Protocol Number:	EIDOS AG10-202
Protocol Title:	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
Indication:	Transthyretin Amyloid Cardiomyopathy
Phase:	2
Investigational Medicinal Product:	Acoramidis
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1.0 SYNOPSIS AND SCHEDULE OF ASSESSMENTS

CLINICAL STUDY SYNOPSIS	
Study Number	AG10-202
Title of Study	An Open-Label Extension and Safety Monitoring Study of Patients with Symptomatic Transthyretin Cardiomyopathy Who Have Completed the Phase II Study AG10-201
Study Centers (Country)	Up to 9 centers (United States)
Development Phase	2
Objectives	**Primary:** The primary objective of this study is to evaluate the long-term safety and tolerability of acoramidis administered to adult patients with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) in patients who have completed the study AG10-201. **Secondary:** The secondary objectives of this study are: • to characterize the pharmacokinetics (PK) of acoramidis administered orally twice daily in patients with symptomatic ATTR-CM, and • to describe the long-term pharmacodynamic (PD) properties of acoramidis as assessed by established assays of transthyretin (TTR) stabilization, including Fluorescent Probe Exclusion (FPE) assay and Western blot, and to describe the PK-PD relationship of acoramidis in adult patients with symptomatic ATTR-CM. **Exploratory:** The exploratory objective of this study is: • to describe the long-term effects of acoramidis on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.
Methodology	This prospective, multicenter open-label study will evaluate the long-term safety, tolerability, PK and PD of acoramidis administered on a background of heart failure therapy.
Number of Patients	Up to 55
Inclusion Criteria	To be eligible to participate in the study, a patient must meet all the following criteria: a. Completed participation in study AG10-201. b. Willing and able to comply with the study medication regimen and all study requirements. c. The ability to understand and provide informed consent, which must be obtained prior to initiation of study participation. d. Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use effective method(s) of contraception.
Exclusion Criteria	To be eligible to participate in the study, a patient must meet none of the following criteria: 1. Hemodynamic instability that would pose too great a risk to the subject. 2. Abnormalities in clinical laboratory tests that would pose too great a risk to the subject based on screening laboratory results from study AG10-201. 3. Any clinically significant ongoing medical condition or any laboratory abnormality or condition that could adversely affect the safety of the patient based on screening laboratory results from study AG10-201. 4. Known hypersensitivity to study drug (AG10), its metabolites, or formulation excipients. 5. Likely to undergo heart transplantation or placement of a mechanical circulatory device within the next year. 6. Receiving current treatment with diflunisal, tafamidis, green tea extracts, doxycycline, TUDCA/ursodiol, patisiran, inotersen or any other investigational ATTR agent within 14 days or 5 half-lives of the prior investigational agent (whichever is longer) prior to dosing with study drug.

	7. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before the study drug is administered. Negative urine pregnancy test at each visit is required for female patients of childbearing potential.
Test Product, Dosage, and Mode of Administration	Acoramidis (AG10) HCl, 400 mg tablets, dosed at 800 mg twice daily, oral administration
Duration of Study and Treatment	Study duration: Study will continue at the sponsor's discretion, or registration of the product for the treatment of symptomatic ATTR-CM.
Primary Outcome Measures	**Safety and Tolerability:** Safety will be assessed by collection of treatment-emergent adverse events (AEs), physical examination findings, vital signs, ECG parameters and clinical laboratory parameters. **Endpoint:** The primary endpoint is to characterize the safety and tolerability of acoramidis administered long-term to adult patients with symptomatic ATTR-CM who have completed the study AG10-201.
Secondary Outcome Measures	**Pharmacokinetics:** The PK measurements of acoramidis and metabolite will be performed by a designated bioanalytical laboratory. **Pharmacodynamics:** The PD measurements of acoramidis will be assessed by established assays of TTR stabilization, including FPE assay and Western blot, and will be used to describe the PK-PD relationship of acoramidis in adult patients with symptomatic ATTR-CM.
Exploratory Outcome Measure	The exploratory objective of this study is to describe the long-term effects of acoramidis on key echocardiographic parameters including global longitudinal strain, stroke volume index and left ventricular mass.
Statistical Methodology	Statistical summaries will be performed using SAS Version 9.4 or higher (SAS Institute, Inc. Cary, NC, USA) or higher. Additional software may be used for the production of graphics. PK parameters will be computed using Phoenix WinNonlin. Applicable analysis sets for the secondary endpoints (eg, PK-PD relationship) will be defined in the Statistical Analysis Plan (SAP). The analysis set for safety analyses will be the Safety Analysis Set: all patients dosed. Baseline values are defined as the last value obtained on or before the date of the first dose from Study AG10-202. **PK Analyses:** Pre-dose plasma PK levels will be measured for each patient as specified in the summary of assessments. **PD Analyses:** TTR stabilization ex vivo will be measured serially as described in the Schedule of Assessments. At each time-point, each of these parameters will be summarized by dose. In addition, these parameters will be plotted vs plasma drug. **Safety Analyses:** AEs will be coded using the MedDRA dictionary. The incidence of each treatment-emergent AE will be summarized by system organ class, and preferred term. Multiple AEs mapped to the same preferred term will be counted once per patient. Concomitant medications will be coded using the WHO Drug Dictionary with generic term and therapeutic use (ATC code) and summarized by ATC code, WHO generic name, and treatment. Reasons for early termination will be summarized. Safety laboratory findings, vital signs, and 12-lead ECG data will be summarized descriptively and listed by 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.
Pharmacokinetic/Pharmacodynamic Sampling Measures	Predose PK and PD blood samples will be collected at Day 1, Day 14, Day 45, Months 3, 6, and 15. After Month 54, samples will be collected every 6 months.

