AL) amyloidosis.
17. Has abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3× upper limit of normal (ULN) or total bilirubin > 3× ULN.
18. Has NT-proBNP levels ≥ 8500 pg/mL at Screening.

19. Has estimated glomerular filtration rate (eGFR) by modification of diet for renal disease (MDRD) formula < 15 mL/min/1.73 m^2 at Screening.
20. Known hypersensitivity to IMP (acoramidis or placebo), its metabolites, or formulation excipients.
21. Treatment for ATTR-CM with tafamidis, with marketed drug products lacking a labeled indication for ATTR-CM (e.g., diflunisal, doxycycline), or with natural products or derivatives used as unproven therapies for ATTR-CM (e.g., green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol) within 14 days prior to dosing; treatment with patisiran, inotersen, or other gene silencing agent: within 90 days for patisiran, 180 days for inotersen, and 5 half-lives for any other gene silencing agent, prior to dosing.
22. If, during participation in the study, subjects gain access to tafamidis, they will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy.
23. Requires treatment with calcium channel blockers with conduction system effects (e.g., verapamil, diltiazem). The use of dihydropyridine calcium channel blockers is allowed. The use of digitalis will only be allowed if required for management of atrial fibrillation with rapid ventricular response.
24. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before IMP is administered. A negative urine pregnancy test at Screening and at Randomization are required for female subjects of childbearing potential.
25. In the judgment of the Investigator or Medical Monitor, has any clinically important ongoing medical condition or laboratory abnormality or condition that might jeopardize the subject's safety, increase their risk from participation, or interfere with the study.
26. Participation in another investigational clinical trial within 30 days prior to dosing with potential residual effects that might confound the results of this study. Participation in observational and/or registry studies should be discussed with the Medical Monitor.
27. Has any condition that, in the opinion of the Investigator or Medical Monitor, would preclude compliance with the study protocol such as a history of substance abuse, alcoholism or a psychiatric condition.

3.4. Discontinuation of Subjects from Therapy or Withdrawal from the Study

Subjects have the right to discontinue IMP or discontinue/withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The Investigator can discontinue a subject from IMP or withdraw a subject from the study at any time prior to study completion.

Reasons for discontinuation of IMP or/and withdrawing from the study prior to Month 30 include but not limited to:

- AEs

  - Note 1: If considered necessary, as per Investigator's discretion, IMP may be interrupted (e.g., in case of AE, hospitalization or procedure), however IMP should be resumed as soon as practically possible, unless there are safety concerns. Investigators are encouraged to discuss such cases with a Medical Monitor.
  - Note 2: If a subject prematurely discontinues from the IMP because of an AE, the study center personnel must record the AE as the reason for discontinuation. (An AE that occurs more than 30 days after the last dose of IMP is not considered a treatment-emergent adverse event [TEAE].)
- Death
- Protocol deviation(s)
- If it is discovered after randomization that the subject did not meet protocol entry criteria, and continued participation would present unacceptable risk to subject's health
- Non-compliance with study treatment or protocol procedures
- Subject's decision to discontinue study drug or withdraw from the study assessments.
- Withdraw of consent
  - Note 3: Subjects may withdraw consent at any time for any reason without prejudice to future treatment. In the event of withdrawal of consent, the ET procedures should occur as a final visit. Note: All participating subjects will be asked to consent to determination of vital status (dead, alive, heart transplant, receiving CMAD) at 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.
  - Note 4: Withdrawal of consent should be distinguished from discontinuation of IMP. Subjects who discontinue IMP permanently will receive phone calls as specified by the protocol to assess vital status, heart transplant or CMAD implantation.
- Received heart or liver transplant or received CMAD at any time during the trial
- Need for medications prohibited during the study
- Lost to follow-up
- Pregnancy at any time after signing the ICF. Study therapy should be discontinued immediately, and pregnancy reported (Section 3.11.6)
- Study terminated by Sponsor
- Site closed by Sponsor
- Subject's treatment assignment unblinded to the Investigator (Section 3.7.9)

All dosed subjects who prematurely discontinue from the IMP permanently or discontinue/withdraw from the study, regardless of cause, will be asked to complete an Early Termination (ET) Visit and a safety follow up visit 30 days after the last dose (Schedule of Assessments [SoA], Appendix A).

A safety follow-up visit 30 days post last dose per SoA will be conducted. If a subject is refusing to come into the study center for an ET Visit, or who cannot be reached must be requested in writing to come into the study center and to return any unused IMP. A copy of the registered letter will be kept by the study center with source documentation.

For subjects who refused to come in for a safety follow-up 30 days after the last dose, a phone call to document the adverse events should be made.

Reason for permanent discontinuation of IMP (end of treatment) and/or withdrawal from the study will be recorded on the appropriate CRF(s). Investigator should evaluate the possible contribution of an adverse event to permanent discontinuation of IMP. In this case, adverse event information will be documented accordingly in the CRF.

In subjects who permanently discontinued IMP, every effort should be made to continue monthly phone contacts for vital status for subjects who discontinue IMP for up to Month 30 by completing monthly contact for vital status or until withdrawal of consent.

Vital status will be determined for all subjects at 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 through public records may not be withdrawn.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If allowed by law, samples that have already been collected may continue to be stored and used to meet legal and regulatory obligations.

3.4.1. Lost to Follow-Up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a registered letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, he/she may be considered to have withdrawn from the study.

3.5. Contraception and Pregnancy Avoidance

Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use a highly effective method of contraception (CTFG guidance v.1.1) beginning with randomization and continuing for 30 days after the last dose of IMP as follows:

- If heterosexually active, must be using a highly effective method of birth control such as hormonal oral contraceptives, intravaginal hormonal contraceptive, contraceptive injections/implant, contraceptive patch, intrauterine device, or bilateral tubal occlusion before subject randomization and must agree to continue to use a highly effective method of birth control throughout the study and for 30 days after the last dose of IMP, consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies.
- Female subjects using oral contraceptives must agree to use an additional birth control method.
- While not considered highly effective, a double-barrier method (e.g., condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel) is acceptable.
- Not heterosexually active (practices complete abstinence). Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire study and for 30 days after the last dose of IMP.

A female subject is considered of childbearing potential (i.e., fertile), following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and has to be confirmed with plasma follicle-stimulating hormone (FSH).

Subjects will be provided with information on method(s) of contraception acceptable for the study as a part of informed consent and will confirm that they understand the requirement to avoid pregnancy during the study and continuing for 30 days after the last dose of IMP.

Pregnancy tests will be performed during the study according to the Schedule of Assessments (Appendix A), and subjects will receive guidance on avoidance of pregnancy throughout the study. Subjects will be instructed to contact their physician immediately if they become pregnant or suspect they may be pregnant. Subjects who become pregnant during the study will be withdrawn from study therapy, and their pregnancy will be followed to term (Section 3.11.6)

A male subject who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a double-barrier method of birth control such as a condom with spermicidal foam/gel/cream.

If a male subject's partner becomes pregnant any time between the start of IMP and 30 days after the last dose, the male subject must inform the Investigator as soon as possible. Follow-up information regarding the outcome of the pregnancy and any post-natal sequelae in the infant will be required.

Study subjects should be reminded at the study visits regarding consistent and correct use of protocol-specified contraception methods.

3.6. End of Study Definition

The end of the study for reporting purposes is defined as the latest date of the following: last visit of the last subject or the last vital status assessment of the last subject in the study globally.

Subjects are considered to have completed the study if they have completed all periods of the study including the follow-up period, except for subjects who enroll in Study AG10-304 on the same day as the Month 30 visit in Study AG10-301. Completion of the follow-up period is defined as completion of the follow-up visit 30 days after the last dose of IMP. Subjects who enroll in Study AG10-304 on the same day as the Month 30 visit in Study AG10-301 will be considered to have completed the study when they have completed the double-blind treatment period including the Month 30 visit.

3.7. Treatments

3.7.1. Treatments Administered

Subjects who meet eligibility criteria listed in Section 3.3 will be randomized in a 2:1 manner (acoramidis:placebo) to receive the following treatment arms in a double-blind fashion:

- 800 mg acoramidis hydrochloride (HCl) BID, orally (two 400 mg acoramidis HCl tablets (equivalent to 356 mg acoramidis), BID)
- Matching placebo BID, orally (two matching placebo tablets, BID)

3.7.2. Identity of Investigational Products

Acoramidis HCl tablets (400 mg) and matching placebo tablets will be supplied by Eidos Therapeutics, Inc. The excipients of acoramidis HCl (400 mg) tablets or matching placebo tablets include microcrystalline cellulose, croscarmellose sodium, silicon dioxide, lactose monohydrate, and magnesium stearate, coated with Opadry.

3.7.3. Packaging

The IMP will be provided as blinded randomized kits assigned to subjects using a randomization code. The kits will be labeled as required by regulations in the countries where the trial is being performed.

Full details regarding IMP packaging are provided in the Investigator's Brochure and Pharmacy Manual.

3.7.4. Storage, Dispensing, and Return of Investigational Product

The Sponsor will provide the study center with IMP supplies. Full details regarding IMP storage are provided in the Pharmacy Manual.

The site research pharmacist or delegated personnel will maintain an accurate record of the receipt of the IMP shipped by the Sponsor, including the date and quantity received. In addition, an accurate drug accountability record will be kept that specifies the amount of IMP, date dispensed to each subject, amount of IMP, and date returned by the subject. This inventory record must be available for inspection at any time, and copies of this record will be provided to the Sponsor at the conclusion of the study.

It is the Investigator's responsibility to ensure that subjects return their unused IMP at each visit. All unused IMP must be returned to the Sponsor or destroyed on-site throughout the course of the study after IMP accountability is completed and with approval by the Sponsor. If unused IMP

is not returned to the Sponsor and destroyed on-site, proof of destruction must be provided to the Sponsor.

3.7.5. Method of Assigning Subjects to Treatment Groups

Screening numbers will be assigned consecutively (e.g., 1, 2, 3,…) through an Interactive Web Response System (IWRS) portal after the subject signs the ICF. Subjects who meet eligibility criteria will be randomized using permuted blocks into the study and assigned a unique subject number through the IWRS. Subjects will be stratified at randomization based on whether they have ATTRm-CM or ATTRwt-CM with a targeted minimum of 20% of subjects with ATTRm-CM. Subjects 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.

3.7.6. Selection of Dosages in the Study

The acoramidis HCl dose of 800 mg chosen for this study is based on nonclinical PK studies, data from the Phase 1, first-in-human, single ascending dose (SAD) and multiple ascending dose (MAD) Study AG10-001 conducted in healthy adult volunteers, and the Phase 2, repeat dose, dose-ranging, safety, tolerability, PK and PD Study AG10-201 in ATTR-CM subjects with NYHA Class II-III heart failure. Further details on these studies can be found in the acoramidis Investigator's Brochure.

3.7.7. Selection and Timing of Dose for Each Subject

Dosing should be administered BID, once in the morning and once in the evening. Acoramidis can be taken with or without food. Additional information on dosing instructions can be found in the study Pharmacy Manual.

