Protocol Title:	A Phase 2, Randomized, Placebo-controlled, Dose-ranging Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AG10 in Patients with Symptomatic Transthyretin Amyloid Cardiomyopathy
Protocol Number	EIDOS AG10-201
NCT Number:	NCT03458130
Protocol Version/Date:	Original: 10 January 2018 Amendment 1: 8 February 2018 Amendment 2: 25 May 2018

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Indication:	Transthyretin Amyloid Cardiomyopathy
Phase:	2
Investigational Medicinal Product:	AG10
Sponsor:	Eidos Therapeutics, Inc. 101 Montgomery Street, Suite 2550 San Francisco, CA 94104
Key Sponsor Contacts:	[redacted]
Protocol Version/Date:	Original: 10 January 2018 Amendment 1: 8 February 2018 Amendment 2: 25 May 2018

1.0 SYNOPSIS AND SCHEDULE OF ASSESSMENTS

CLINICAL STUDY SYNOPSIS: Study AG10	
Study Number	AG10-201
Title of Study	A Phase 2, Randomized, Placebo-controlled, Dose-ranging Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AG10 in Patients with Symptomatic Transthyretin Amyloid Cardiomyopathy
Study Centers (Country)	Approximately 10-15 centers (United States)
Development Phase	2
Objectives	**Primary:** The primary objective of this study is to evaluate the safety and tolerability of AG10 administered to adult patients with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM). Secondary: The secondary objectives of this study are: • to characterize the pharmacokinetics (PK) of AG10 administered orally twice daily in patients with symptomatic ATTR-CM, and • to describe the pharmacodynamic (PD) properties of AG10 as [redacted] in adult patients with symptomatic ATTR-CM.
Methodology	This prospective, randomized, multicenter, double-blind, parallel group, placebo-controlled, dose-ranging study will evaluate the safety, tolerability, PK and PD of AG10 compared to placebo administered on a background of stable heart failure therapy. Screening and randomization will be followed by a 28-day blinded, placebo-controlled treatment period.
Number of Patients	Approximately 55
Main Criteria for Inclusion	To be eligible to participate in the study, patients must meet all of 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. Be a male or female ≥18 to ≤90 years of age. 3. Have an established diagnosis of ATTR-CM with either wild-type transthyretin or a variant transthyretin genotype (assessed by genotyping, with patients with concurrent monoclonal gammopathy of undetermined significance requiring a confirmatory test using mass spectrometry) as defined by either positive endomyocardial biopsy or positive technetium pyrophosphate scan. 4. Have a history of heart failure evidenced by at least one prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) requiring medical management. 5. Have NYHA Class II-III symptoms. 6. Male patients and female patients of childbearing potential who engage in heterosexual intercourse must agree to use appropriate method(s) of contraception. 7. For patients 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.
Main Criteria for Exclusion	To be eligible to participate in the study, patients must meet none of the following criteria:

	1. Acute myocardial infarction, acute coronary syndrome or coronary revascularization within 90 days prior to Screening. 2. Experienced stroke within 90 days prior to Screening. 3. Has hemodynamic instability at Screening or Randomization that, in the judgment of the PI, would pose too great a risk for participation in the study. 4. Has estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 at Screening. 5. Is likely to undergo heart transplantation within the next year. 6. Has confirmed diagnosis of light-chain amyloidosis. 7. Has abnormal liver function tests at Screening, defined as ALT or AST >3 × upper limit of normal (ULN) or total bilirubin >2 × ULN. 8. Has abnormalities in clinical laboratory tests at Screening or Randomization that, in the judgment of the PI, would pose too great a risk for participation in the study. 9. Known hypersensitivity to study drug (AG10 or placebo), its metabolites, or formulation excipient 10. Current treatment with diflunisal, tafamidis, green tea, doxycycline, TUDCA/Ursodiol, Patisiran or Inotersen within 14 days or 5 half-lives of the prior investigational agent (whichever is longer) prior to dosing with study drug. 11. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before the study drug is administered. A negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization visit are required for female patients of childbearing potential. 12. In the judgment of the investigator, has any clinically significant ongoing medical condition that might jeopardize the patient's safety or interfere with the study, including participation in another investigational drug or investigational device study within the 30 days prior to Screening with potential residual effects that might confound the results of this study. 13. Has any laboratory abnormality or condition that, in the investigator's opinion, could adversely affect the safety of the patient or impair the assessment of study results. 14. Has any condition that, in the opinion of the investigator, would preclude compliance with the study protocol such as a history of substance abuse, alcoholism or a psychiatric condition. 15. Has participated in another investigational study within 14 days or 5 half-lives of the prior investigational agent (whichever is longer) prior to dosing with study drug. Exceptions can be made in the case of observational and/or registry studies upon consultation with the Medical Monitor.
Test Product, Dosage, and Mode of Administration	AG10, [redacted] and [redacted] mg twice daily, oral administration
Duration of Study and Treatment	Study duration: Total of 35 to 42 days, Day 1 through the last treatment taken on Day 28, followed by a follow-up visit within 7 to 14 days from Day 28 or last dose. In addition, there will be a 28-day Screening period. Treatment duration: 28 days of dosing
Reference Therapy, Dosage, and Mode of Administration	Placebo tablets matching AG10 twice daily, oral administration

Primary Outcome Measures	**Safety and Tolerability:** Safety will be assessed by collection of treatment-emergent adverse events (AEs), post-randomization physical examination findings, clinical events (including death, myocardial infarction, stroke, heart failure hospitalization, emergency presentation for worsening heart failure), vital signs, electrocardiogram (ECG) data (PR, RR, QRS, and QT intervals), and clinical laboratory parameters. **Endpoint:** The primary endpoint is to characterize the safety and tolerability of AG10 administered to adult patients with symptomatic ATTR-CM over 28 days of dosing.
Secondary Outcome Measures	**Pharmacokinetics:** The PK measurements of AG10 and metabolite will be performed by a designated bioanalytical laboratory after the first dose and at steady state (Day 14, Day 28). **Pharmacodynamics:** The PD measurements of AG10 will be [redacted] in adult patients with symptomatic ATTR-CM.
Statistical Methodology	All statistical summaries will be performed using SAS Version 9.2 ([redacted]) or higher. Additional software may be used for the production of graphics. PK parameters will be computed using [redacted]. 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. **PK Analyses:** PK parameters will be calculated for each patient and summarized by dose levels. Parameters will be reported for the first dose and PK profile at steady-state, i.e. after the last dose. Only patients with sufficient data to calculate each PK parameter will be included in the summary of each PK endpoint. **PD Analyses: ex vivo** [redacted] 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, [redacted] levels and the concentration response may be modeled as appropriate. **Safety Analyses:** AEs will be coded using the 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 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 by treatment group assignment. Safety laboratory findings, vital signs, and 12-lead ECG data 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. Total number of major clinical events will be summarized by treatment and time to event analyses will also be performed.
Pharmacokinetic/Pharmacodynamic Sampling Measures	PK blood samples will be collected on Days 1, 14, and 28. PD blood samples will be collected on Days 1, 14 and 28.

Table 1. Schedule of Assessments

	Screening Period (Day -28)	Double Blind Treatment Period (days)					Follow-up (ET)[b]
		Day 1[a]	Day 7 (± 3)	Day 14[a] (± 3)	Day 21 (± 3)	Day 28[a] (± 3)	7 to 14-day follow-up visit
Written Informed Consent	X						
Inclusion/Exclusion Criteria Review	X	X					
Medical History	X						X
Physical Exam[c]	X	X		X		X	X
Resting transthoracic echocardiogram		X					
Vital Signs	X	X		X		X	X
12-lead resting ECG	X	X		X		X	X
PD assays[d]		X		X		X	
PK sample collection[d]		X		X		X	
Study drug dosing during visit		X		X		X	
Clinical laboratory assessments	X	X		X		X	X
Pregnancy test[e]	X	X		X		X	X
Contact Patient[f]			X		X		
Concomitant medications	X	X	X	X	X	X	X
[redacted]							
Adverse events	X	X	X	X	X	X	X

a. Recommended order of assessments (as applicable) at Day 1, Day 14 and Day 28 visits: (1) ECG, (2) echocardiogram (3) predose PK/PD sample collection and, all other blood sample collection (4) witnessed study drug dosing, and (5) postdose PK/PD sample. All other required visit assessments may occur at any point during the study visit.