Table 1. Schedule of Assessments

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

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

2.0 TABLE OF CONTENTS

1.0 SYNOPSIS AND SCHEDULE OF ASSESSMENTS 3

2.0 TABLE OF CONTENTS 6

3.0 LIST OF ABBREVIATIONS 8

4.0 ETHICAL CONSIDERATIONS 9
4.1 Institutional Review Board 9
4.2 Ethical Conduct of the Study 9
4.3 Patient Information and Consent 9

5.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 10
5.1 Eidos Therapeutics or Designee 10
5.2 Clinical Laboratory Analysis 10
5.3 Bioanalytical Laboratory 10
5.4 Data Analysis 10

6.0 INTRODUCTION 11
6.1 Known and Potential Risks and Benefits of acoramidis to human subjects 11

7.0 STUDY OBJECTIVES 13
7.1 Primary Objective 13
7.2 Secondary Objectives 13
7.3 Exploratory Objective 13

8.0 INVESTIGATIONAL PLAN 14
8.1 Overall Study Design and Plan: Description 14
8.2 Discussion of Study Design 14
8.3 Selection of Study Population 14
8.3.1 Inclusion Criteria 14
8.3.2 Exclusion Criteria 15
8.3.3 Discontinuation of Patients from Therapy or Assessment 15
8.4 TREATMENTS 16
8.4.1 Treatments Administered 16
8.4.2 Identity of Investigational Medicinal Product 17
8.4.3 Method of Assigning Identifiers to Patients 18
8.4.4 Selection of Dosage in the Study 18
8.4.5 Selection and Timing of Dose for Each Patient 18
8.4.6 Prior and Concomitant Therapy 18
8.4.7 Treatment Compliance 18
8.4.8 Assessments 19
8.4.9 Safety Assessments 23
8.5 Data Quality Assurance 29
8.5.1 Data Monitoring 29
8.5.2 Data Recording and Documentation 29
8.6 Statistical Methods and Determination of Sample Size 30
8.6.1 General Considerations 30
8.6.2 Timing of Analyses 30
8.6.3 Analysis Sets and Analysis Conventions 30
8.6.4 Demographics and Other Baseline Characteristics 30
8.6.5 Extent of Exposure 30

8.6.6 Pharmacokinetic Analyses....30
8.6.7 Safety Analyses....31
8.6.8 Pharmacodynamic Analysis....31
8.6.9 Interim Analysis....31
8.6.10 Determination of Sample Size....32
8.7 Changes in the Conduct of the Study or Planned Analyses....32

9.0 STUDY SPONSORSHIP....33
9.1 Study Termination....33
9.2 Reporting and Publication....33

10.0 INVESTIGATOR OBLIGATIONS....34
10.1 Documentation....34
10.2 Performance....34
10.3 Use of Investigational Materials....34
10.4 Case Report Forms, Laboratory Data, and Other Vendor Data....35
10.5 Retention and Review of Records....35
10.6 Patient Confidentiality....35

11.0 INVESTIGATOR'S STATEMENT....36

12.0 REFERENCES....37

13.0 SUMMARY OF CHANGES....38

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ATTR	TTR amyloidosis
ATTR-CM	TTR cardiomyopathy
ATTR-PN	TTR polyneuropathy
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
ECHO	echocardiogram
ECG	electrocardiogram, electrocardiographic
EDC	electronic data capture
ET	Early termination
FDA	US Food and Drug Administration
FPE	Fluorescent Probe Exclusion
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
PR	pulse rate
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TTR	transthyretin

4.0 ETHICAL CONSIDERATIONS

4.1 INSTITUTIONAL REVIEW BOARD

It is the responsibility of the Principal Investigator (PI) to obtain the approval of the Institutional Review Board (IRB) before the start of the study. The IRB must be registered and active with the Office for Human Research Protections of the US Department of Health and Human Services. A copy of the approval letter will be supplied to the Sponsor, along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the PI (or appropriately trained designee) will provide timely and accurate reports to the IRB on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. The PI (or appropriately trained designee) will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements (if any), and amendments (if any) will be approved by the IRB at each study center in conformance with CFR, Title 21, Part 56.

4.2 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study is designed to comply with ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authority for Pharmaceuticals (75 FR 3471, 21 Jan 2010), Good Clinical Practice: Consolidated Guidance (ICH-E6; 62 FR 25692, 09 May 1997), and Part 312 of the CFR.

4.3 PATIENT INFORMATION AND CONSENT

On Day 1 of the study, eligible patients will read the ICF and a HIPAA authorization form (if applicable) after being given an explanation of the study. Before signing the ICF and the HIPAA form (if applicable), patients will have an opportunity to discuss the contents of these forms with study center staff. Patients must assent understanding of and voluntarily sign these forms in compliance with 21 CFR, Parts 50 and 312, before participating in any study-related procedures. Patients 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; the HIPAA authorization, if applicable, contains all the core elements and mandatory statements as defined in the CFR. Signed copies of the ICF and the HIPAA authorization form, if applicable, will be given to the patient, and both documents will be placed in the PI's study files. The Sponsor will review the ICF before it is submitted to the IRB.

5.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

5.1 EIDOS THERAPEUTICS OR DESIGNEE

This study will be performed in up to 9 study centers located in the United States (U.S.). The PI at each study center will be responsible for ensuring that the investigation is conducted according to the signed Investigator's statement (Section 11.0), the protocol, and ICH GCP guidelines.

The PI at each study center will be responsible for the management of the study, which will include but not be limited to maintenance of the study file and patient records, correspondence with the IRB, and completion of the electronic case report forms (CRFs).

5.2 CLINICAL LABORATORY ANALYSIS

All clinical laboratory tests will be conducted by a central laboratory in the U.S. Study center local laboratories may also be used to conduct some clinical laboratory tests. The name and address of the study center local laboratories will be listed on the study center's Form FDA1572.

5.3 BIOANALYTICAL LABORATORY

The acoramidis concentrations and its predominant metabolite, AG10-acylglucuronides in plasma samples will be analyzed by a central laboratory in the U.S.

5.4 DATA ANALYSIS

The Sponsor will be responsible for pharmacokinetic (PK), pharmacodynamic (PD), and biostatistical evaluations; report preparation; and auditing of bioanalytic work. Statistical programming of safety data may be conducted by a contract research organization.

6.0 INTRODUCTION

Acoramidis is a potent and selective stabilizer of transthyretin (TTR) that is being developed by Eidos Therapeutics, Inc. for the treatment of ATTR-CM, 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 ATTR-PN, or familial amyloid polyneuropathy (FAP), are driven by pathogenic point mutations in the ATTR 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 or SSA). In ATTRwt, the major organ involved is almost exclusively the heart, although carpal tunnel syndrome and tendon involvement is 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 ATTRm and ATTRwt) and ATTR-PN.