3.7.8. Blinding

Blinding of study treatment is critical to the integrity of this clinical trial and every effort will be made to protect the blind. If a subject's treatment assignment is disclosed to the Investigator, the subject will have study treatment discontinued (Section 3.4). The Sponsor or a designated safety representative may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

However, regardless of any unblinding, accidental or due to Investigator request in the context of an AE, all subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject (see Section 3.4). Note: all participating subjects will be asked to consent to determination of vital status (e.g., alive, death, heart transplant, receiving CMAD) at 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 through public records may not be withdrawn.

Blinding for Part A and Part B

Analysis for Part A will be performed by a team within an independent data reporting center who will be unblinded after the last enrolled subject in Part A has completed 12 months of treatment. Subject level CV-related hospitalizations data will not be available to the Sponsor Part A team;

however, the aggregated overall summary without treatment group information may be available to the Sponsor Part A team.

A separate Part B team within the independent data reporting center will remain blinded to Part A subject level data prior to and following unblinding of Part A.

Blinding to individual subject treatment allocation will be maintained for the subjects, Investigators, Clinical Events Committee (CEC), and Sponsor designated site monitoring personnel throughout the study to completion. The operational details of maintaining the blind and data access will be described and the process will be governed by a Data Access Management Plan.

3.7.9. Emergency Unblinding

Unblinding by Investigator should occur only if the knowledge of IMP assignment is required to enable urgent clinical decision making. In this situation, the decision to unblind a subject's treatment assignment rests with the Investigator who has access to IWRS treatment assignment. The Investigator should attempt to contact the Medical Monitor (or designee) to discuss options prior to unblinding, unless the urgency of the subject's medical situation prevents this. Detailed instructions for IMP unblinding will be provided in a Study Procedures Manual. In the event of emergency unblinding of a subject's IMP assignment, a full written explanation of events requiring IMP unblinding should be provided to the Medical Monitor within 24 hours of occurrence.

3.7.10. Prior and Concomitant Therapy

At all visits, study center personnel will ask each subject specifically about all prior and concomitant medications and record the medication, dosage, and duration of use in the appropriate CRF.

3.7.11. Prohibited Medications

- Use of patisiran, inotersen, tafamidis (see Note below) or any other approved or investigational agent for the treatment of ATTR-CM is prohibited during the study.
- Use of marketed drug products lacking a labeled indication for ATTR-CM (e.g., diflunisal, doxycycline) or of natural products or derivatives used as unproven therapies for ATTR-CM (e.g., green tea extract, tauroursodeoxycholic acid [TUDCA]/ursodiol) is prohibited.
- Use of calcium channel blockers with conduction system effects (e.g., verapamil, diltiazem) is prohibited. Use of dihydropyridine calcium channel blockers is allowed. The use of digitalis will only be allowed if required for management of atrial fibrillation with rapid ventricular response.

Note: If, during participation in the study, tafamidis becomes available for the indication of ATTR-CM and subjects have access to it, subjects will be permitted to initiate therapy with tafamidis as a concomitant medication if they have completed at least 12 months of blinded study therapy. (Currently, tafamidis is approved for the treatment of ATTR-CM in some regions.) Subjects initiating therapy with tafamidis indicated for ATTR-CM must have

completed the Month 12 visit. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, they should have an unscheduled visit with study assessments prior to initiation of the concomitant therapy.

3.7.12. Treatment Compliance

IMP compliance will be closely monitored by counting the amount of IMP dispensed and returned at each study visit. Before dispensing new IMP at each visit, study center personnel will make every effort to collect all unused IMP.

3.8. Study Procedures

3.8.1. Schedule of Assessments

The schedule of study procedures and assessments are tabulated by study day in the Schedule of Assessments in Appendix A. The descriptions of the procedures to be performed throughout the study are provided below.

3.8.2. Screening (Day -35 to Day -1)

Screening will be performed within ≤ 35 days before administration of the first dose of IMP. The following procedures will be performed at Screening:

- Informed consent administration
- Review Inclusion/Exclusion criteria to confirm subject is eligible
- Confirm genotype either through existing documentation or testing during Screening. Genotyping must be confirmed prior to randomization.
- Submission of source documents required for the Diagnostic Confirmation Committee (DCC) should be completed as early as possible during the Screening period and must include either:
  - endomyocardial biopsy report with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry;

    OR
  - positive ^{99m}Tc-PYP or -bisphosphonate (DPD or HMDP/HDP) scan,
  - AND clinical laboratory evidence excluding the diagnosis of AL amyloidosis (based on both IFE of serum and urine, and sFLC analysis);
  - Subjects with concurrent MGUS may require confirmation of the diagnosis of ATTR-CM by tissue biopsy with confirmatory TTR amyloid typing by either mass spectrometry, immunoelectron microscopy, or immunohistochemistry.
- Medical and surgical history assessment
- NYHA Class assessment (Appendix F)

- Physical examination including body weight and height measurements (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- Resting transthoracic ECHO or CMR, if LV wall (interventricular septum or LV posterior wall) thickness not documented in medical history within 10 years of Screening based on ECHO or CMR (Section 3.3)
- 6MWT, two assessments > 24 hours to ≤ 3 weeks apart. If one of the first two tests is not ≥ 150 m or the first two tests are not within 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. If the third test is still not ≥ 150 m or within 15% of one of the first two tests, the subject will not be eligible for participation (Section 3.10.1)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Blood sample collection for serum and plasma exploratory tests
- Urine pregnancy test, for female subjects of childbearing potential only
- Prior and concomitant medication use assessment

3.8.3. Treatment Days

Study procedures are listed below by study day, ideally performed in the order listed below, for each day.

Screening safety assessments completed on the same day as Day 1 (e.g., physical exam, vital signs, ECG, clinical laboratory tests) may be used as Day 1 assessments at the investigator's discretion provided that they are predose.

3.8.4. Day 1 and Repeated Assessments

These assessments will occur in-clinic at Day 1 and Months 3, 6, 9, 15, 18, 21, 24, and 27 (±7 Days):

- Review Inclusion/Exclusion criteria to confirm subject is eligible (Day 1)
- Randomize subject to treatment arm and assign randomization number (Day 1)
- NYHA Class assessment (Appendix F)
- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- KCCQ (Schedule of Assessments in Appendix A and Section 3.10.2)
- EQ-5D-5L (Schedule of Assessments in Appendix A and Section 3.10.3)

- 6MWT (Schedule of Assessments in Appendix A and Section 3.10.1)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- PD blood sample collection for analysis of TTR stabilization (predose) in PK-PD substudy (Section 3.9.2)
- PK blood sample collection (predose) in PK-PD substudy (Section 3.9.1)
- Prealbumin blood sample collection (predose) (Section 3.9.3)
- Dispense/collect and administer IMP with designated witness (i.e., site personnel)
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- IMP compliance assessment (all visits except Day 1)

3.8.5. Day 28 (±3 Days)

- NYHA Class assessment (Appendix F)
- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG at predose (in a supine position after a 5-minute rest) and at 1-hour postdose (Section 3.11.10)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- PD blood sample collection for analysis of TTR stabilization (predose and at 1-hour postdose) in PK-PD substudy (Section 3.9.2)
- PK blood sample collection (predose and at 1-hour postdose) in PK-PD substudy (Section 3.9.1)
- Prealbumin blood sample collection (predose) (Section 3.9.3)
- Dispense/collect and administer IMP with designated witness (i.e., site personnel)
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- IMP compliance assessment

3.8.6. Month 12 (±7 Days)

- NYHA Class assessment (Appendix F)

- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- KCCQ (Section 3.10.2)
- EQ-5D-5L (Section 3.10.3)
- 6MWT (Section 3.10.1)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- PD blood sample collection for analysis of TTR stabilization (predose) in PK-PD substudy (Section 3.9.2)
- PK blood sample collection (predose) in PK-PD substudy (Section 3.9.1)
- Prealbumin blood sample collection (predose) (Section 3.9.3)
- Dispense/collect and administer IMP with designated witness (i.e., site personnel)
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- IMP compliance assessment

3.8.7. Monthly Telephone Contact (±7 Days)

These telephone contacts will occur during months without scheduled in clinic visits (e.g., Months 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, and 29):

- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- IMP compliance assessment

Subjects who discontinue IMP may be asked to continue monthly phone contacts and determination of vital status at Month 30.

3.8.8. Month 30 (±7 Days)

- NYHA Class assessment (Appendix F)
- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- KCCQ (Section 3.10.2)

- EQ-5D-5L (Section 3.10.3)
- 6MWT (Section 3.10.1)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- PD blood sample collection for analysis of TTR stabilization (predose) in PK-PD substudy (Section 3.9.2)
- PK blood sample collection (predose) in PK-PD substudy (Section 3.9.1)
- Prealbumin blood sample collection (predose) (Section 3.9.3)
- Collect IMP with designated witness (i.e., site personnel)
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- IMP compliance assessment

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). Subjects who are planning to enroll in Study AG10-304 should take the evening dose of IMP the day before the Month 30 visit and should not take the morning dose on the day of the Month 30 visit.

3.8.9. Unscheduled Visit

Unscheduled visits can be performed at any time during the study according to the Investigator's judgment (e.g., if needed to assess or to follow up on an AE) or prior to initiation of tafamidis for ATTR-CM in subjects who complete at least 12 months of the study and the Month 12 visit study assessments. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, they should have an unscheduled visit with study assessments prior to initiation of the concomitant therapy.

For any unscheduled visit, the date and reason for the unscheduled visit must be recorded in the source documentation, concomitant medications reviewed, and adverse events evaluated.

If the unscheduled visit is for assessment or follow up of an AE, only procedures and assessments deemed necessary by the Investigator (e.g., physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test) need to be conducted. Other procedures (e.g., KCCQ, EQ-5D-5L, 6MWT) may not be needed.

Any subject initiating therapy with tafamidis for the treatment of ATTR-CM and remaining in the trial must have completed the Month 12 visit. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, they should have an unscheduled visit with study assessments performed prior to initiation of tafamidis including but not necessarily limited to:

- NYHA Class assessment (Appendix F)

- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- KCCQ (Section 3.10.2)
- EQ-5D-5L (Section 3.10.3)
- 6MWT (Section 3.10.1)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- PD blood sample collection for analysis of TTR stabilization (predose) in PK-PD substudy (Section 3.9.2)
- PK blood sample collection (predose) in PK-PD substudy (Section 3.9.1)
- Prealbumin blood sample collection (predose) (Section 3.9.3)
- Dispense/collect and administer IMP with designated witness (i.e., site personnel)
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- IMP compliance assessment

3.8.10. Follow-up 30 days After Last Dose of IMP (± 7 Days)

Subjects who complete the Month 30 visit will have a visit 30 days (± 7 days) after the last dose of IMP. 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). The following procedures will be performed:

- NYHA Class assessment (Appendix F)
- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- Blood sample collection for hematology, serum chemistry, urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)

Any clinically relevant findings obtained during the final examination, including clinically relevant laboratory abnormalities and the manner in which they are treated, will be followed until

the condition returns to pre-study status, has resolved or stabilized, or has been determined to be unrelated to the IMP.