b. If a patient prematurely discontinues study participation before completing the 28-Day treatment period, the patient will be asked to return to the study center for the Follow-up Visit. The Follow-up Visit should be performed within 7 to 14 days after last dose.

c. Complete PE including body weight and height measurements, and BMI calculation at Screening, abbreviated PE with weight at all other visits.

d. Please refer to updated lab manual on timing of PK and PD collections.

e. Females of Child-Bearing Potential only. Serum pregnancy test at Screening and urine pregnancy test at all other visits.

f. Contact patient at Day 7 (±3) and Day 21 (±3) to review adverse events, concomitant medications and study drug compliance.

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ATTR	TTR amyloidosis
ATTR-CM	TTR cardiomyopathy
ATTR-PN	TTR polyneuropathy
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
CRF	case report form
CI	confidence interval
ECHO	echocardiogram
ECG	electrocardiogram, electrocardiographic
EDC	electronic data capture
ET	Early termination
FDA	US Food and Drug Administration
[redacted]	[redacted]
GCP	good clinical practice
β-hCG	β–human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IB	Investigator's Brochure
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
IRTS	Interactive Response Technology System
MABEL	minimum anticipated biological effect level
NDA	New Drug Application
PCS	potentially clinically significant
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic

QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
QTcNi	QT interval corrected for heart rate using an individual correction
SAE	serious adverse event
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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

At screening, competent 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 at up to 15 study centers located in the United States (US). 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 AG10 concentrations and its key metabolites in plasma samples will be analyzed at [redacted].

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

AG10 is a new chemical entity that is a potent and selective stabilizer of transthyretin (TTR) amyloidosis (ATTR) that is initially being developed by Eidos Therapeutics, Inc. for the treatment of ATTR-CM. ATTR is 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. The initial focus of development of AG10 is for the treatment of ATTR-CM.

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 100 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.

AG10 is a potent, highly selective, small molecule TTR stabilizer. [redacted] A Phase I study in healthy volunteers is ongoing with no safety signals identified to date.

6.1 KNOWN AND POTENTIAL RISKS AND BENEFITS OF AG10 TO HUMAN SUBJECTS

To date, there have been no adverse effects in adult animals or humans with other TTR stabilizers in development that suggest on-target adverse effects of [redacted],

[redacted] Given this observation, the AG10 program will monitor for such events [IB].

The AG10 toxicology program has documented a wide safety margin and low potential for adverse effects at predicted therapeutic exposures. [redacted]

As of [redacted], a total of [redacted] subjects have been exposed to AG10 in the ongoing study AG10-001. This first-in-human study is a randomized, double-blind, placebo-controlled single ascending (SAD) and multiple ascending (MAD) oral dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AG10 in healthy subjects. [redacted] In general, AG10 has been well tolerated, and no clinically significant changes in vital signs, adverse events (AEs) or laboratory findings have been observed. AG10 has demonstrated an acceptable tolerability and safety profile, with no clinically significant changes in vital signs or laboratory parameters. There have been no serious adverse events related to AG10 in this study.

Additional information for AG10 can be found in the Investigator's Brochure.

7.0 STUDY OBJECTIVES

7.1 Primary Objective

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

7.2 Secondary Objectives

The secondary objectives of this study are:

- to characterize the pharmacokinetics (PK) of AG10 administered orally twice daily in patients with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of AG10 as [redacted] in adult patients with symptomatic ATTR-CM.