Acoramidis demonstrated high oral bioavailability in all animal species tested, binding selectivity, and ability to stabilize TTR in vivo following oral dosing to nonhuman mammals, in healthy volunteers and in subjects with ATTR.

6.1 KNOWN AND POTENTIAL RISKS AND BENEFITS OF ACORAMIDIS TO HUMAN SUBJECTS

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 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 (Judge et al., 2019; Masri et al., 2022).

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

7.0 STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVE

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

7.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

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

7.3 EXPLORATORY OBJECTIVE

The exploratory objective of this study is:

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

8.0 INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This study is a Phase 2 long-term, open-label study in up to 55 male and/or female patients with symptomatic ATTR-CM, ≥18 years of age.

Study will continue at the sponsor's discretion, or registration of the product for the treatment of symptomatic ATTR-CM. This prospective multicenter, open-label study will evaluate the long-term safety, tolerability, PK and PD of acoramidis administered to eligible patients with stable heart failure therapy.

Eligible patients will begin dosing acoramidis (AG10) HCl 800 mg administered twice daily.

The Schedule of Assessments is provided in Section 1.0. Detailed descriptions of each study day can be found in Section 8.4.8.1.

8.2 DISCUSSION OF STUDY DESIGN

This prospective study is designed to evaluate the long-term safety and tolerability of acoramidis in patients with ATTR-CM. An open-label design is considered to be the most appropriate study design for meeting this objective. On the basis of information gained from previous clinical experience with AG10, the doses used in this study will be selected to match the highest dose that has an acceptable safety and tolerability profile.

8.3 SELECTION OF STUDY POPULATION

Up to 55 males and/or females ≥18 years of age with chronic, stable, symptomatic ATTR-CM will be enrolled and begin dosing with acoramidis (AG10) HCl 800 mg twice daily.

8.3.1 Inclusion Criteria

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

1. Completed the study AG10-201.

2. Willing and able to comply with the study medication regimen and all other study requirements.

3. The ability to understand and provide informed consent, which must be obtained prior to initiation of study participation.

4. Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use effective method(s) of contraception.

8.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Hemodynamic instability that would pose too great a risk to the subject.
2. Abnormalities in clinical laboratory tests that would pose too great a risk to the subject based on screening laboratory results from study AG10-201.
3. Any clinically significant ongoing medical condition or any laboratory abnormality or condition that could adversely affect the safety of the patient based on screening laboratory results from study AG10-201.
4. Known hypersensitivity to study drug (acoramidis), its metabolites, or formulation excipients.
5. Likely to undergo heart transplantation or placement of a mechanical circulatory device within the next year.
6. Receiving current treatment with diflunisal, tafamidis, green tea, doxycycline, TUDCA/ursodiol, patisiran, inotersen or any other investigational ATTR agent within 14 days or 5 half-lives of the prior investigational agent (whichever is longer) prior to dosing with study drug.
7. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before the study drug is administered. Negative urine pregnancy test at each visit is required for female patients of childbearing potential.

The clinical significance of any abnormal findings found in the physical examination, clinical laboratory evaluations, vital sign assessments, and ECGs must be evaluated and documented by the PI or a Sub-Investigator. For clinical laboratory tests, the PI or Sub-Investigator will assess and document the clinical significance of any values outside the reference ranges provided by the clinical laboratory.

The Sponsor reserves the right to exclude any patient from the study on the basis of the medical histories, physical examination findings, clinical laboratory results, prior medications, or other entrance criteria.

8.3.3 Discontinuation of Patients from Therapy or Assessment

A premature discontinuation will occur, if a patient who signs the ICF and is dosed, ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures. Patients can be prematurely discontinued from the study for any of the following reasons:

- Adverse event (AE)
- Protocol violation
- Non-compliance with IMP

- Withdrawal of consent: Subjects may withdraw consent at any time for any reason without prejudice to future treatment. In the event of study withdrawal, the ET procedures should occur as a final visit.
- Need for medications prohibited during the study
- Lost to follow-up (site should attempt at least 3 documented telephone calls, followed by a registered letter to the subject's last known mailing address)
- Pregnancy at any time after signing the ICF. Study therapy should be discontinued immediately, and pregnancy reported (Section 8.4.9.4).
- Heart or liver transplant or CMAD at any time during the trial
- Other reasons, such as administrative reasons
- Study terminated by Sponsor
- Site closed by Sponsor

All dosed patients who prematurely discontinue from the study, regardless of cause, will be seen for an Early Termination (ET) Visit. Patients refusing to come to the study center for an ET Visit or who cannot be reached must be mailed a registered letter requesting that they come to the study center and return any unused IMP. A copy of the registered letter will be kept by the study center with the source documentation. The reason for premature discontinuation from the study will be reflected on the study termination page of the CRF.

If a subject discontinues, all efforts must be made to have the subject return for a final safety follow-up visit 30 days after the last dose of IMP.

8.4 TREATMENTS

8.4.1 Treatments Administered

Patients who satisfy the inclusion and exclusion criteria listed in Section 8.3 will be enrolled into a single study arm.

- 800-mg dose of acoramidis (AG10) HCl twice daily

The study was initiated with acoramidis (AG10) HCl 200 mg tablets. Upon completion of a Phase 1 relative bioavailability study, acoramidis (AG10) HCl 400 mg tablets were introduced. Subjects will switch to the new formulation for the remainder of the trial.

8.4.1.1 *Dose Modification for Adverse Events*

- The investigator is encouraged to manage adverse events (depending on their severity) with standard medical therapy prior to consideration of dose modification. Downward adjustment of dose or interruption of study drug is discouraged but permitted if necessary, in the event of intolerance to study drug. Subsequent upward adjustment of study drug back to the target dose should be attempted whenever possible If it is believed that an adverse event may be drug-related, and depending on its severity, the study drug may be reduced from 800 mg twice daily to 400 mg twice daily

- interrupted temporarily with a plan to re-initiate treatment

- discontinued permanently

Subjects who are unable to tolerate a dose of 400 mg twice daily will discontinue study drug dosing. If a subject discontinues study drug, every attempt should be made for the subject to be seen for an ET Visit.