3.8.11. Early Termination (ET)

All dosed subjects who prematurely discontinue study treatment permanently and/or discontinue/withdraw from the study, regardless of cause, will be asked to complete the ET Visit (Section 3.4) including the following assessments and procedures:

- NYHA Class assessment (Appendix F)
- Physical examination including body weight measurement (Section 3.11.11)
- Vital signs assessment (Section 3.11.9)
- 12-lead resting ECG (in a supine position after a 5-minute rest) (Section 3.11.10)
- KCCQ (Section 3.10.2)
- EQ-5D-5L (Section 3.10.3)
- 6MWT (Section 3.10.1)
- Blood sample collection for hematology, serum chemistry (including circulating biomarkers), urinalysis (Section 3.11.8)
- Urine pregnancy test, for female subjects of childbearing potential only
- PD blood sample collection for analysis of TTR stabilization (predose) in PK-PD substudy (Section 3.9.2)
- PK blood sample collection (predose) in PK-PD substudy (Section 3.9.1)
- Prealbumin blood sample collection (predose) (Section 3.9.3)
- Concomitant medication use assessment
- AE/Vital status assessment/Hospitalization determination (Section 3.4)
- Collect unused IMP
- IMP compliance assessment

If a subject discontinues IMP or discontinues/withdraws from the study, subjects will be asked to complete an ET visit and associated assessments and procedures. All participating subjects will be asked to consent to determination of vital status (e.g., alive, death, heart transplant, receiving CMAD) at 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 through public records may not be withdrawn (refer to Section 3.4 for further details).

3.9. Drug Concentration Measurements

3.9.1. PK Blood Draw Schedule

In a subgroup of subjects at participating sites, PK samples will be collected at the following times to determine acoramidis plasma concentrations:

- Day 1: Predose
- Day 28: Predose and 1-hour postdose
- Months 3 - 27: Predose
- Month 12: Predose
- Month 30: Predose
- ET
- Unscheduled visit (e.g., Investigator's discretion)

3.9.2. PD Blood Draw Schedule

In a subgroup of subjects at participating sites, PD properties of acoramidis will be assessed by established assays of TTR stabilization, including fluorescent probe exclusion (FPE) assay and Western blot. Sampling will be done at the following times to perform these PD assays:

- Day 1: Predose
- Day 28: Predose and 1-hour postdose
- Months 3 - 27: Predose
- Month 12: Predose
- Month 30: Predose
- ET
- Unscheduled visit (e.g., Investigator's discretion)

3.9.3. Prealbumin Blood Sampling Procedures

To measure prealbumin concentrations, blood sampling will be done at the following times:

- Day 1: Predose
- Day 28: Predose
- Months 3 - 27: Predose
- Month 12: Predose
- Month 30: Predose
- ET
- Unscheduled visit (e.g., Investigator's discretion)

3.10. Efficacy Assessments at Scheduled Visits

For details on timings, refer to the Schedule of Assessments in Appendix A.

3.10.1. Six-Minute Walk Test (6MWT)

Prior to randomization, two 6MWTs will be conducted > 24 hours to ≤ 3 weeks apart. The walking distances must be ≥ 150 meters and the distance walked must be within 15% on two tests on different days. If one of the first two tests is not ≥ 150 m or the first two test results are not within the 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. If the third test is still not ≥ 150 m or within 15% of one of the first two tests, the subject will not be eligible for participation.

If the subject has a need for a walking aid (e.g., cane) or supplemental oxygen at baseline, it must be used consistently at each subsequent 6MWT throughout the study. If a subject develops a need for a walking aid (e.g., cane) or supplemental oxygen after baseline, it must be used consistently at each subsequent 6MWT throughout the study.

The 6MWT should be conducted after completion of the KCCQ and EQ-5D-5L at the visits where required.

The 6MWT with Borg Scale will be conducted based on the guidelines of the American Thoracic Society with appropriate modifications for the subject population. Complete details on the procedures for the 6MWT are provided in a Study Procedures Manual.

3.10.2. Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item questionnaire developed to measure health status and health-related quality of life (QoL) in subjects with heart failure. Items include heart failure symptoms, impact on physical and social functions, and how their heart failure impacts their quality of life. It should be completed by the subject at predose. Complete details are provided in a Study Procedures Manual.

3.10.3. EuroQoL 5-Dimensions 5-Level Health Outcomes Assessment (EQ-5D-5L)

EQ-5D-5L is a brief, self-administered generic health status instrument that takes about 5 minutes to complete and 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 EuroQol-Visual Analog Scale (EQ 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 administration and scoring are provided in a Study Procedures Manual.

3.11. Safety Assessments

Subjects must be seen by a physician or an appropriately trained health professional at every in-clinic visit. The evaluation must be documented. The procedures discussed in this section will be assessed at every in-clinic visit beginning from the time the subject signs the ICF. The clinical relevance of any abnormal findings found in the physical examination, clinical laboratory evaluations, vital sign assessments, and ECGs must be evaluated and documented by the Investigator. For clinical laboratory tests, the Investigator will assess and document the clinical relevance of any values outside the reference ranges provided by the clinical laboratory.

3.11.1. Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an IMP and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A).

It is the responsibility of the Investigator to document all AEs that occur during the study. AEs should be elicited by asking the subject a nonleading question (e.g., “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). AEs will be reported on the AE CRF.

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 (refer to Section 3.11.5 or further details).

Examples of AEs are as follows:

- Changes in the general condition of the subject that represents a decline in health or functional status
- Symptoms offered by or elicited from the subject
- Objective signs observed by the Investigator or other study personnel
- All diseases that occur after the start of the study, including a worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition. Any medical condition present at Screening and which does not deteriorate should not be reported as an AE. However, any pre-existing medical condition that deteriorates during the study should be reported as an AE.

An AE does not include:

- A medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion); an AE is the underlying condition that leads to the procedure
- Pre-existing diseases or conditions present or detected before start of IMP administration that do not worsen or increase in severity or frequency after the administration of IMP

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a patient)
- Overdose of either IMP or concomitant medication without any signs or symptoms

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and not the individual signs/symptoms. If a diagnosis is not available, the sign/symptom may be reported as the AE.

All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study should be reported as an AE. A clinically relevant laboratory value or physical finding is one associated with signs and symptoms and/or requires medical intervention.

3.11.2. Causality Assessment

The Investigator must assess the relationship of the event to the IMP. The causal relationship of the AE is assessed using a binary system, and AEs are classified as either 'Related' or 'Not Related' as defined below.

Related: The available evidence suggests the adverse event is most likely due to the IMP. For example, a temporal relationship exists between the AE onset and administration of the IMP that cannot be readily explained by the subject's clinical state, concurrent disease or concomitant therapies.

Not related: The available evidence suggests the adverse event is most likely related to factors other than the administration of the IMP. Such other factors may include the underlying disease state, comorbidities, an intercurrent illness, concomitant medication(s) or procedures.

The causality assessment evaluates the likelihood that the event was caused by the drug, the underlying disease, comorbidities, intercurrent illness or other factors, and determines which factor is the most likely cause of the event. Causality assessment is not an assessment of whether or not the study drug can be ruled out.

The Investigator must assess and report the relationship of an SAE to the IMP within 24 hours of when the site first becomes aware of the event.

The Investigator may change the causality assessment at any time based on new accumulated information.

An AE with causal relationship not initially determined will require follow-up to assign causality.

3.11.3. Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's CRF. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a subject

outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

3.11.4. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening; i.e., in the opinion of the Investigator, the AE places the subject at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Results in subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Results in a 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

Emergency room visits that do not result in hospitalization should be evaluated for one of the other seriousness outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (e.g., elective procedures for preexisting conditions that did not worsen) are excluded from SAE reporting.

Note that death is an outcome of an AE and not an AE in itself. The event that was the proximate cause of death should be reported as the AE term.

3.11.5. Reporting Adverse Events and Serious Adverse Events

Any untoward event that is reported from the time that the subject signs the ICF until 30 days after the last dose of IMP must be collected. Thus, any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment,

treatment, or posttreatment period are to be considered AEs (and SAEs if appropriate), and consequently recorded and reported as such.

Subjects are to be queried regarding any AEs or SAEs at the time of each vital sign assessment, as well as at each visit, according to the Schedule of Assessments (Appendix A). Subjects will be asked to volunteer information with a nonleading question such as, "How do you feel?" Study center personnel will then record all pertinent information in the subject's CRF.

All AEs and SAEs reported by the subject (or subject representative) or observed or otherwise identified by the Investigator (or other study center personnel) at a defined study visit or during any communication with the subject (or subject representative) occurring outside a defined study visit (from the time the subject signs the ICF to 30 days after the last dose of IMP) must be documented.

All AEs must be recorded on the appropriate AE reporting page of the subject's CRF whether or not they are considered causally related to the IMP.

For every AE, the Investigator must:

- Provide an assessment of the severity, causal relationship to the IMP, and seriousness of the event (i.e., whether it is an SAE)
- Document all actions taken with regard to the IMP
- Detail any other treatment measures taken for the AE
- Document outcome of the AE (with or without sequelae); ongoing; or lost to follow-up.

3.11.6. Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time a female subject signs the ICF until 30 days after the last dose of IMP. Within 24 hours of learning of the pregnancy, study center personnel must report the event to the Sponsor on the Clinical Trial Pregnancy Form, even if no AE has occurred.

The pregnancy must be followed to term and the outcome reported by completing a follow-up Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (e.g., if the female subject is hospitalized for hemorrhage), a separate SAE Form must be completed (in addition to the Pregnancy Form) as described in Section 3.11.6, with the appropriate serious criterion (e.g., hospitalization) indicated.

In the event that a female subject becomes pregnant, the Investigator is required to contact the Medical Monitor within 24 hours of awareness.

If a female subject becomes pregnant, administration of the IMP must be discontinued immediately.

If a male subject's partner becomes pregnant any time between the start of acoramidis and 30 days after the last dose, the study investigator should be informed as soon as possible. Completion of the "Pregnant Partner ICF" will be requested at that time. Follow-up information regarding the outcome of the pregnancy will be requested.

3.11.7. Immediate Reporting of Serious Adverse Events and Events of Clinical Interest

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to the Sponsor or its designated representative on the SAE Form.

In addition, SAEs that are assessed by the Investigator as related to IMP and occurring after 30 days post the last dose of IMP will also be reported to the Sponsor within 24 hours of when the site first becomes aware of the event.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center personnel must transmit the SAE Form to the Sponsor within 24 hours of when the site first becomes aware of the event. Even if the site has discussed the event with a Sponsor representative, the study center personnel must complete the SAE Form with all available details and transmit the form within 24 hours of when the site first becomes aware of the event. Supplemental information related to the SAE shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary to treat and promote resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the subject's CRF. The study center personnel must follow all SAEs until resolution or until the SAE is deemed stable. The Sponsor may contact the study center to solicit additional information or follow-up on the event.

A 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).

Events of clinical interest (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. EOCI are considered as part of the efficacy endpoint of CV-related hospitalizations.

Mortality, heart transplant, CMAD, and CV-related hospitalizations are endpoints for Part B of the trial but the events that lead to death or hospitalization will be reported as Serious Adverse Events on the SAE Form to the Sponsor throughout the trial.