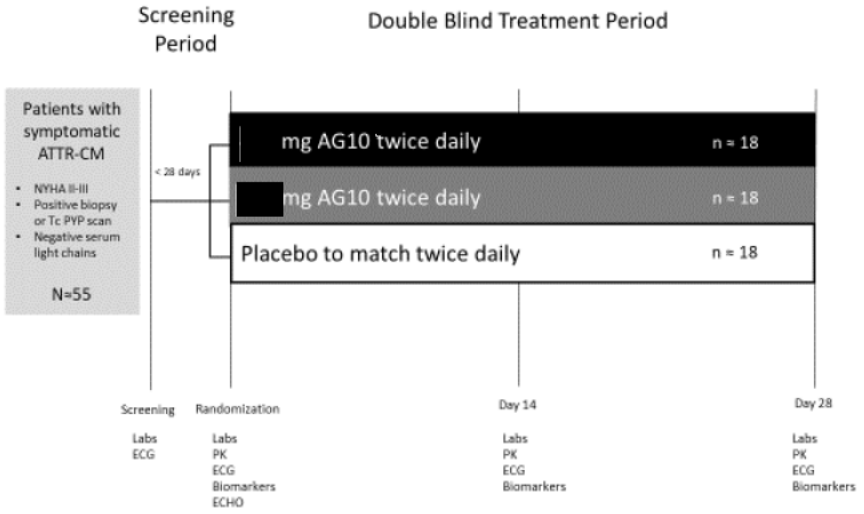
8.0 INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This study will be a Phase 2, randomized, placebo-controlled, dose-ranging study in approximately 55 male and/or female patients with symptomatic ATTR-CM aged 18 through 90 years.

If all doses are well tolerated, the duration of each patient's participation in the study will be 28 days of treatment. In addition, there will be a 28-day screening period before treatment and a 7 to 14-day follow-up period before the final Follow-up Visit.

This prospective, randomized, multicenter, double-blind, parallel group, placebo-controlled, dose-ranging study will evaluate the safety, tolerability, PK and PD of AG10 compared to placebo administered on a background of stable heart failure therapy. Screening and randomization will be followed by a 28-day blinded, placebo-controlled treatment period.



ATTR-CM – Transthyretin amyloid cardiomyopathy; NYHA – New York Heart Association; Tc PYP – Technetium Pyrophosphate; PK – Pharmacokinetics; ECG – electrocardiogram; ECHO - echocardiogram

Eligible patients will be randomized in a 1:1:1 ratio to placebo or one of two different doses of AG10 administered twice daily. Approximately 30% of patients enrolled will be mutant ATTR-CM.

Participation in this Phase 2 study does not preclude participation in other studies of AG10, as long as the patient meets eligibility criteria.

The Schedule of Assessments is provided in Section 1.0. Detailed descriptions of each study day can be found in Section 8.5.1.

8.2 DISCUSSION OF STUDY DESIGN

This prospective study is designed to evaluate the safety and tolerability of AG10 in patients with ATTR-CM. A randomized, double-blind, placebo-controlled, dose-ranging 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 determine the dose with the better safety and tolerability profile.

8.3 SELECTION OF STUDY POPULATION

Approximately 55 males and females ≥18 and ≤90 years of age with chronic, stable, symptomatic ATTR-CM will be randomized in a 1:1:1 ratio (~ 18 patients per arm) in the study. Approximately 30% of patients enrolled will have mutant ATTR-CM.

8.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet all of 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. Be a male or female ≥18 to ≤90 years of age.

3. Have an established diagnosis of ATTR-CM with either wild-type transthyretin or a variant transthyretin genotype (assessed by genotyping, with patients with concurrent monoclonal gammopathy of undetermined significance requiring a confirmatory test using mass spectrometry) as defined by either positive endomyocardial biopsy or positive technetium pyrophosphate scan.

4. Have a history of heart failure evidenced by at least one prior hospitalization for heart failure or clinical evidence of heart failure (without hospitalization) requiring medical management.

5. Have NYHA Class II-III symptoms.

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

7. For patients 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.

8.3.2 Exclusion Criteria

Patients who meet any of the following criteria 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. Experienced stroke within 90 days prior to Screening.