After a period of consistent tolerability at the dose 400 mg twice daily, the subject may attempt to adjust upwards to the target dose of 800 mg twice daily, at the discretion of the investigator and in consultation with the Medical Monitor. The Medical monitor should be made aware of any planned dose adjustments or re-initiation of study drug after an interruption due to an adverse event. All dose adjustments should be documented in the database.

8.4.2 Identity of Investigational Medicinal Product

Acoramidis (AG10) HCl 400 mg film coated tablets will be supplied by Eidos Therapeutics, Inc. The excipients of acoramidis HCl (400 mg) tablets include microcrystalline cellulose, croscarmellose sodium, silicon dioxide, and magnesium stearate, coated with Opadry.

8.4.2.1 Packaging

The investigational medicinal product (IMP) will provided as kits assigned to patients using their study identification (ID) code from Study AG10-201. The kits will be labeled with the protocol number, storage information, warning language (“Caution: New Drug - Limited by Federal Law to Investigational Use. Keep Out of Reach of Children”), and instructions to take as directed.

8.4.2.2 Storage, Dispensing and Return of Investigational Product

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

The site research pharmacy (or appropriately trained designee) 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 disposition record will be kept that specifies the amount dispensed to each patient, the date dispensed, and any amount returned by the patient. 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. Also, at the completion of the study, the site research pharmacy (or appropriately trained designee) will provide the Sponsor with a complete record of IMP accountability.

It is the PI's responsibility to ensure that patients return their unused IMP and empty bottles at each visit.

8.4.3 Method of Assigning Identifiers to Patients

Patients will keep their assigned study ID number from Study AG10-201.

8.4.4 Selection of Dosage in the Study

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

8.4.5 Selection and Timing of Dose for Each Patient

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

8.4.6 Prior and Concomitant Therapy

Patients will not be permitted to use any concomitant medications listed in the exclusion criteria during the study.

At Day 1, at each visit during the treatment period, and at the Follow-up Visit, study center staff will question each patient specifically on the use of all concomitant medications and record the medication, dosage, and duration of use in the appropriate CRF.

8.4.7 Treatment Compliance

The study investigator must maintain exact records of the amount of study drug dispensed and returned at each study visit by recording the following information:

- Patient study number
- Date(s) and visit number when study drug was dispensed
- Amount of study drug dispensed
- Date of return of study drug
- Amount of study drug returned

An accountability log will be provided by the Sponsor and maintained at the study site to record information for each patient. Before dispensing new IMP at each visit, study center personnel will make every effort to collect all unused IMP.

8.4.8 Assessments

8.4.8.1 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by study day in the Schedule of Assessments in Section 1.0. The descriptions of the procedures to be performed throughout the study are provided below.

8.4.8.2 Study Treatment Days

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

Day 1 (Enrollment)

- Review inclusion/exclusion criteria to confirm patient is eligible
- Medical history
- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Perform resting transthoracic echocardiogram
- Collect PK blood sample (predose)
- Collect PD assay blood sample (predose)
- Collect prealbumin (predose)
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Assess concomitant medication use
- Administer and Dispense IMP
- AE assessment

Day 14 (± 3 days)

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Collect PK blood sample (predose)

- Collect PD sample (predose)
- Collect prealbumin (predose)
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Assess concomitant medication
- AE assessment

Day 45 (±7 days)

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Collect PK blood sample (predose)
- Collect PD sample (predose)
- Collect prealbumin (predose)
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Assess concomitant medication
- Collect any unused IMP
- AE assessment

Every 6 Month Visit (±7 days)

From study start to Month 54, clinic visits were every 3 months. After the Month 54 clinic visit, clinic visits will be every 6 months.

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG through Month 12, then annually thereafter.
- Perform resting transthoracic echocardiogram through Month 12, then annually thereafter
- Collect PK blood sample (predose) **at Months 3, 6, and 15 and then every 3 months after Month 15. After the Month 54 clinic visit, collect samples every 6 months.**

- Collect PD sample (predose) **at Months 3, 6, and 15 and then every 3 months after Month 15. After the Month 54 clinic visit, collect samples every 6 months.**
- Collect prealbumin (predose) **at Months 3, 6, and 15 and then every 3 months after Month 15. After the Month 54 clinic visit, collect samples every 6 months.**
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Assess concomitant medication
- Dispense IMP
- Collect any unused IMP
- AE assessment

8.4.8.3 Telephone Contact Every 3 Months

After Month 54, telephone contact will occur every 3 months (±7 days) during months without scheduled in-clinic visits (eg, Months 57, 63, etc.).

- AE collection
- Concomitant medication use assessment
- IMP compliance assessment

8.4.8.4 Unscheduled Visit

Unscheduled visits can be performed at any time during the study if needed, for example to assess or follow up on an adverse event. For any unscheduled visit, the date and reason for the unscheduled visit should be documented, concomitant medications reviewed, and adverse events evaluated.

If the unscheduled visit is for assessment or follow up of an adverse event, only procedures that are indicated for assessment or follow up of the adverse event may be conducted as needed (eg, physical exam, vital signs, 12-lead resting ECG, clinical laboratory assessments, and urine pregnancy test, may be conducted as indicated by the Investigator).

Procedures for Unscheduled Visits may include:

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Perform resting transthoracic echocardiogram
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test

- Assess concomitant medication
- Collect any unused IMP
- AE assessment

8.4.8.5 Early Termination Visit (ET)

All subjects who prematurely discontinue from the study, regardless of cause, will be seen for an Early Termination (ET) Visit. The visit should be performed as soon as possible after stopping IMP.

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Perform resting transthoracic echocardiogram (only if not obtained in prior 6 months)
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Assess concomitant medication
- Collect any unused IMP
- AE assessment

8.4.8.6 Follow-up Visit

Patients will have a Follow-up Visit 30 days after the last dose of IMP, or if the study is ended.

The following procedures will be performed at the Follow-up Visit:

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Assess concomitant medication
- AE assessment (If the subject is unable to attend visit in person, at a minimum a telephone contact must be performed in order to collect this information.)

Any clinically significant findings obtained during the final examination at the Follow-up Visit, including clinically significant 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 can be explained as being unrelated to the IMP.