The Investigator is responsible for ensuring potential study endpoints, including dates of admissions and discharge, are collected and well documented for adjudication purposes (this includes but is not limited to: admission notes describing signs and symptoms, cardiology or other relevant clinical notes, hospital discharge summary); for providing Investigator assessment whether the hospitalization is CV-related; and for submitting the SAE Form for all AEs that result in deaths or hospitalizations.

CV-related hospitalizations and events of clinical interest will not be included in periodic safety reporting and may not require expedited safety reporting to regulatory authorities and Investigators (unless requested by a regulatory authority or an IRB/IEC/REB) because they will be anticipated due to the nature of the disease under study. These events will be adjudicated by an independent Clinical Events Committee (CEC) and reviewed cumulatively and individually (as needed) by an independent Data Monitoring Committee (DMC) and analyzed as primary endpoints for Part B. Hospitalizations that are submitted for adjudication and are deemed as not CV-related by the CEC will be considered SAEs. EOCI that are submitted for adjudication and are deemed as not CV-related by the CEC will be considered AEs or SAEs (for EOCIs that meet criteria for seriousness other than hospitalization).

Email all SAE or pregnancy report forms to the Sponsor at the following email address:

Email for SAEs and pregnancy: [redacted]

For questions on SAE or pregnancy reporting contact the above email address.

If email is not possible, send via fax:

US fax: [redacted]

EU fax: [redacted]

3.11.8. Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the times detailed in the Schedule of Assessments (Appendix A). At Screening, the Investigator will assess the clinical relevance of any values outside the reference ranges provided by the laboratory, and subjects with abnormalities judged to be clinically relevant will be excluded from the study. Additional information on laboratory tests performed can be found in the supplementary Laboratory Manual.

The following clinical laboratory tests will be performed:

Hematology	Hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, complete blood count (CBC), and differential
Chemistry	Sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, prealbumin, retinol-binding protein (RBP), free thyroxine (FT4), alkaline phosphatase, calcium, phosphorus, total and fractionated (indirect or direct) bilirubin, uric acid, thyroid-stimulating hormone (TSH), troponin I, creatine kinase (CK), creatine kinase-MB fraction (CK-MB), and NT-proBNP
Urinalysis	Complete urinalysis (specific gravity, pH, glucose, protein, hemoglobin, leukocyte esterase, and nitrite). Additionally, albumin to creatinine ratio and a microscopic urinalysis will be performed on every specimen and will specifically look for casts, bacteria, white blood cells, epithelial cells, and red blood cells
Others	FSH only to confirm post-menopausal status at Screening in female subjects who do not have menses for at least 12 months and are not using hormonal contraception or hormone replacement therapy (Section 3.5).
Pregnancy test	Highly sensitive urine test at all visits as outlined in the Schedule of Assessments (Appendix A) (female subjects of childbearing potential only)

Samples will be collected, processed, and stored according to the instructions provided in the supplementary Laboratory Manual.

Clinical laboratory test data will be reviewed by the Investigator or qualified Sub-Investigator. If the test is considered inaccurate based on the subject's medical history or is an error from the Central Laboratory, clinical laboratory tests may be repeated at the Investigator's or qualified Sub-Investigator's discretion.

The Investigator or qualified Sub-Investigator will review all laboratory results for clinical relevance. Any laboratory result deemed clinically relevant (e.g., is associated with signs and symptoms and/or requires medical intervention) will be recorded as an AE as described in Section 3.11.1.

3.11.9. Vital Signs

Vital signs will be assessed at the times detailed in the Schedule of Assessments (Appendix A). Study center personnel will assess vital signs predose after a 5-minute rest. The investigator will determine whether abnormal vital signs are clinically relevant. Any abnormal vital sign that is deemed clinically relevant by the Investigator (e.g., is associated with symptoms and/or requires medical intervention) will be recorded as an AE as described in Section 3.11.1.

3.11.10. Electrocardiograms

A standard 12-lead ECG will be assessed at the times detailed in the Schedule of Assessments in Appendix A. ECGs will be performed in the supine position after a 5-minute rest at predose and 1-hour postdose on Day 28.

The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical relevance. Any ECG interpretation deemed to be clinically relevant (e.g., is associated with symptoms and/or requires medical intervention) will be reported as an AE as described in Section 3.11.1.

3.11.11. Physical Examinations

At the times detailed in the Schedule of Assessments in Appendix A, subjects will undergo a complete physical examination (PE) including body weight and height measurements, which is to be completed by a physician or an appropriately trained health professional. Any abnormal physical examination finding that is deemed clinically relevant by the Investigator (e.g., is associated with symptoms and/or requires medical intervention) will be recorded as an AE as described in Section 3.11.1.

3.11.12. Definition of Cardiac Mechanical Assist Device, Cardiovascular-related Hospitalization and Events of Clinical Interest

In this study, CMAD and heart transplant are included in the "All-cause mortality" component of the primary endpoint for Part B, and therefore should be collected for all randomized patients even if they discontinued treatment permanently or withdrew consent (see also Section 3.4). CMAD is defined as a durable CMAD implanted in a patient with end-stage heart failure as a bridge to transplant or as a destination therapy. Temporary cardiac mechanical support (i.e., those interventions that can only be employed in the inpatient setting, e.g., Intra-Aortic Balloon Pump [IABP], Impella, or Extra-corporeal membrane oxygenation [ECMO]) are not considered CMAD. In addition, other cardiac interventions such as pacemaker, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG), valvular percutaneous intervention or surgery are not considered CMAD.

A 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 (Section 3.11.7) re 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. EOCI are considered as part of the efficacy endpoint of Part B CV-related hospitalizations.

The Investigator is responsible for ensuring potential study endpoints, including dates of admissions and discharge, are collected and well documented for adjudication purposes (this includes but is not limited to: admission notes describing signs and symptoms, cardiology or other relevant clinical notes, hospital discharge summary); for providing Investigator assessment

whether the hospitalization is CV-related; and for submitting the SAE Form for all AEs that result in deaths or hospitalizations (Section 3.11.7).

3.12. Study Committees

3.12.1. Data Monitoring Committee

An independent DMC will monitor the safety and conduct of the trial. The DMC will consist of clinical experts in cardiovascular disease, trial design and conduct, and biostatistics. The DMC's role and responsibilities, timing of meetings and the scope of analysis to be provided to the DMC are documented in an established and mutually agreed upon charter. The DMC may provide recommendations regarding stopping the study or modifying the study design or conduct. Sites will be informed of DMC recommendations only if the recommendations lead to changes in study conduct. Additional details regarding the responsibilities of the DMC and frequency of meetings will be described in the DMC Charter. Specifically, all safety data as well as mortality and CV-related hospitalizations will be monitored by the independent DMC, according to the DMC Charter, throughout the study.

3.12.2. Clinical Events Committee

An independent CEC will review and adjudicate EOCI, Investigator-reported events of death, heart transplant, CMAD, and CV-related hospitalizations to determine whether reason for EOCI, hospitalizations and/or cause of death, heart transplant, and CMAD, meet the definition of protocol-specified efficacy endpoints for Part B. Investigators will follow the SAE notification process (Section 3.11.7). Additional details regarding the responsibilities of the CEC will be described in the CEC Charter.

3.12.3. Diagnostic Confirmation Committee

An independent ATTR-CM DCC will review the evidentiary basis for the qualifying diagnosis of ATTR-CM (Inclusion Criteria, Section 3.3). Submission of documentation of diagnosis of ATTR-CM should be during Screening. Review by DCC may occur after randomization.

The committee will include experts in TTR and AL amyloidosis qualified in the interpretation of test data used to distinguish between TTR and AL amyloidosis.

The DCC will operate in accordance with its established charter.

3.13. Statistical Methods and Determination of Sample Size

3.13.1. General Considerations

All statistical summaries may be performed using SAS Version 9.2 [redacted] or higher, as specified in the Statistical Analysis Plan (SAP). Additional software may be used to produce graphics. PK parameters will be computed using Phoenix WinNonlin. Additional information regarding statistical analyses can be found in the SAP. Formal statistical testing will be at the 0.01 level for Part A and 0.04 for Part B unless noted otherwise.

Efficacy analyses will adjust for randomization stratification factors. Adjustments for additional covariates, if any, will be mentioned separately for different endpoints.

3.13.2. Determination of Sample Size

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.

Part A:

The primary endpoint of Part A is the change from baseline in the distance achieved in the 6MWT following 12 months of double-blind study treatment.

The sample size calculation for the primary endpoint in Part A is based on the following assumptions: two-sided alpha = 0.01, power = 0.9, normally distributed data per group, equal within group standard deviations. Based on the ATTR-ACT study (Maurer 2018), it is estimated that the between group mean change from baseline is 30 meters with an estimated within group standard deviation of 70 meters. Under these assumptions, with a t-test, a total sample size of approximately 365 subjects will provide 90% power to reject the null hypothesis of no mean difference between groups. To allow for the possibility that approximately 20% of subjects may not complete the Month 12 6MWT, and that approximately 10% of subjects will have baseline eGFR < 30 mL/min/1.73 m^2 the adjusted sample size is approximately 510 subjects (340 allocated to acoramidis and 170 allocated to placebo).

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 test). Simulations based on estimates of mortality and CV-related hospitalizations 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 hospitalizations 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 over a 30-month fixed treatment duration.

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%.

3.13.3. Timing of Analyses

Part A analyses will occur following the last subject completing the Month 12 visit. For Part B analyses, when final in-clinic visits and safety follow-up visits have been completed for all subjects and all data is entered, the database will be cleaned and locked, randomized treatment assignments will be obtained, and safety analyses will be performed.

3.13.4. Analysis Sets and Analysis Conventions

The modified intent-to-treat (ITT) population will be primary for efficacy endpoints. The ITT population is defined as all randomized subjects who have received at least one dose of IMP and have at least one post baseline efficacy evaluation. The modified ITT (mITT) population will exclude subjects with baseline eGFR < 30 mL/min/1.73 m^2. For both Parts A and B, the primary efficacy analysis will be performed on the mITT population. The per-protocol (PP) population will be secondary for the primary and key secondary endpoints. The PP population will include all subjects from the mITT set who did not have one of a pre-defined list of important protocol deviations. The list of subjects with one of these important protocol deviations will be identified prior to unblinding the Part A and Part B, respectively. For safety, the analysis population will include all subjects who received at least one dose of IMP.

Unless otherwise specified, baseline values are defined as the last measurement obtained before the first dose of IMP.

3.13.5. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment.

3.13.6. Extent of Exposure and Treatment Compliance

The Investigator must maintain exact records of the amount of IMP dispensed to each subject by recording the following information:

- Subject randomization number
- Date(s) and visit number when IMP was dispensed
- Amount of IMP dispensed
- Date of return of IMP
- Amount of IMP returned

An accountability log will be maintained at the study site to record IMP compliance for each subject.

Additional details about IMP dispensing can be found in the study specific Pharmacy Manual.

3.13.7. Efficacy Analyses

The alpha for Part A is 0.01 and 0.04 for Part B.

Part A

Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed using a mixed model repeated measures (MMRM). The model will include terms for randomization stratification factors, treatment, time, treatment by time interaction. An unstructured variance-covariance model will be used.