3. Has hemodynamic instability at Screening or Randomization that, in the judgment of the PI, would pose too great a risk for participation in the study.

4. Has estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 at Screening.

5. Is likely to undergo heart transplantation within the next year.

6. Has confirmed diagnosis of light-chain amyloidosis.

7. Has abnormal liver function tests at Screening, defined as ALT or AST >3 × upper limit of normal (ULN) or total bilirubin >2 × ULN.

8. Has abnormalities in clinical laboratory tests at Screening or Randomization that, in the judgment of the PI, would pose too great a risk for participation in the study.

9. Known hypersensitivity to study drug (AG10 or placebo), its metabolites, or formulation excipient.

10. Current treatment with diflunisal, tafamidis, green tea, doxycycline, TUDCA/Ursodiol, Patisiran or Inotersen within 14 days or 5 half-lives of the prior investigational agent (whichever is longer) prior to dosing with study drug.

11. Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before the study drug is administered. A negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization visit are required for female patients of childbearing potential.

12. In the judgment of the investigator, has any clinically significant ongoing medical condition that might jeopardize the patient's safety or interfere with the study, including participation in another investigational drug or investigational device study within the 30 days prior to Screening with potential residual effects that might confound the results of this study.

13. Has any laboratory abnormality or condition that, in the investigator's opinion, could adversely affect the safety of the patient or impair the assessment of study results.

14. Has any condition that, in the opinion of the investigator, would preclude compliance with the study protocol such as a history of substance abuse, alcoholism or a psychiatric condition.

15. Has participated in another investigational study within 14 days or 5 half-lives of the prior investigational agent (whichever is longer) prior to dosing with study drug. Exceptions can be made in the case of observational and/or registry studies upon consultation with the Medical Monitor.

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. Abnormal findings that are considered not clinically significant by the PI or Sub-Investigator may be reviewed by the Sponsor's Study Physician.

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

8.3.3 Removal 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
- Lost to follow-up (every effort must be made to contact the patient; a registered letter must be sent)
- Other reasons, such as administrative reasons or pregnancy
- Study terminated by Sponsor

- Site terminated by Sponsor

If a patient prematurely discontinues from the study because of an AE or for any other reason, the study center staff must record the AE as the reason for discontinuation. 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 in to the study center for an ET Visit or who cannot be reached must be requested in writing to come in to the study center and to return any unused IMP. A copy of the 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.

8.3.4 Replacement Procedures

Patients 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 assessment.

The investigators or Medical Monitor may withdraw a patient from treatment for any reason (treatment withdrawal) at any time, and all planned study assessments should then be offered for the duration of the trial to ensure appropriate medical care is provided to the patient. Patients who develop a new significant medical condition at any point during the trial may be withdrawn.

Patients who prematurely discontinue from the study will be replaced, but their patient number will not be reassigned.

8.4 TREATMENTS

8.4.1 Treatments Administered

Patients who satisfy the inclusion and exclusion criteria listed in Section 8.3 will be randomized to 1 of the following 3 study arms.

- [redacted]-mg dose of AG10 ([redacted] mg tablet + [redacted] placebo tablets) twice daily
- [redacted]-mg dose of AG10 ([redacted] mg tablets) twice daily
- Matching placebo ([redacted] placebo tablets) twice daily

8.4.2 Identity of Investigational Products

AG10
Eidos Therapeutics, Inc.
[redacted]

Matching placebo tablets

8.4.2.1 Packaging

The investigational medicinal product (IMP) will provided as blinded randomized kits assigned to patients using a randomization code. 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.

Details regarding IMP are provided in the IB and IMP Manual.

8.4.2.2 Storage, Dispensing, and Return of Investigational Product

The Sponsor will provide the study center with drug supplies. AG10 should be stored at [redacted]. 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 administered to each patient, the date of administration, 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 Patients to Treatment Groups/Sequences

Screening numbers will be assigned through an Interactive Response Technology System (IRTS) portal after the patient signs the ICF. Patients who are qualified will be randomized into the study and assigned a unique patient number through the IRTS.