8.4.8.7 PK and PD Blood Sampling Procedures

Additional details on PK and PD blood sampling procedures and storage can be found in the supplementary Laboratory Manual.

8.4.9 Safety Assessments

Patients must be seen by a physician or an appropriately trained health professional at every visit, and the evaluation must be documented. The procedures discussed in this section will be performed on the designated study days.

8.4.9.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product 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-E6).

For the purpose of data collection for this study, any untoward event that is reported from the time that the patient signs the ICF until 30 days after the last dose of IMP is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Symptoms offered by or elicited from the patient
- Objective signs observed by the PI or other study personnel
- All diseases that occur after the start of the study, including any changes in severity or frequency of preexisting disease. 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.
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study

8.4.9.1.1 Causality Assessment

The Investigator must assess the relationship of the event to the study drug. The causal relationship of the AE is assessed using a binary system, and AEs are classified as either ‘related’ or ‘unrelated’ as defined below.

Related: The available evidence suggests the adverse event is most likely due to the study drug. For example, a temporal relationship exists between the AE onset and administration of the study drug 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 study drug. Such other factors may include the underlying disease state, comorbidities, an intercurrent illness, concomitant medication(s) or procedures.

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.

8.4.9.1.2 Severity Assessment

The PI or Sub-Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's CRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 8.4.9.2). Severity will be assessed according to the following scale:

Mild: A type of adverse event 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 adverse event 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 participant.

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

8.4.9.2 Serious Adverse Events

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

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or

- Results in a congenital anomaly or birth defect
- Important medical event

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 patient 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 serious outcomes to determine whether they qualify as SAEs.

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

8.4.9.3 Reporting Adverse Events and Serious Adverse Events

Any untoward event that is reported from the time that the patient 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, in treatment, or post-treatment period are to be considered AEs (and SAEs if appropriate), and consequently recorded and reported as such.

Patients 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 (Section 8.4.8.1). Patients 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 patient’s CRF.

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

In addition, SAEs that are assessed by the Investigator as related to study drug(s) 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 becomes aware of the event.

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

For every AE, the PI (or appropriately trained designee) must

- Provide an assessment of the severity, causal relationship to the IMP, and seriousness of the event (ie, whether it is an SAE)

- Document all actions taken with regard to the IMP
- Detail any other treatment measures taken for the AE
- Document resolution of the AE

Additional information regarding the expedited reporting required for SAEs is provided in Section 8.4.9.5.

8.4.9.4 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy (including the pregnancy of a male patient's partner) that occurs from the time the patient 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 and email it to the SAE/Pregnancy email address (safety@eidostx.com), 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 (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be completed (in addition to the Pregnancy Form) as described in Section 8.4.9.5, with the appropriate serious criterion (eg, hospitalization) indicated.

In the event that a female study subject or the partner of a study subject becomes pregnant, the Investigator is required to contact the Medical Monitor within 24 hours of becoming aware of the event.

If a female subject becomes pregnant, administration of the study drug(s) must be discontinued immediately.

8.4.9.5 Immediate Reporting of Serious Adverse Events and Events of Special 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 on the SAE Form for Clinical Trials. The Sponsor's Study Physician may also be notified by telephone.

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

The study center staff must transmit the SAE Form for Clinical Trials to the SAE email (safety@eidostx.com). Even if an initial report is made by telephone, the study center staff must still complete the SAE Form for Clinical Trials with all available details and transmit the form within 24 hours of knowledge of the event.

Supplemental information 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 PI (or appropriately trained designee) is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's CRF. The study center staff 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.

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

Email for SAEs and pregnancy: Safety@eidostx.com

Contact information for the Sponsor's personnel is as follows:

Suresh Siddhanti, PhD
Vice President, Clinical Development
Sponsor Medical Monitor
suresh.siddhanti@bridgebio.com
415-997-2015
Eidos Therapeutics, Inc.
1800 Owens Street, Suite C-1200
San Francisco, CA 94158

Alternate contact information for Sponsor:

Jean-François Tamby, MD
Vice President, Clinical Development
jf.tamby@bridgebio.com
415-573-1526

8.4.9.6 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the times detailed in the Schedule of Assessments (Section 1.0). Urine screen for drugs of abuse will be collected at Day 1. From Day 1, the PI or Sub-Investigator will provide ongoing assessment of any Clinical Laboratory Values outside the reference range to determine their clinical significance. Additional information on laboratory tests performed can be found in the supplementary study specific 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, alkaline phosphatase, calcium, phosphorus, total and fractionated (indirect or direct) bilirubin, uric acid, thyroid-stimulating hormone (TSH), troponin I, creatine kinase (CK), CK-MB, and NT-proBNP
Urinalysis:	Complete urinalysis (specific gravity, pH, glucose, protein, hemoglobin, leukocyte esterase, and nitrite and Urine screen for drugs of abuse) by dipstick. 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:	Follicle-stimulating hormone [FSH], estradiol, and progesterone (in females of Child-Bearing potential only) will be assessed.
PT/PTT/INR:	Coagulation laboratory tests will be completed at all study visits for patients who are receiving warfarin (Coumadin®)

Pregnancy test:
(females of Child-Bearing Potential only) Urine test at all visits and at Follow-up.

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

8.4.9.7 Vital Signs

Vital signs will be assessed at the times detailed in the Schedule of Assessments (Section 1.0). Study center staff will assess vital signs after a 5-minute rest as specified in Section 8.4.8.1

8.4.9.8 Electrocardiograms

A standard 12-lead ECG will be assessed at the times detailed in the Schedule of Assessments (Section 1.0). ECGs will be performed in the supine position after a 30-minute rest as specified in Section 8.4.8.1 ECG collected annually after 12 months.

8.4.9.9 Echocardiograms

A standard resting transthoracic echocardiogram will be assessed at the times detailed in the Schedule of Assessments (Section 1.0). Echocardiograms are to be performed in the supine position as specified in the Study ECHO Manual. Echocardiogram collected annually after 12 months.

8.4.9.10 Other Safety Assessments

8.4.9.10.1 Physical Examinations

At the times detailed in the Schedule of Assessments (Section 1.0), patients will undergo a complete physical examination with body weight, which is to be completed by a professionally trained physician or health professional.