Analysis of Secondary Endpoints

The key secondary endpoint will be analyzed similarly. The secondary endpoint of change from baseline in TTR level will also be analyzed similarly at Month 12. To control alpha, KCCQ-OS and change from baseline in TTR level will be formally tested sequentially in this order at significance level of 0.01 if the primary endpoint is statistically significant at the 0.01 level. The proportion of subjects who achieve TTR stabilization at Month 12 will be analyzed by the Cochran-Mantel-Haenszel test.

Part B

Primary Efficacy Analysis

The primary analysis will use a hierarchical combination of the Finkelstein-Schoenfeld method (Finkelstein 1999) applied to All-cause mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWT at the last available visit over the 30-month fixed treatment duration. In this study, "All-cause mortality" includes death due to any cause, heart transplant, or CMAD (see Section 3.11.12).

The test is based on the principle that each subject is compared to every other subject in each stratum in a pair-wise manner. The hierarchical approach recognizes the greater importance of the mortality endpoint. 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) For CV-related hospitalizations, change from baseline in NT-proBNP, and change from baseline in 6MWT, missing data will not be imputed for the Finkelstein-Schoenfeld method.

The null hypothesis is that all of the four components of All-cause mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWT are the same between placebo and acoramidis groups. Rejection of the null hypothesis implies that at least one of the four components of the primary endpoint is different between the treatment groups.

Analysis of Secondary Endpoints

The key secondary endpoints adjusted for alpha are:

a. Change from baseline to Month 30 in the distance walked during the 6MWT
b. Change from baseline to Month 30 on the KCCQ-OS
c. Change from baseline to Month 30 in serum TTR level

d. All-Cause Mortality by Month 30, including death due to any cause, heart transplant, or CMAD

To control alpha at the 0.04 level, the key secondary endpoints will be formally tested sequentially in the order shown above if the primary endpoint is statistically significant at the 0.04 level. Change from baseline in 6MWT, KCCQ-OS and serum TTR level will be analyzed using an MMRM with an unstructured covariance matrix. The model will include additional terms for randomization stratification factors, visit, and treatment by visit interaction. 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.

Additional secondary endpoints (not adjusted for alpha) include:

- A hierarchical combination of All-cause mortality and cumulative frequency of CV-related hospitalization over a 30-month fixed treatment duration
- A hierarchical combination of All-Cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWT over a 30-month fixed treatment duration
- Change in NT-proBNP from baseline to Month 30 of treatment
- Cumulative frequency of CV-related hospitalization by Month 30
- CV mortality by Month 30
- TTR stabilization measured in established ex-vivo assays (FPE and Western blot) in the PK-PD substudy

TTR stabilization measured in established ex-vivo assays (FPE and Western blot) in the PK-PD substudy. The components of the combined endpoint will also be analyzed separately. Mortality will be analyzed by the Mantel-Haenszel test. All-cause mortality will also be analyzed by a Cox regression model adjusting for stratification factors. Similar analyses will be performed for CV mortality.

The cumulative frequency of CV-related hospitalization will be analyzed by: (a) negative binomial regression. An offset term will be included. The offset will be the log of each subject's study duration; (b) Cochran-Mantel-Haenszel row means scores tests.

Subgroups

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.

Missing Data

Following the conclusion of Part A and Part B, sensitivity and supplementary analyses will be conducted with adjustments for missing data. Imputation details on handling of missing data will be described in the SAP.

3.13.8. Pharmacokinetic Analyses

Population PK (PopPK) analysis will be conducted for both Part A and Part B in the PK-PD substudy according to a separate analysis plan.

3.13.9. Pharmacodynamic Analyses

TTR stabilization will be measured serially as described in the Schedule of Assessments (Appendix A) for subjects in the substudy. At each time point, each of these parameters will be summarized by treatment. In addition, these parameters will be plotted vs plasma drug concentration and the concentration response may be modeled as appropriate.

3.13.10. Exploratory Analyses

Change from baseline in EQ-5D-5L will be analyzed similarly as the key secondary endpoints. Troponin I will be summarized descriptively. Details of these and other exploratory analyses will be provided in the SAP.

3.13.11. Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The incidence of each treatment-emergent AE will be summarized by system organ class, preferred term and treatment assignment. Multiple AEs mapped to the same preferred term will be counted once per subject. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary with generic term and Anatomical Therapeutic Chemical (ATC) code and summarized by ATC code, WHO generic name, and treatment. Safety laboratory findings, vital signs, and 12-lead ECGs will be summarized descriptively and listed by treatment assignment and visit. Values and changes from baseline at scheduled time points will be summarized. Laboratory data will be listed and values and changes from baseline at each visit will be summarized. An additional listing of treatment-emergent laboratory abnormalities will be provided.

3.13.12. Adverse Events

An AE (classified by preferred term) 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. If more than 1 AE is reported before the first dose of IMP and is coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that preferred term and that occurred during the period. An AE that occurs more than 30 days after the last dose of IMP will not be counted as a TEAE.

3.13.13. Interim Analysis

No interim analysis is planned for this study.

4. REFERENCES

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APPENDIX A. SCHEDULE OF ASSESSMENTS

	Screening Period	Treatment Period						Follow-up[1]	ET[1]	Unscheduled Visit[2]
	(within 35 days of Day 1)	Day 1	Day 28 (± 3 Days)	Monthly Phone Contact (± 7 Days)[3]	Month 3 – 27 (Every 3 Months [± 7 Days])[4]	Month 12 (± 7 Days)	Month 30 (±7 Days)[5]	30 days postdose (± 7 Days)		
Written Informed Consent	X									
Inclusion/Exclusion Criteria Review	X	X								
Confirm genotype[6]	X									
Source documents submission to DCC	X									
Randomization		X								

[1] All dosed subjects who prematurely discontinue from the IMP or discontinue/withdraw from the study, regardless of cause, will be asked to complete an Early Termination (ET) Visit and a safety follow up visit 30 days after the last dose as soon as possible and to return any unused IMP.

[2] Subjects who complete ≥ 12 months of blinded study therapy and initiate therapy with tafamidis for ATTR-CM must have completed the Month 12 visit. If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit, they should complete an unscheduled visit with all study assessments performed prior to initiation of tafamidis. For an assessment or follow up of an AE, only procedures and assessments deemed necessary by the Investigator need to be performed (e.g., physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test) [Section 3.7.11].

[3] Telephone contact will occur during months without scheduled in clinic visits (e.g., Months 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, and 29).

[4] In-clinic visits will occur at Month 3, and every 3 months up to Month 27.

[5] Subjects who complete the Month 30 visit will have a visit 30 days (± 7 days) after the last dose of IMP. 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). Subjects not entering the OLE (Study AG10-304) will be required to have the follow-up visit.

[6] Confirm genotype either through existing documentation or testing during Screening. Genotyping must be confirmed prior to randomization.

	Screening Period	Treatment Period						Follow-up[1]	ET[1]	Unscheduled Visit[2]
	(within 35 days of Day 1)	Day 1	Day 28 (± 3 Days)	Monthly Phone Contact (± 7 Days)[3]	Month 3 – 27 (Every 3 Months [± 7 Days])[4]	Month 12 (± 7 Days)	Month 30 (±7 Days)[5]	30 days postdose (± 7 Days)		
Medical/Surgical History	X									
NYHA Class Assessment	X	X	X		X	X	X	X	X	X
Physical Exam[7]	X	X	X		X	X	X	X	X	X
Vital Signs[8]	X	X	X		X	X	X	X	X	X
12-lead resting ECG[9]	X	X	X		X	X	X	X	X	X
Resting transthoracic ECHO or CMR[10]	X									
KCCQ[11]		X			X	X	X		X	X
EQ-5D-5L[12]		X			X	X	X		X	X
6MWT[13]	X				X	X	X		X	X
Clinical laboratory assessments (Section 3.11.8)	X	X	X		X	X	X	X	X	X

[7] Full PE with body weight measurement at all visits; height measurement at Screening only.

[8] Study center personnel will assess vital signs predose after a 5-minute rest.

[9] ECGs will be obtained in supine position after a 5-minute rest at predose and Investigator or qualified Sub-Investigator will review at all visits. On Day 28 an additional ECG will be obtained at 1-hour postdose (Section 3.11.10)

[10] Resting transthoracic ECHO or CMR will be performed at Screening and read locally, if LV wall (interventricular septum or LV posterior wall) thickness not documented in medical history within 10 years of Screening based on ECHO or CMR.

[11] KCCQ will be obtained on Day 1, M6, M9, M12, M18, M24, and M30.

[12] EQ-5D-5L will be obtained on Day 1, M6, M9, M12, M18, M24, and M30.

[13] Two 6MWTs prior to randomization will be conducted >24 hours to ≤3 weeks apart. (Section 3.10.1). 6MWT will be obtained on M6, M9, M12, M18, M24, and M30 and should be conducted after completion of KCCQ and EQ-5D-5L.

	Screening Period	Treatment Period						Follow-up[1]	ET[1]	Unscheduled Visit[2]
	(within 35 days of Day 1)	Day 1	Day 28 (± 3 Days)	Monthly Phone Contact (± 7 Days)[3]	Month 3 – 27 (Every 3 Months [± 7 Days])[4]	Month 12 (± 7 Days)	Month 30 (±7 Days)[5]	30 days postdose (± 7 Days)		
Exploratory blood collection (serum, plasma)	X									
Pregnancy test[14]	X	X	X		X	X	X	X	X	X
PD assays[15]		X	X		X	X	X		X	X
PK sample collection[15]		X	X		X	X	X		X	X
Prealbumin collection		X	X		X	X	X		X	X
IMP dosing during visit		X	X		X	X	X[16]			X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events/ Vital status/ Hospitalization determination[17]		X	X	X	X	X	X	X	X	X
Dispense/collect IMP		X	X		X	X	X[18]		X	X
IMP compliance assessment			X	X	X	X	X		X	X

[14] For females of childbearing potential: urine pregnancy test at all visits.
[15] In a subgroup of subjects at participating sites in the PK-PD substudy, PK and PD samples will be collected at predose and 1-hour postdose at Day 28; predose at all other visits.
[16] Subjects who are planning to enroll in Study AG10-304 should take the evening dose of IMP the day before the Month 30 visit and should not take the morning dose on the day of the Month 30 visit.
[17] 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.
[18] To collect IMP only and no IMP dispensing will occur.

APPENDIX B. ETHICS

Ethical Conduct of the Study

The trial will be conducted in accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 CFR Parts 11, 50, 54, 56, and 312; the EU Clinical Trials Directive (and Clinical Trial Regulation when in effect); principles enunciated in the Declaration of Helsinki; and all human clinical research regulations of the countries where the trial is conducted.

The Investigator(s) and the Sponsor will sign the protocol and study contract, to confirm agreement. The Investigator(s) will not implement any amendment (deviation or changes of the protocol) without agreement by the Sponsor and IRB/IEC approval, except where necessary to eliminate immediate hazard(s) to study subjects, or when change(s) involve only logistical or administrative aspects of the study.

Protocol deviations will only be recognized and assessed for ethical, medical, scientific, and regulatory implications and for impact on the subject's participation in the study and will be documented.

Records that may reveal the identities of subjects must be well protected, with consideration given to confidentiality and the right to privacy of subjects.