8.4.4 Selection of Dosages in the Study

AG10 doses chosen for this study are based on nonclinical PK studies and available data from the first-in-human single ascending dose (SAD) and multiple ascending dose (MAD) study. Pharmacokinetics of AG10 have been studied in mouse, rat, dog, and monkey. In all species studied, AG10 was well absorbed with good absolute oral bioavailability, low systemic clearance and low volume of distribution at steady-state (Vss).

[redacted]

In summary, at doses of [redacted] mg twice daily and [redacted] mg twice daily, AG10 is expected to be safe and well-tolerated with measurable pharmacodynamic activity. Therefore, for this study, the [redacted] mg twice daily and [redacted] mg twice daily doses of AG10 were chosen for evaluation versus placebo.

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 Blinding

A list of patient randomization numbers and corresponding treatment assignments will be generated by an assigned unblinded-statistician using a statistical programming. The randomization numbers will be retained in electronic form saved on a secure server. A hard copy will be retained by the assigned unblinded-statistician in a secure locked area.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject. Sponsor may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

The investigator is requested to contact the Medical Monitor within 24 hours upon any instances of treatment unblinding.

For a medical emergency in which unblinding of study drug assignment is required to enable urgent clinical decision making, the Investigator should first attempt to contact the Medical Monitor (or designee). If the Medical Monitor or designee cannot be reached, the Investigator may obtain a subject's study drug assignment by following the Emergency Unblinding Procedures outlined in the study procedures manual. Every attempt should be made to contact the Sponsor prior to unblinding. In the event of emergency unblinding of a subject's study drug assignment, a full written explanation of events requiring study drug unblinding must be provided to the Medical Monitor. Once unblinded, the subject will be permanently discontinued from study drug but may continue to participate in all other study-related activities including assessments of efficacy.

8.4.7 Prior and Concomitant Therapy

Patients will not be permitted to use any concomitant medications listed in the exclusion criteria during the study. Patients will be instructed not to take any of those drugs for at least 14 days or 5 half-lives (whichever is longer) before the first day of dosing and during the course of the study.

At Screening, 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.

8.4.8 Treatment Compliance

IMP compliance will be closely monitored by counting the number of tablets 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 and empty bottles.

The study center will keep an accurate drug disposition record that specifies the amount of IMP administered to each patient and the date of administration.

8.5 PHARMACOKINETIC, SAFETY, AND PHARMACODYNAMIC VARIABLES

8.5.1 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.

8.5.1.1 Screening (Day –28 to Day -1)

Screening will be performed within 28 days before administration of the first dose of IMP. At Screening, inclusion and exclusion criteria will be reviewed to determine the patient's eligibility for enrollment. Study procedures will be reviewed with the patient, and documentation of informed consent will be obtained.

The following procedures will also be performed at Screening:

- Medical and surgical history assessment
- Physical examination (Section 8.5.3.10)
- Vital signs assessment (Section 8.5.3.7)
- 12-lead ECG (Section 8.5.3.8)

- Blood sample collection for hematology, serum chemistry, urinalysis (Section 8.5.3.6)
- Blood sample collection for serum β–human chorionic gonadotropin (β-hCG) pregnancy test (females of child-bearing potential only)
- Prior medication use assessment (Section 8.4.7)
- AE assessment (Section 8.5.3.1)

8.5.1.2 Double-blind Treatment Days

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

Day 1 (Randomization) – Site Visit

- Review inclusion/exclusion criteria to confirm patient is eligible
- Randomize patient to treatment arm and assign randomization number
- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Conduct resting transthoracic echocardiogram (Section 8.5.3.9)
- Collect PK blood sample (predose and at 0.5, 1 and 2 hours postdose)
- Collect PD assay blood sample (predose and at 0.5, 1 and 2 hours postdose)
- Collect [redacted] (predose)
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy testAdminister IMP with designated witness
- Assess concomitant medication use
- AE assessment