8.5 DATA QUALITY ASSURANCE

8.5.1 Data Monitoring

Before the first patient is dosed in the study, a representative of the Sponsor will meet with the PI and the PI's staff to review the procedures for conducting the study and to train the staff 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 PI and his or her staff. The PI will make available to the Sponsor representative the source documents, the signed consent forms, and all other study-related documents. The PI (or appropriately trained designee) 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 patient 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.

8.5.2 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 PI's approval of all changes performed on his or her patients' 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 patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of CRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and FDA officials.

8.6 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.6.1 General Considerations

Statistical summaries may be performed using statistical software specified in the Statistical Analysis Plan (SAP). Additional software may be used for the production of graphics. PK parameters may be computed using WinNonlin Professional. Additional information regarding statistical analyses can be found in the SAP.

8.6.2 Timing of Analyses

When final in-clinic visits and posttreatment follow-up have been completed for all patients, the database will be cleaned and locked, and analyses will be performed.

8.6.3 Analysis Sets and Analysis Conventions

Applicable analysis sets for the secondary endpoints (eg, PK-PD relationship) will be defined in the Statistical Analysis Plan (SAP).

The analysis set for safety analyses will be the Safety Analysis Set: all patients dosed.

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

8.6.4 Demographics and Other Baseline Characteristics

Demographic and Baseline Characteristics will be summarized using the descriptive statistics for subjects in the Safety Analysis Set. Demographic and baseline data will also be listed for subjects in the Safety Analysis Set. General medical history will be coded by MedDRA (version 21.0 or later), as applicable at time of analysis and will be presented by subject listing.

8.6.5 Extent of Exposure

Exposure to study drug, number of subjects with missed doses, and total number of tablets administered will be summarized for the safety analysis set for exposure during the AG10-202 study. The amount of study drug dispensed and returned will be presented for each subject in listings.

8.6.6 Pharmacokinetic Analyses

PK parameters will be calculated for each patient and summarized by dose levels. Parameters will be reported for the PK profile at steady-state (ie, after the last dose). Only patients with sufficient data to calculate each PK parameter will be included in the summary of each PK profile.

8.6.7 Safety Analyses

AEs will be coded using the MedDRA dictionary. The incidence of each treatment-emergent AE will be summarized by system organ class, and preferred term. Multiple AEs mapped to the same preferred term will be counted once per patient. Concomitant medications will be coded using the WHO Drug Dictionary with generic term and therapeutic use (ATC code) and summarized by ATC code and WHO generic name. Safety laboratory findings, vital signs, and 12-lead ECG data will be summarized descriptively and listed by 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.

8.6.7.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present before the first dose of IMP or if it was present before the first dose of IMP but increased in severity during the treatment period. If more than 1 AE is reported before the first dose of IMP and is coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that preferred term and that occurred during the period. An AE that occurs more than 30 days after the last dose of IMP will not be counted as a TEAE.

8.6.7.2 Data Monitoring Committee (DMC)

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. An independent data monitoring committee will monitor the safety and conduct of the trial. The DMC will be comprised of medical and statistical representatives. 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.

8.6.8 Pharmacodynamic Analysis

TTR stabilization will be measured serially as described in the Schedule of Assessments. At each time-point, each of these parameters will be summarized by dose. In addition, these parameters will be plotted vs plasma drug concentration and the concentration response may be modeled as appropriate.

8.6.9 Interim Analysis

No interim analysis is planned for this study.

8.6.10 Determination of Sample Size

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

8.7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided in writing by the Sponsor to the PI. No protocol amendment may be implemented (with the exception noted below) before it has been approved by the IRB and before the signature page, signed by the PI, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

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

9.0 STUDY SPONSORSHIP

9.1 STUDY TERMINATION

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

9.2 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 PI will be pursuant to mutual agreement between the PI and the Sponsor.

10.0 INVESTIGATOR OBLIGATIONS

10.1 DOCUMENTATION

The PI (or appropriately trained designee) must provide the following to the Sponsor before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and forwarded to the Sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae and licensure for the PI and all Sub-Investigators listed on Form FDA 1572, as well as for the Clinical Laboratory Director
- A copy of the initial IRB 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, as described in Section 4.1.
- A copy of the IRB-approved ICF
- A copy of the HIPAA authorization form (if applicable)
- A list of the IRB members or the US Department of Health and Human Services general assurance number
- A copy of the clinical laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol (Section 11.0) signed and dated by the PI
- A financial disclosure statement completed and signed by the PI and all Sub-Investigators listed on Form FDA 1572. If applicable, the PI and Sub-Investigators will provide an updated financial disclosure statement to the Sponsor 1 year after the completion of the study.

10.2 PERFORMANCE

The PI must demonstrate reasonable efforts to obtain qualified patients for the study.

10.3 USE OF INVESTIGATIONAL MATERIALS

The PI 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 PI or Sub-Investigators listed on Form FDA 1572. 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 PI 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 may be returned to the Sponsor after all patients have returned for this exit/final visit and a final IMP accountability has been completed for the study site. If unused IMP is not returned to the Sponsor, proof of destruction must be provided to the Sponsor. The PI will be responsible for ensuring that patients return their IMP.

10.4 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 PI will be responsible for verifying that all data entries in the CRFs are accurate. The PI 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.

10.5 RETENTION AND REVIEW OF RECORDS

The PI must maintain the documentation relating to this study. If the sponsor, the FDA, or another regulatory authority wishes to review any documentation relating to the study, the PI must permit access to such records.

The PI must retain a copy of all records that support CRFs for this study (eg, 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 PI 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.

10.6 PATIENT CONFIDENTIALITY

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

11.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study (Study AG10-202) in accordance with the protocol and with all applicable government regulations and Good Clinical Practice (GCP) guidance.