Institutional Review Board or Independent Ethics Committee

It is the responsibility of the Investigator to obtain the approval of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) before the start of the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals not to exceed 1 year and at the completion of the study. The Investigator will notify the IRB/IEC of serious adverse events (SAEs) or other significant safety findings if appropriate according to local requirements. The study protocol and amendments, informed consent form (ICF), information sheet, advertisements, will be approved by the IRB/IEC at each study center in conformance with requirements of the controlling regulatory authority.

Subject Information and Consent

At screening, the subject will read the ICF and after being given an explanation of the study. Before signing the ICF and the HIPAA form (if applicable), subjects will have an opportunity to discuss the contents of these forms with study center personnel. Subjects must assent understanding of and voluntarily sign these forms. Subjects will be made aware that they may withdraw from the study at any time.

The ICF contains all the elements of informed consent listed in this protocol. Signed copies of the ICF will be given to the subject, and both documents will be placed in the Investigator's study files. The Sponsor will review the ICF before it is submitted to the IRB/IEC.

APPENDIX C. DATA QUALITY ASSURANCE

Data Monitoring

Before the first subject is dosed in the study, a representative of the Sponsor will meet with the Investigator and the Investigator's personnel to review the procedures for conducting the study and to train the personnel on recording the data on the CRFs using the electronic data capture (EDC) system. The Sponsor representative will periodically monitor the progress of the study by conducting on-site visits thereafter. The Sponsor representative will also be able to review query statuses remotely, which may warrant more frequent communication with the Investigator and his or her personnel. The Investigator will make available to the Sponsor representative the source documents, the signed consent forms, and all other study-related documents. The Investigator will be responsible for reviewing CRFs, resolving data queries generated by the Sponsor representative via the system, providing missing or corrected data, approving all changes performed on the data, and endorsing the subject data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password that together will represent a traditional handwritten signature.

Data Audit

Members of the Sponsor Quality Assurance department or designee may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an inspection of the study. If informed of such an inspection, the Investigator should notify the Sponsor immediately. The Investigator will ensure that the auditors have access to the study site facilities, investigational products, original source documentation, and all study files.

Data Recording and Documentation

Data collection will involve the use of an EDC system, to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by the Sponsor personnel and/or authorized Sponsor representatives, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study center and answered electronically by that study center. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on his or her subjects' data, will be collected.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to local regulatory requirements and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and regulatory officials.

APPENDIX D. STUDY SPONSORSHIP

Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center at any time and for any reason.

Reporting and Publication

All data generated in this study will be the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to agreement between the Investigator and the Sponsor.

APPENDIX E. INVESTIGATOR OBLIGATIONS

Documentation

The Investigator must provide the following to the Sponsor before the start of the study:

- A written and signed document verifying the Investigator has the experience and background needed to conduct the trial and that it will be done in a way that is ethical and scientifically sound. The document should be comparable to the US FDA Form 1572.
- A fully executed contract
- The curricula vitae and licensure for the Investigator and all Sub-Investigators, as well as for the Clinical Laboratory Director
- A copy of the initial IRB/IEC/REB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC/REB, as described in the protocol.
- A copy of the IRB/IEC/REB-approved ICF
- A list of the IRB/IEC/REB members
- A copy of the clinical laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the Investigator
- A financial disclosure statement completed and signed by the Investigator and all Sub-Investigators listed on the US FDA Form 1572, or comparable document. If applicable, the Investigator and all Sub-Investigators will provide an updated financial disclosure statement to the Sponsor during the study and for one year after the completion of the study.

Performance

The Investigator must demonstrate reasonable efforts to obtain qualified subjects for the study.

Use of Investigational Materials

The Investigator will acknowledge that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator. After receipt of the documentation package, the Sponsor will arrange for the shipment of IMP. The IMP must be stored in a safe and secure place. At study initiation, a representative from the Sponsor will inventory the IMP at the study center.

The Investigator must ensure adequate records are maintained documenting the receipt and disposition of all study supplies. The Sponsor will supply forms on which to record the date and amount of IMP received and the lot number of the IMP.

All unused IMP must be returned to the Sponsor or destroyed on-site throughout the course of the study, after IMP accountability is completed and with approval by the Sponsor. If unused IMP is not returned to the Sponsor and destroyed on-site, proof of destruction must be provided to the Sponsor. The Investigator will be responsible for ensuring that subjects return their IMP.

Case Report Forms, Laboratory Data, and Other Vendor Data

All data relating to the study will be recorded in the CRF. The CRFs are to be completed in a timely manner. The Investigator will be responsible for verifying that all data entries in the CRFs are accurate. The Investigator must sign the completed CRF upon notification from the Sponsor.

The laboratory data must be transferred to the Sponsor in electronic format acceptable to the Sponsor specifications.

Retention and Review of Records

The Investigator must maintain the documentation relating to this study. If the Sponsor or any regulatory authority wishes to review any documentation relating to the study, the Investigator must permit access to such records.

The Investigator must retain a copy of all records that support CRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, IMP dispensing records) for a period of at least 15 years after study completion unless local regulations or study center policies require a longer retention period or otherwise notified in writing by the Sponsor.

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study center or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian before such transfer is made.

No study records shall be destroyed without notifying the Sponsor and giving the Sponsor the opportunity to arrange long-term storage for such study records or to authorize in writing the destruction of records after the required retention period.

Subject Confidentiality

All subject records will only be identified by subject initials and subject number. Subjects' names are not to be transmitted to the Sponsor. The Investigator will keep a master subject list on which the subject number and the full name, address, and telephone number of each subject are listed.

APPENDIX F. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Class	Description
I	Patients have cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, palpitations or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, dyspnea, palpitations or anginal pain.
III	Patients have cardiac disease with marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, dyspnea, palpitations or anginal pain.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX G. SUMMARY OF CHANGES

CHANGE	RATIONALE	SECTIONS AFFECTED
Original Protocol vs Amendment 1.0		
Statements clarifying contraception requirements and acceptable methods were added in several places in the protocol.	To be consistent with the Clinical Trial Facilitation Group (CTFG) requirements.	• Synopsis • Section 3.3 • Section 3.5
Amendment 1.0 vs Amendment 2.0		
Changed address	Administrative change	• Cover page
Designation for acoramidis changed to "acoramidis HCl"	To clarify the strength of acoramidis is in the hydrochloride form.	• Synopsis • Section 3.6
Simplified text in the Introduction	Because up-to-date information is provided in the Investigator's Brochure, the current simplified Introduction provides the major findings from prior investigations.	• Section 1
Exploratory endpoints for circulatory biomarkers and EQ-5D-5L were changed change from baseline.	To allow for analysis at the end of both Parts A and B.	• Synopsis • Section 2
Clarified the ability to use tafamidis after at least 24 months of double-blind treatment during the study.	The change was needed due to the recent approval of tafamidis in some regions.	• Synopsis • Section 3
Removed the statement to encouragement subjects to remain in the trial.	To clarify that the subjects are allowed to withdraw at any time.	• Synopsis • Section 3
Clarified that the 35th day will be included in the Screening period.	For additional clarification only.	• Section 3 Figure 1
Deleted ability to grant exceptional approval for subjects who refuse genetic testing.	The change was in response to regulatory authorities and to ensure that all subjects have documented genotyping prior to the randomization.	• Synopsis • Section 3.2.1 • Appendix A
Inclusion Criteria: • #3 1: clarified Screening criteria for ATTR-CM with addition of mass spectrometry or immunoelectron microscopy • #3 2 clarified that IFE of serum and urine is needed. • Confirmation of diagnosis by central review of clinical data was deleted. • #8 6MWT to be completed ≥ 150 m on the 6MWT on 2 tests	• To allow for immune electron microscopy for diagnosis of ATTR-CM • To be consistent with the clinical practice based on feedback from DCC. • Clarified the timeframe for confirmation of diagnosis by DCC in Section 3.11.3 • To clarify that the 2 6MWT do not need to be consecutive.	• Synopsis • Section 3.3.1 • Section 3.7.2
Exclusion Criteria: • #2: TIA is excluded • #7: changed Screening NT-proBNP to ≥8500 pg/mL from≥7000 pg/mL	• Based on feedback from advisors, the threshold was changed to allow for	• Synopsis • Section 3.3.2

CHANGE	RATIONALE	SECTIONS AFFECTED
• #10: removed reference to any investigational agent • #11: clarified exclusion of calcium channel blockers was for those with conduction system effects and allowed for use of dihydropyridine and limit the use of digoxin.	risk/benefit assessments at higher levels of NT-proBNP • Exclusion of investigational drug is covered in EC#14. • The changes in concomitant medications changed based on advisors' feedback and current medical practice.	
Simplified the section and refer to the Data Access Management Plan for Details.	• For additional clarification only.	• Synopsis • Section 3.6.8
Subjects should be discontinued if treatment assignment has been unblinded to the investigator. The reason for discontinuation is to be recorded in the CRF.	• To harmonize with other parts of the protocol.	• Section 3.4
Treatment compliance will be monitored by recording drug accountability.	• To be consistent with deletion of drug dosing diaries.	• Section 3.6.4
• Clarified exclusion of calcium channel blockers with conduction system effects and allowed for use of dihydropyridine. And limit the use of digoxin. • Clarified that tafamidis for indication of ATTR-CM will be allowed after at least 24 months of blinded study therapy.	• To be consistent with Exclusion criteria • To clarify that tafamidis use is to be for indication of ATTR-CM	• Section 3.6.11
Deleted the use of study drug dosing diaries during the study.	• Prior to study initiation, a decision was made to monitor drug use by drug accountability.	• Section 3.6.12
Clarified need for medical history of ECHO or CMR to be within 10 years of Screening.	• To be consistent with IC #10	• Synopsis • Section 3.7.2 • Appendix A
• Renamed header from "Day 1 and Every 3 Months (±7 Days to "Day 1 and Repeated Assessments" • Refer to the Schedule of Assessments for 6MWT	• Changed to better characterize the contents of the section • To clarify the assessment schedule for 6MWT is different from other repeated assessments.	• Section 3.7.4
Clarified the collection of vital status for subjects who discontinue study drug and study assessments continue up to month 30.	• For additional clarification only.	• Section 3.7.7
Revised header for Section 3.9 from Efficacy Assessments to Efficacy Assessments at Scheduled Visits.	• Clarification due to the content of this section.	• Section 3.9
To clarify that a third 6MWT if needed should be repeated within 24 hours to 1 week of last 6MWT.	• To clarify the time frame for a third test, if required.	• Section 3.9.1