Day 7 (±3 days) – Telephone Contact

- Assess concomitant medication use

- IMP compliance assessment
- AE assessment

Day 14 (±3 days) – Site Visit

- Physical examination
- Vital signs assessment
- Conduct 12-lead ECG
- Collect PK blood sample (predose and at 0.5, 1 and 2 hours postdose)
- Collect PD assay blood sample (pre-dose and at 0.5, 1 and 2 hours postdose)
- Collect [redacted] (predose)
- Collect any unused IMP and check compliance and accountability

  Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Administer IMP with designated witness
- Assess concomitant medication
- IMP compliance assessment
- AE assessment

Day 21 (±3 days) – Telephone Contact

- Assess concomitant medication use
- IMP compliance assessment
- AE assessment

Day 28 (±3 days) – Site Visit

- Medical history update
- Physical examination
- Vital signs assessment

- Conduct 12-lead ECG
- Collect PK blood sample (predose and at 0.5, 1 and 2 hours postdose)
- Collect PD assay blood sample (pre-dose and at 0.5, 1 and 2 hours postdose)
- Collect [redacted] (predose)
- Collect any unused IMP, check compliance and accountability
- Collect blood and urine samples for clinical laboratory analysis and urine pregnancy test
- Administer IMP with designated witness
- Assess concomitant medication
- IMP compliance assessment
- AE assessment

8.5.1.3 Follow-up Visit (or Early Termination)

Patients will have a Follow-up Visit 7 to 14 days after Day 28 or after early withdrawal.

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

- Medical history update
- 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

Any clinically significant findings obtained during the final examination at the Follow-up or at premature discontinuation (ET visit), including clinically significant laboratory abnormalities and the manner in which they are treated, will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the IMP.

8.5.2 Drug Concentration Measurements

8.5.2.1 PK Blood Draw Schedule

Sampling will be done at the following times to determine AG10 plasma concentrations:

Days 1, 14 and 28: Predose and at 0.5, 1 and 2 hours Postdose

8.5.2.2 PD Blood Draw Schedule

PD properties of AG10 will be assessed by established assays [redacted]. Sampling will be done at the following times to perform these PD assays:

- Days 1, 14 and 28: Predose and at 0.5, 1 and 2 hours Postdose

Sampling will be done at the following times to measure [redacted] concentrations:

- Day 1, Day 14 and Day 28 Predose

8.5.2.3 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.

8.5.3 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.

8.5.3.1 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-E2A).

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 the Follow-up visit 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
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study

8.5.3.1.1 Causality Assessment

For each AE, the PI or Sub-Investigator must provide an assessment of causal relationship to the IMP. The causality assessment must be recorded on the appropriate AE reporting page of the patient's CRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility that the IMP caused the event?

Yes: There is evidence to suggest a causal relationship between the IMP and AE, ie:

- There is a reasonable temporal relationship between the IMP and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors, and/or
- Positive dechallenge and/or rechallenge exist.

No: There is no evidence to suggest a causal relationship between the IMP and AE, ie:

- There is no reasonable temporal relationship between the IMP and the event, or
- The patient did not take the IMP, or
- The event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, or

– The event is commonly occurring in the study population independent of drug exposure.

8.5.3.1.2 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. 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.

8.5.3.2 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 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.

8.5.3.3 Reporting Adverse Events and Serious Adverse Events

Any untoward event that is reported from the time that the patient signs the ICF until the Follow-up visit 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 posttreatment 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 8.5.1). 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 to the Follow-up visit after the last dose of IMP) must be documented.

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 8.5.3.5.

8.5.3.4 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy (including the pregnancy of a male patient's partner) 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 [redacted], 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 8.5.3.5, with the appropriate serious criterion (eg, hospitalization) indicated.

8.5.3.5 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 recorded as a new SAE.