_____ _____/_____/_____
Principal Investigator's Signature Date

_____
Principal Investigator's Name

12.0 REFERENCES

Judge, D. P., Heitner, S. B., Falk, R. H., Maurer, M. S., Shah, S. J., Witteles, R. M., Grogan, M., Selby, V. N., Jacoby, D., Hanna, M., Nativi-Nicolau, J., Patel, J., Rao, S., Sinha, U., Turtle, C. W., & Fox, J. C. (2019, Jul 23). Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. *J Am Coll Cardiol, 74*(3), 285-295. https://doi.org/10.1016/j.jacc.2019.03.012

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13.0 SUMMARY OF CHANGES

CHANGE	RATIONALE	SECTIONS AFFECTED
Amendment 1 vs Original		
Confidentiality statement updated	Legal update to confidentiality statement	• Cover page
Number of centers changed	Updated to current number of participating study centers	• Synopsis (Study Centers (Country) subsection) • Section 5.1
Changed "AG10 administered on a background of heart failure therapy" to "AG10 administered on a background of stable heart failure therapy"	Updated to account for natural history of disease ATTR-CM in patients enrolled in study AG10-201	• Synopsis (Methodology subsection)
Number of patients enrolled in study and eligible for participation changed	Updated current number of patients enrolled in study AG10-201 and eligible for participation in this study	• Synopsis (Number of Patients subsection) • Section 8.1 • Section 8.3 • Section 8.6.10
Removed redundant wording in inclusion and exclusion criteria	All patient eligibility criteria for the study is determined by judgement of the PI	• Synopsis (Inclusion/Exclusion criteria subsection) • Section 8.3.1 • Section 8.3.2
Updated duration of study to be dependent on periodic recommendations of the AG10 DMC and/or registration of product for treatment of symptomatic ATTR-CM	As of June 2018, toxicology data currently supports AG10 dosing in clinical trials for up to 90 days; the study design and schedule of assessments has been updated accordingly	• Synopsis (Duration of Study and Treatment subsection)
Updated schedule of assessments table and footnotes, changed cadence of assessments, changed cadence of collection of predose PK and PD blood samples to Day 1, Day 14,	As of June 2018, toxicology data currently supports AG10 dosing in clinical trials for up to 90 days; the study design and schedule of assessments has been updated accordingly	• Synopsis (Pharmacokinetic/ Pharmacodynamic Sampling Measures subsection, Schedule of Assessments) • Section 8.5

CHANGE	RATIONALE	SECTIONS AFFECTED
and Day 60 (End of Treatment), changed cadence of follow-up visits		
Updated abbreviations list	Updated abbreviations used in protocol	• Section 3.0
Deleted specific bioanalytical laboratory location and changed to central laboratory	Updated reference	• Section 5.3
Updated information to align with IB: removed dated references to old IB version; added information on 90-day repeated-dose toxicity studies in dog and rat and plan to dose eligible patients for up to 90 days, inclusive of the 28 days of prior dosing in Study AG10-201; added IB reference for further detail on dose selection	Alignment with IB	• Section 6.0 • Section 6.1 • Section 8.1 • Section 8.4.4
Added text with detail on treatment administered	Supply of 400 mg tablets may become available in the future	• Section 8.4.1
Clarified that if a participant discontinues study drug, every attempt should be made to continue to perform study-related follow-up and procedures through the 7 to 14-Days Follow-Up Visit (changed from 3- Day End-of-Study Visit)	Clarification of Dose Modification and conditions for discontinuation from treatment	• Section 8.4.1.1 • Section 8.5.1.2 • Section 8.5.2.6
Removed references to number of tablets dispensed and returned “at each study visit”	IMP will be returned only at the Day 60 visit	• Section 8.4.7
Changed causal relationship of AE to be assessed using a binary system with AEs classified as either ‘related’ or ‘unrelated’	Updated causality assessment to binary classification system	• Section 8.5.2.1.1
Added information on DMC charter	Based on current information from DMC charter	• Section 8.7.7.2

CHANGE	RATIONALE	SECTIONS AFFECTED
Added statement on requiring proof of destruction of IMP	Updated to account for investigative sites that will destroy IMP onsite per their institution policy	• Section 10.3
Copyedits and corrections	Administrative updates to improve accuracy and cohesion	• Throughout document
Amendment 2 vs Amendment 1		
Updated key sponsor contacts	Change in medical monitor contact information	• Cover page • Section 8.5.2.5
Deleted eGFR exclusion criteria (eGFR <30 mL/min/1.73 m^2)	ATTR-CM patients with renal impairment will not be excluded from this long-term safety monitoring study.	• Synopsis (Exclusion Criteria subsection) • Section 8.3.2
Adjusted exclusion criteria pertaining to abnormalities in clinical laboratory tests or clinically significant ongoing medical condition or any laboratory abnormality or condition that could adversely affect safety of the patient to add that this determination would be based on screening laboratory results from study AG10-201	Clarified exclusion 3 and 4 should be ruled out based on the central laboratory results from the Phase II Study AG10-201 Screening visit. Remaining Exclusion Criteria were renumbered to reflect the deletion of one of the original exclusions.	• Synopsis (Exclusion Criteria subsection) • Section 8.3.2
Revised duration of study to be dependent on periodic recommendations of the AG10 DMC and/or registration of the product for the treatment of symptomatic ATTR-CM	The FDA approved continuing to treat patients beyond 90 days before the chronic toxicology data are available. In a communication on 30 July 2018, FDA agreed with the Eidos proposal for an exception to the ICH standard for conduct of chronic toxicology studies before unrestricted duration of human treatment. All available nonclinical and clinical safety data were reviewed and considered with respect to the patient population in concluding the benefit-risk assessment supports continuing treatment;	• Synopsis (Duration of Study and Treatment subsection)