CHANGE	RATIONALE	SECTIONS AFFECTED
Provided further clarity for the events of clinical interest. Added that CV-related hospitalizations will not be included in periodic safety reporting.	• To provide additional clarification for the definition of events of clinical interest • To clarify that the study endpoint of CV-related hospitalizations will not be included in the periodic safety reporting	• Section 3.10.7
Clarification of single repeat of clinical laboratory tests and additional repeat test was added.	• For additional clarification only.	• Section 3.10.8
Vital signs will be assessed at predose only and not at pre and postdose.	• Post-dose vital signs are included in error, as it is not indicated in this Phase 3 trial.	• Section 3.10.9 • Appendix A
Definition of CV-related hospitalization was clarified.	• For additional clarification only.	• Section 3.10.12
Clarified that review and confirmation by DCC may occur after randomization but not later than Day 28.	• For additional clarification only.	• Section 3.11.3
Clarified Primary Analysis is for efficacy. The per-protocol population will include subjects in the modified ITT set.	• For additional clarification only.	• Section 3.12.4
Additional secondary endpoint analyses will include Cox regression model adjusting for stratification factors.	• Inclusion of an additional analysis method	• Section 3.12.7
"Exploratory Analyses" section was added to statistical analyses.	• To harmonize with the listed endpoints.	• Section 3.12.10
Reference added for use of contraception in clinical trials.	• To provide a source for the contraceptive use during the trial	• Section 4
• Row added for "confirm genotype" in Schedule of Assessments • Reference to Section 3.9.1 was added for 6MWT	• For consistency • For additional clarification only	Appendix A
Other minor editorial changes.	• For accuracy with no change to details or study design.	Throughout the document
Amendment 2.0 vs Amendment 3.0		
Clarified that tafamidis approved for indication of ATTR-CM will be allowed as a concomitant medication after at least 12 months of blinded study therapy.	• To allow subjects that complete Part A and gain access to tafamidis approved for ATTR-CM as part of their routine care, to be eligible to remain in the trial (as opposed to discontinuing the study).	• Synopsis • Exclusion criteria #10 • Section 3.1 • Section 3.6.11
Increased number of centers worldwide.	• To update current number of centers worldwide	• Synopsis
6MWT: Added distance walked must be within 15% on two tests. If one of the first two tests is not ≥ 150 m or the first two	• To align inclusion criteria 8 with Section 3.9.1 6MWT of	• Synopsis • Section 3.3.1 • Section 3.7.2

CHANGE	RATIONALE	SECTIONS AFFECTED
tests are not within 15% of distance walked, a third test must be conducted and must meet the inclusion criteria.	the protocol, with no change to the inclusion criteria	• Section 3.9.1 • Appendix A
6MWT: Two tests and the third test (if needed) must be conducted within 3 weeks.	• Simplified the time frame for all three tests based on feedback from Investigators to align with subjects' standard of care visits.	• Synopsis • Section 3.3.1 • Section 3.7.2 • Section 3.9.1 • Appendix A
Added guideline for walking aid or supplemental oxygen at subsequent 6MWT after baseline.	• To standardize 6MWT after baseline	• Section 3.9.1
Clarified acceptable diagnostic method of ATTR-CM includes endomyocardial biopsy with immunohistochemistry. Subjects with concurrent MGUS may require confirmation of diagnosis of ATTR-CM by tissue biopsy with confirmatory TTR amyloid typing.	• Based on advisors' feedback and current medical practice	• Synopsis • Section 3.3.1 • Section 3.7.2 • Section 3.11.3
Revised frequency of KCCQ and EQ-5D-5L administration.	• To be consistent with 6MWT visits	• Appendix A
Deleted adjustment to 400 mg.	• To be consistent with current Investigator's Brochure, with no change to the risk/benefit of acoramidis	• Section 3.6.1
Other minor editorial and template changes.	• For accuracy, with no change to study design.	• Throughout the document
Amendment 3.0 vs Amendment 4.0		
• Corrections, clarifications, administration changes	• Administrative updates have been made throughout for consistency (e.g., minor changes to grammar, punctuation, or formatting)	• Throughout the document
• Incorporated acoramidis where AG10 is mentioned	• Incorporated acoramidis as international nonproprietary name (INN) for AG10	• Throughout the document
• Updated Key Sponsor contacts	• Addition of new Sponsor contacts.	• Cover page • Section 3.10.7
• Inclusion criteria ≥18 to ≤ 90 years of age: Added at time of randomization	• For additional clarification only; included in Protocol Amendment 3.0 Clarification Letter dated 23 Sep 2020	• Synopsis • Section 3.2.1 • Section 3.3.1
• Added abbreviation PYP and HDP • Corrected abbreviation HMPD to HMDP	• pyrophosphate (PYP) or -bisphosphonate (DPD or HMDP/HDP); these abbreviations appear to be used interchangeably in current medical practice	• Synopsis • Section 3.3.1 • Section 3.7.2

CHANGE	RATIONALE	SECTIONS AFFECTED
	• Transposition error corrected, with no change to study design	
• Clarified barrier method as double-barrier method	• For consistent use throughout the protocol	• Synopsis • Section 3.3.1 • Section 3.5
• Added abbreviations AL, ATTRm, ATTRwt, CK, CK-MB, CRF, DPD, EOCI, EQ VAS, FAP, HCl, HDP, HMDP, IWRS, IFE, IXRS, KCCQ, MGUS, PE, PYP, sFLC, SSA, TIA, TSH, 99mTc	• Updated list of abbreviations	• List of Abbreviations
• Removed Voice from abbreviation IXRS and replaced with IWRS	• Interactive Voice not currently used in study; Only Interactive Web Response System	• List of Abbreviations • Section 3.6.5
• Removal of acoramidis high oral bioavailability and binding selectivity in all animal species	• Current information included in Investigator's Brochure	• Section 1.1
• Insertion of exploratory objective: To evaluate the effects of acoramidis on circulating biomarkers of myocardial wall stress and microvascular ischemia in subjects with symptomatic ATTR-CM	• Text present in Synopsis but missing from Section 2; Text reinserted with no change to study design	• Section 2
• Added list of excipients of acoramidis or placebo	• For additional clarification only	• Section 3.6.2
• Added IMP returns to Sponsor for destruction or on-site destruction can occur upon authorization from the Sponsor and throughout the course of the study	• For additional clarification only; included in Protocol Amendment 3.0 Clarification Letter dated 23 Sep 2020	• Section 3.6.4 • Appendix E
• Added guidance on genotyping	• For additional clarification only	• Section 3.7.2 • Appendix A
• Added guidance on collection of ECGs after a 5-minute rest in a supine position	• For additional clarification only	• Section 3.7.2 • Section 3.7.4 • Section 3.7.5 • Section 3.7.6 • Section 3.7.8 • Section 3.7.9 • Section 3.7.10 • Section 3.7.11 • Section 3.7.12 • Section 3.7.13
• Added guidance on when telephone contacts should occur	• For additional clarification only	• Section 3.7.7 • Appendix A

CHANGE	RATIONALE	SECTIONS AFFECTED
• Added guidance on visit window for subjects who initiate tafamidis after Month 12 or a later visit	• For additional clarification only; included in Protocol Amendment 3.0 Clarification Letter dated 23 Sep 2020	• Section 3.6.11 • Section 3.7.11 • Appendix A
• Added guidance on ET visit	• For additional clarification only	• Section 3.7.13
• Added guidance on walking aid for 6MWT	• Added to reflect existing procedures and guidance on conduct of 6MWT	• Section 3.9.1
• Documentation of outcome of AE is requested for safety reporting, rather than resolution of AE	• For additional clarification, as AE may not resolve at time of safety reporting	• Section 3.10.5
• Added events of clinical interest (EOCI) negatively adjudicated by CEC will be considered as adverse events	• No change to original intent or to study conduct, wording was missing previously	• Section 3.10.7
• Added clarification that EOCI are considered as part of the efficacy endpoint of CV-related hospitalizations	• For additional clarification	• Section 3.10.7 • Section 3.10.12
• Removal of language around PK-PD relationship to QTc	• The removed sentences refer to actions the Sponsor might take under hypothetical future circumstances not to current or planned/committed to study conduct or analyses	• Section 3.10.10
• Removed "If immunohistochemistry is employed for TTR amyloid typing, the analyzing pathology laboratory's methodology and reagents must be reviewed by the Diagnostic Confirmation Committee as meeting acceptable standards of sensitivity and specificity" and requirement by Day 28 for confirmation of ATTR-CM by DCC	• Function of DCC is to provide an independent review of submitted diagnostic data supporting diagnosis of ATTR-CM; This independent review can provide the basis for an assessment of clinical consistency and robustness of diagnosis in a global clinical trial of ATTR-CM. The 28-day timeframe is not required since review can be completed after randomization, and this requirement was removed	• Section 3.11.3
• Updated language to be consistent with language used in the synopsis	• For additional clarification only	• Section 3.12.9
• Added additional footnotes to clarify timing of assessments	• For additional clarification only	• Appendix A
• Specified procedure for Sponsor audit of clinical sites	• Added to reflect existing procedure	• Appendix C
Amendment 4.0 vs Amendment 5.0		
• Corrections, clarifications, administration changes	• Administrative updates have been made throughout for	• Throughout the document

CHANGE	RATIONALE	SECTIONS AFFECTED
	consistency (e.g., address changes, minor changes to grammar, punctuation, or formatting, etc.)	
• Added "change from baseline in 6MWT" to the key primary objective/endpoint for component of Part B	• Initiation of tafamidis after Month 12 is expected to reduce the power of Finkelstein-Schoenfeld test for the hierarchical combination of All-cause mortality and CV-related hospitalizations. To compensate for the reduction in power, the primary endpoint was changed to a hierarchical combination of All-cause mortality, CV-related hospitalization, and change from baseline in 6MWT	• Synopsis • Section 2 • Section 3.1 • Section 3.13.2 • Section 3.13.7.2.1
• Updated power estimate for Part B analysis	• To update power estimate as the primary endpoint was changed to a hierarchical combination of All-cause mortality, CV-related hospitalization, and change from baseline in 6MWT	• Synopsis • Section 3.13.2
• Added "A hierarchical combination of All-Cause mortality and CV-related hospitalization over a 30-month period"	• Added to align with the secondary objective for Part B	• Synopsis • Section 2 • Section 3.13.7.2.1
• Removed "mutations" from TTR and added "variants" for exploratory endpoints for Part A and B	• Harmonized with variants described in IB.	• Synopsis • Section 2
• Revised the open-label extension (OLE) throughout the protocol	• A separate protocol (AG10-304) is being developed for those subjects who rollover into the OLE study	• Synopsis • Section 3.1 • Section 3.2.2 • Section 3.6 • Section 3.8.8 • Section 3.8.10 • Appendix A
• Removed "and established ex vivo assays of…." And added "measured in established ex-vivo assays (fluorescent probe exclusion ([FPE)] and Western blot) at Day 28 and subsequent visits in the PK-PD substudy" for Part A and Part B Secondary endpoints	• This is a substudy and added for consistency with other endpoints that will be assessed only in the substudy population	• Synopsis • Section 2