The study center staff must transmit the SAE Form for Clinical Trials to the SAE email [redacted]. 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 fax 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: [redacted]

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

[redacted]
Sponsor's Study Physician
[redacted]
Eidos Therapeutics, Inc.,
101 Montgomery Street
San Francisco, CA 94104

8.5.3.6 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at Screening, Day 1, Day 14, Day 28, and at the Follow-up Visit 7 to 14-days after the last dose. At screening, the PI or Sub-Investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and patients with abnormalities judged to be clinically significant will be excluded from the study. 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 at Screening only

PT/PTT/INR: Coagulation laboratory tests will be completed at all study visits for patients who are receiving warfarin (Coumadin®)

Pregnancy test: **S**erum β-hCG pregnancy test at Screening; urine test on Day 1, Day 14, Day 28, and Follow-up (in females of child-bearing potential only)

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

8.5.3.7 Vital Signs

At Screening, Day 1, Day 14, Day 28, and at the Follow-up Visit, study center staff will assess vital signs pre- and postdose after a 5-minute rest.

8.5.3.8 Electrocardiograms

At Screening, Day 1, Day 14, Day 28, and at the Follow-up Visit, a standard 12-lead ECG will be performed in the supine position after a 30-minute rest.

8.5.3.9 Echocardiogram

At Day 1, a resting transthoracic echocardiogram will be performed in the supine position as specified in the study procedures manual. Additional details surrounding transthoracic echocardiogram acquisition and transmission can be found in the study procedures manual.

8.5.3.10 Other Safety Assessments

8.5.3.10.1 Physical Examinations

At Screening, patients will undergo a complete physical examination (PE) which is to be completed by a professionally trained physician or health professional including body weight and height measurements, and BMI. An abbreviated PE with weight at all other visits, including Day 14, Day 28 and Follow-up Visit.

8.6 DATA QUALITY ASSURANCE

8.6.1 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.

8.6.2 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.

8.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.7.1 General Considerations

All 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 [redacted]. Additional information regarding statistical analyses can be found in the SAP.

8.7.2 Timing of Analyses

When final in-clinic visits and post treatment follow-up have been completed for all patients, the database will be cleaned and locked, randomized treatment assignments will be obtained, and safety analyses will be performed.

8.7.3 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

8.7.4 Demographics and Other Baseline Characteristics

PK parameters will be calculated by patient and summarized by dose levels. Parameters will be reported for the first dose as well as at steady-state, i.e. after the last dose. Only patients with sufficient data to calculate each PK parameter will be included in the summary of each PK endpoint.

8.7.5 Extent of Exposure and Treatment Compliance

The study investigator must maintain exact records of the number of tablets/ bottles of study drug dispensed to each patient by recording the following information:

- Patient randomization number
- Date(s) and visit number when study drug was dispensation
- Number of bottles of study drug dispensed
- Number of tablets in each bottle
- Date of return of each study drug kit.

- Number of tablets in each bottle returned

An Investigational Product Dose Log will be provided by the Sponsor and maintained at the study site to record information for each patient.

All used and partially used bottles of study drug will be returned to the site for inspection and drug accountability reconciliation.

In addition, the PK listing will be used if needed to corroborate administration of AG10.

8.7.6 Pharmacokinetic Analyses

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

8.7.7 Safety Analyses

AEs will be coded using the MedDRA dictionary. The incidence of each treatment-emergent AE will be summarized by system organ class, preferred term and treatment assignment. 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 by treatment group assignment. Safety laboratory findings, vital signs, and 12-lead ECG data 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.

8.7.7.1 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.

Total number of major clinical events will be summarized by treatment and time to event analyses will also be performed.

8.7.7.2 DMC Safety Reviews

The DMC's role and responsibilities, timing of meetings and the scope of analysis to be provided to the DMC will be provided in a mutually agreed upon charter.

8.7.8 Pharmacodynamic Analysis

[redacted] 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.

8.7.9 Interim Analysis

No interim analysis is planned for this study.

8.7.10 Determination of Sample Size

The planned number of patients per dosing cohort is based on feasibility and clinical judgment.

8.8 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 exceptions 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 patient 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. The PI will be responsible for ensuring that patients return their IMP. If unused IMP is not returned to the Sponsor, proof of destruction must be provided to the Sponsor.

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 AG10-201) in accordance with the protocol and with all applicable government regulations and GCP guidance.

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

_____
Principal Investigator's Name