CHANGE	RATIONALE	SECTIONS AFFECTED
	the schedule of assessments was updated accordingly.	
Predose PK and PD blood sample collection cadence changed from Day 1, Day 24, and Day 60 (End of Treatment) to Day 1, Day 14, Day 45, 3 months, and 6 months from Day 1 visit	The FDA approved continuing to treat patients beyond 90 days before the chronic toxicology data are available. In a communication on 30 July 2018, FDA agreed with the Eidos proposal for an exception to the ICH standard for conduct of chronic toxicology studies before unrestricted duration of human treatment. All available nonclinical and clinical safety data were reviewed and considered with respect to the patient population in concluding the benefit-risk assessment supports continuing treatment; the schedule of assessments was updated accordingly.	• Synopsis (Pharmacokinetic/ Pharmacodynamic Sampling Measures subsection)
Adjusted description of overall study design and plan, updated schedule of assessments: changed Day 60 to Day 45 and added column for visits every 3 months in schedule of assessments table, adjusted schedule of assessments table footnotes, adjusted assessments cadence, adjusted cadence of follow-up visits, added and/or removed assessments to study visits	The FDA approved continuing to treat patients beyond 90 days before the chronic toxicology data are available. In a communication on 30 July 2018, FDA agreed with the Eidos proposal for an exception to the ICH standard for conduct of chronic toxicology studies before unrestricted duration of human treatment. All available nonclinical and clinical safety data were reviewed and considered with respect to the patient population in concluding the benefit-risk assessment supports continuing treatment; the schedule of assessments was updated accordingly.	• Synopsis and Schedule of Assessments • Section 8.1 • Section 8.5.1.1 • Section 8.5.1.2 • Section 8.5.2.6 • Section 8.5.2.7 • Section 8.5.2.8 • Section 8.5.2.9 • Section 8.5.2.10.1
Changed number of tablets per dose; added another strength of tablets	Supply of 400mg tablets may become available in the future and quantity of the tablets per dose will change.	• Section 8.4.1 • Section 8.4.1.1 • Section 8.4.2

CHANGE	RATIONALE	SECTIONS AFFECTED
Added Section 12 Appendix: Interim Safety Appendix	The FDA approved continuing to treat patients beyond 90 days before the chronic toxicology data are available. In a communication on 30 July 2018, FDA agreed with the Eidos proposal for an exception to the ICH standard for conduct of chronic toxicology studies before unrestricted duration of human treatment. All available nonclinical and clinical safety data were reviewed and considered with respect to the patient population in concluding the benefit-risk assessment supports continuing treatment; the schedule of assessments was updated accordingly.	• Appendix: Interim Safety Appendix
Amendment 3 vs Amendment 2		
Changed Eidos contact information from Jonathan Fox to Lenny Katz and Marisol Temech	Change in primary point of contact	• Cover page • Section 8.4.9.5
Added PK and PD sampling times beyond 6 months at Month 15 and then every 3 months after Month 15.	To continue to collect data on trough PK over a longer period of time.	• Synopsis • Table 1, footnote d • Section 8.4.8.2, Every 3 Month Visit information
Changed Echocardiogram and ECG intervals from every 3 months to annually after 12 months.	Consistent with published clinical data demonstrating minimal effect of ATTR stabilizers on echocardiogram parameters and equivocal effect on ECG parameters. Annual echocardiograms and ECGs are adequate for assessment in this study.	• Table 1, footnote c • Section 8.4.8.2, Every 3 Month Visit information • Section 8.4.9.8 • Section 8.4.9.9
Removed statement referencing periodic reviews by Data Monitoring Committee	Given that this is an ongoing open label study, the scope and frequency of review will be agreed upon with the DMC and documented in the charter.	• Synopsis • Section 8.1 and 8.6.7.2

CHANGE	RATIONALE	SECTIONS AFFECTED
Added Early Termination Visit and Unscheduled Visits	To provide clarification to investigators and assure consistency across the Eidos Clinical Development Program for AG10	• Table 1 • Section 8.4.8.3 and 8.4.8.4
Changed timing of Follow-Up Visit to occur 30 days after date of last dose of IMP instead of 7-14 days after date of last dose	Assures consistent adverse event evaluation across the Eidos Clinical Development Program for AG10	• Table 1 • Section 8.4.8.5
Changed 'patient dosing diary' to 'patient dosing record' and added details on its use	For clarification purposes only	• Table 1 • Section 8.4.8.7
Added additional items/reasons for discontinuation from therapy or assessment	For clarification and to assure consistency across the Eidos Clinical Development Program for AG10	• Section 8.3.3
Designation for AG10 changed to "AG10HCl"	To clarify the strength of AG10 is in the hydrochloride form	• Synopsis • Section 8.1, 8.4.1, and 8.4.2
Moved details regarding treatment compliance from statistical analysis section to compliance section	For clarification purposes only	• Section 8.4.7 • Section 8.6.5
Definitions of "related" and "not related" provided for causality assessment of adverse events.	• Not provided in earlier versions • Assures consistent adverse event evaluation across the Eidos Clinical Development Program for AG10	• Section 8.4.9.1.1
Clarified reporting period for adverse events to 30 days after date of last dose of IMP	Assures consistent adverse event evaluation across the Eidos Clinical Development Program for AG10	• Section 8.4.9.1 • Section 8.4.9.3
The reporting period for pregnancy has been changed from the last dose to 30 days after the date of last dose	Aligns the reporting period for pregnancy with that for adverse events.	• Section 8.4.9.4
Reporting of pregnancy to the Sponsor to be done within 24 hours of awareness	Not specified in earlier versions of the protocol.	• Section 8.4.9.4

CHANGE	RATIONALE	SECTIONS AFFECTED
Added details on Safety Analysis Set	For clarification purposes only	• Section 8.6.4
Added details on analysis set for extent of exposure	Not specified in earlier versions of the protocol.	• Section 8.6.5
Other minor editorial changes	For accuracy with no change to details or study design.	• Throughout the document
Amendment 4 vs Amendment 3		
Updated Sponsor address	Eidos Therapeutics location moved	• Cover page • Section 8.4.9.5
Updated Key Sponsor contacts	Change in points of contact	• Cover page • Section 8.4.9.5
Changed clinic visit frequency from every 3 months to every 6 months after Month 54	Alignment with study AG10-304, preemptively addressing patients' fatigue from frequent study visits	• Synopsis and Schedule of Assessments • Section 8.4.8.2
Added telephone contact every 3 months after Month 54	Alignment with study AG10-304	• Synopsis and Schedule of Assessments • Section 8.4.8.3
Removed Patient Dosing Record	AG10-202 is an open-label study	• Synopsis and Schedule of Assessments • Section 8.4.8
Added changes from previous protocol amendments to the Summary of Changes table	Accuracy and completion of comprehensive Summary of Changes from Original Protocol to Protocol Amendment 4	• Section 13
Incorporated acoramidis where AG10 is mentioned	Incorporated acoramidis as international nonproprietary name (INN) for AG10	• Throughout document
Made copyedits and formatting changes	Accuracy	• Throughout document