CHANGE	RATIONALE	SECTIONS AFFECTED
• Moved PK/PD correlation to exploratory objective/endpoint "To describe the PD properties and the pharmacokinetic (PK)-PD relationship of acoramidis as assessed by circulating prealbumin (transthyretin, TTR) concentration as an in vivo biomarker of stabilization and by established ex vivo assays of TTR stabilization, and correlated with acoramidis PK" and "Describe the PK-PD relationship of acoramidis in adult subjects with symptomatic ATTR-CM in the PK-PD substudy"	• PK PD correlation analysis will be exploratory	• Synopsis • Section 2
• Updated PK-PD substudy	• Clarified that PK-PD samples will be collected in the PK-PD substudy and the PopPK and PD measures analyses will be separate analyses	• Synopsis • Section 2 • Section 3.8.4 • Section 3.8.5 • Section 3.8.6 • Section 3.8.8 • Section 3.8.9 • Section 3.8.11 • Appendix A
• Added "To describe the population PK (PopPK) of acoramidis in subjects with ATTR-CM" and "PopPK analysis of acoramidis in the PK-PD substudy" for Part A and B objectives/endpoints	• PopPK analysis will be exploratory in the PK-PD substudy	• Synopsis • Section 2 • Section 3.13.8
• Added "If a subject chooses to initiate treatment with another therapy, including tafamidis in the first 12 months of the study, they will be asked to complete an ET visit and associated procedures prior to discontinuation/ withdrawal."	• Clarification if subjects decide to initiate treatment with another therapy, they need to complete an ET visit	• Synopsis • Section 3.1
• Added "If a subject plans to initiate therapy with tafamidis more than 7 days after the Month 12 visit or a later scheduled visit" and removed "…if it has been more than 7 days since the Month 12 visit or a later visit"	• Clarify when an unscheduled visit should occur if the subject initiates therapy with tafamidis	• Synopsis • Section 3.1 • Section 3.7.11 • Section 3.8.9 • Appendix A
• Changed the statement from 'will' to 'may' in "Subject level CV-related hospitalization data will not be available to the Sponsor Part A team; however, the aggregated overall summary without treatment group information 'may' be available to the Sponsor Part A team."	• To accurately reflect data summary and access plan	• Synopsis • Section 3.7.8

CHANGE	RATIONALE	SECTIONS AFFECTED
• Added "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)."	• The Open-label portion of this study has been removed as the OLE is now a separate study (AG10-304)	• Synopsis • Section 3.8.10 • Appendix A
• Removed from Part A Efficacy Analyses "To control alpha, the key secondary endpoint will be formally tested if the primary endpoint is statistically significant at the 0.01 level."	• To reflect the update in alpha-control plan	• Synopsis • Section 3.13.7.1.1
• Added to Efficacy Analyses "The secondary endpoint of change from baseline in TTR level will also be analyzed similarly at Month 12. To control alpha, KCCQ-OS and change from baseline in TTR level will be formally tested sequentially in this order at significance level of 0.01 if the primary endpoint is statistically significant at the 0.01 level."	• To reflect the alpha control of the TTR level in the secondary endpoint	• Synopsis • Section 3.13.7.1.1
• Updated text on Discontinuation of IMP, and Withdrawal from the study; change was made to the title of the section "assessments" to "withdrawal from the study"	• To align with the language across the protocols in cardiomyopathy and polyneuropathy programs	• Synopsis • Section 3.4
• Category of "Death" is added to harmonize with the categories captured in the case report form	• Added clarification on discontinuation of therapy or withdrawal from the study and to harmonize with the categories captured in the case report form	• Section 3.4
• Added "All participating subjects will be asked to consent to determination of vital status (alive, death, heart transplant, receiving CMAD) at 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 through public records may not be withdrawn."	• Update guidance on vital status during the study	• Synopsis • Section 3.1 • Section 3.4 • Section 3.7.8 • Section 3.8.11 • Section 3.13.7.2.1
• Added a statement, "(Terms KCCQ overall score and KCCQ overall summary score are interchangeably used in this document)"	• Added for the clarity of terms used	• Section 3.1

CHANGE	RATIONALE	SECTIONS AFFECTED
• Added a statement, "All dosed subjects who prematurely discontinue from the IMP or discontinue/withdraw from the study, regardless of cause, will be asked to complete an Early Termination (ET) Visit and a safety follow up visit 30 days after the last dose"	• Added for clarification and consistency across sections	• Section 3.4 • Appendix A
• Added section on "Lost to Follow-up"	• To define if a subject is lost to follow-up	• Section 3.4.1
• Added "CTFG guidance v.1.1" and "bilateral tubal occlusion"	• To clarify the CTFG guidance and effective method of birth control	• Section 3.5
• Added a new section 'End of Study Definition"	• Added for clarification and align with the protocol template	• Section 3.6
• Added "(equivalent to 356 mg acoramidis)"	• To introduce free base strength for acoramidis	• Section 3.7.1
• Added "Screening safety assessments completed on the same day as Day 1 (e.g., physical exam, vital signs, ECG, clinical laboratory tests) may be used as Day 1 assessments at the investigator's discretion provided that they are predose."	• Clarification on safety assessments at Screening can be completed at Day 1	• Section 3.8.3
• Added "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)." "Subjects who are planning to enroll in AG10-304 should take the evening dose of IMP the day before the Month 30 visit and should not take the morning dose on the day of the Month 30 visit."	• Clarification on completion of Month 30 visit assessments • To align across sections	• Section 3.8.8 • Appendix A
• Added "e.g., Investigator's discretion" to the unscheduled visit	• Clarification that the investigator can conduct an unscheduled visit at their discretion	• Section 3.9.1 • Section 3.9.2 • Section 3.9.3
• Removed "The Sponsor's Medical Monitor may also be notified by telephone."	• Protocol template has been updated to remove this information	• Section 3.11.7
• Revised the following paragraph "The study center personnel must transmit the SAE Form to the Sponsor within 24 hours of when the site first becomes aware of the event. Even if the site has discussed the event with a Sponsor	• Clarification only	• Section 3.11.7

CHANGE	RATIONALE	SECTIONS AFFECTED
representative, the study center personnel must still complete the SAE Form with all available details and send the form within 24 hours of when the site first becomes aware of the event."		
• Added "The investigator will determine whether abnormal vital signs are clinically relevant."	• Clarification on determining abnormal vital signs	• Section 3.11.9
• Updated the section on Analysis of Secondary Endpoints	• To clarify the specific statistical test used	• Section 3.13.7.1.1 • Section 3.13.7.1.2
• Removed "… will be considered censored at the time of subject discontinuation from the study" and added "missing data will not be imputed for the Finkelstein-Schoenfeld method"	• Clarification on missing data	• Section 3.13.7.2.1
• Added clarification on the conduct of the study and information on Declaration of Helsinki • Added "and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines" • Added Research Ethics Board	• Clarification on Ethical conduct of the study	• Appendix B
Amendment 5.0 vs Amendment 6.0		
• Updated Key Sponsor contacts	• Addition of new Sponsor contacts.	• Cover page
Revised the Primary Endpoint in Part B to reflect addition of NT-proBNP: • 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 over a 30-month fixed treatment duration	• Blinded data review suggested that the initial design assumptions were not being met. To maintain the original anticipated power of the study, the primary analysis approach for Part B was modified as described.	• Synopsis, (Objectives and endpoints; Study design and Investigational plan; Statistical methodology) • Section 2 • Section 3.1 • Section 3.13.2 (Part B) • Section 3.13.7.2.1 Primary Efficacy Analysis; Analysis of secondary endpoints
<u>Key Secondary Objectives/Endpoints, Part B</u>: Promoted two Secondary objectives/endpoints to Key Secondary objectives/endpoints • Change from baseline to Month 30 in serum TTR (prealbumin) level (an in vivo measure of TTR stabilization) • All-Cause Mortality by Month 30 including death due to any cause, heart transplant, or CMAD	• To reflect the change of analytical approach made in SAP Part B Version 2.0 (Effective Date 13 December 2021) that was finalized prior to Part A unblinding.	• Synopsis, (Objectives and endpoints; Statistical methodology) • Section 2 • Section 3.11.7 • Section 3.13.7.2.1

<u>Secondary Objectives/Endpoints, Part B:</u> Revised Secondary objectives and associated endpoints: • Moved key primary endpoint "A hierarchical combination of All-Cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWT over a 30-month fixed treatment duration" and the associated objective to the secondary endpoint/objective section • Promoted exploratory endpoint "Change in NT-proBNP from baseline to Month 30 of treatment" and associated objective to secondary objective/endpoint section	• Previous primary objective/ endpoint in Amendment 5.0, moved to secondary endpoint. • Previous exploratory endpoint promoted to secondary endpoint	• Synopsis, (Objectives and endpoints; Study design and Investigational plan; Statistical methodology). • Section 2 • Section 3.1 • Section 3.13.2 (Part B) • Section 3.13.7.2.1
<u>Exploratory Objectives/Endpoints, Part A:</u> • Separated the Part A exploratory objective/endpoint evaluating the effects of acoramidis on circulating biomarkers (NT-proBNP and TnI)	• For clarification only	• Synopsis, (Objectives and endpoints) • Section 2
<u>Statistical methodology: Sample size for Part B</u>: • Added new text summarizing changes in 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 over a 30-month fixed treatment duration."	• Revised the text to align with the revised objectives and endpoints	• Synopsis, (Statistical methodology- Sample size for Part B • Section 3.13.2
<u>Discontinuation of Subjects from Therapy or Withdrawal from the Study</u> • For AEs, added "Note 1: If considered necessary, as per Investigator's discretion, IMP may be interrupted (e.g., in case of AE, hospitalization or procedure), however IMP should be resumed as soon as practically possible, unless there are safety concerns. Investigators are encouraged to discuss such cases with a Medical Monitor." • Previous AE "Note" numbered to "Note 2" • Previous Withdrawal of Consent bullet numbered to "Note 3" • Added "Note 4: Withdrawal of consent should be distinguished from discontinuation of IMP. Subjects who	• For additional clarification only • For additional clarification only	• Section 3.4

discontinue IMP permanently will receive phone calls as specified by the protocol to assess vital status, heart transplant or CMAD implantation." • Added the word "*permanently*" to clarify the language on early termination of study treatment. • Added text "Investigator should evaluate the possible contribution of an adverse event to permanent discontinuation of IMP. In this case, adverse event information will be documented accordingly in the CRF."	• For additional clarification only • For additional clarification only	Section 3.8.11
<u>Immediate Reporting of SAEs and EOCIs Definition of Cardiac Mechanical Assist Device, Cardiovascular-related Hospitalization and Events of Clinical Interest</u> • Added text "for adjudication purposes (this includes but is not limited to: admission notes describing signs and symptoms, cardiology or other relevant clinical notes, hospital discharge summary)"	• Clarification on Investigator responsibility	• Section 3.11.7 • Section 3.11.12
• Changed section title. • Added "In this study, CMAD and heart transplant are included in the "All-cause mortality" component of the primary endpoint for Part B, and therefore should be collected for all randomized patients even if they discontinued treatment permanently or withdrew consent (see also Section 3.4). CMAD is defined as a durable CMAD implanted in a patient with end-stage heart failure as a bridge to transplant or as a destination therapy. Temporary cardiac mechanical support (i.e., those interventions that can only be employed in the inpatient setting, e.g., Intra-Aortic Balloon Pump [IABP], Impella, or Extra-corporeal membrane oxygenation [ECMO]) are not considered CMAD. In addition, other cardiac interventions such as pacemaker, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG), valvular percutaneous	• Defined CMAD	• Section 3.11.12

intervention or surgery are not considered CMAD."		
• Added text clarifying that an independent CEC will review and adjudicate "heart transplant, CMAD" to determine whether they meet the definition of protocol-specified efficacy endpoints for Part B.	• For additional clarification only	• Section 3.12.2