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
SAP Version/Date:	Version 2.0: 05 October 2018

Statistical Analysis Plan

Sponsor:	Eidos Therapeutics, Inc.
Protocol No:	AG10-201
[redacted] Project Id:	[redacted]
Version Date:	05-Oct-2018
Version No.:	2.0
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
CRF Version No./Date:	2.1/20-Jun-2018

1.0 Approvals

Sponsor	
Representative/ Title:	[redacted] / [redacted]
Signature /Date:	[redacted] 10 OCT 2018
[redacted]	
Project Manager/Title:	[redacted] / Project Manager
Signature /Date:	
Biostatistician / Title (Owner):	[redacted] / Senior Principal Biostatistician
Signature /Date:	

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

Table of Contents

2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Eidos Therapeutics, Inc. Protocol AG10-201.

3.0 Scope

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

The Statistical Analysis Plan outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data and physical examinations

4.0 Introduction

The SAP describes the statistical methods to be used during the reporting and analyses of data collected under Eidos Therapeutics, Inc. Protocol AG10-201.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 25May2018 and CRF dated 20Jun2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

5.0 Study Objectives

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).

The secondary objectives of this study are:

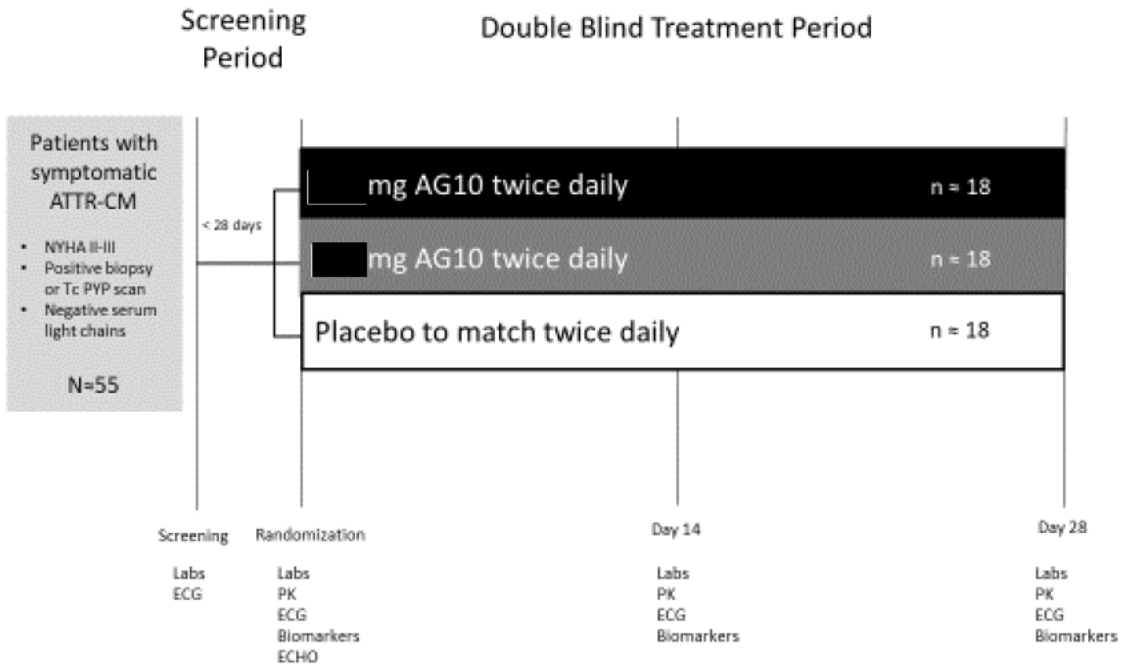
- to characterize the pharmacokinetics (PK) of AG10 administered orally twice daily in patients with symptomatic ATTR-CM, and
- to describe the pharmacodynamic (PD) properties of AG10 as assessed by [redacted] in adult patients with symptomatic ATTR-CM.

6.0 Study Design

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.

The schedule of assessments is provided in Table 1 below.

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.

6.1 Sample Size Considerations

The planned number of patients per dosing cohort is based on feasibility and clinical judgment. Since patients that prematurely discontinue from the study may be replaced, the final sample size may be larger than 55.

6.2 Randomization

Patients who satisfy the inclusion and exclusion criteria will be randomized in 1:1:1 ratio to 1 of the following 3 study arms using an Interactive Response Technology System (IRT). Approximately 30% of patients enrolled will be mutant ATTR-CM.

- [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

7.0 Study Endpoints, Variables and Covariates

7.1 Primary Endpoint

The primary objective of this study is to characterize the safety and tolerability of AG10 administered to adult patients with symptomatic ATTR-CM over 28 days of dosing. This will be assessed by the following endpoints: 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.

7.2 Secondary Endpoints

Pharmacokinetics: The PK measurements of AG10 and metabolite [redacted] 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 assessed by [redacted] in adult patients with symptomatic ATTR-CM. Changes in circulating [redacted] levels will also be measured as a PD marker.

8.0 Definitions

Baseline and Change from Baseline

Baseline values are defined as the average of all pre-treatment values.

Change from Baseline = (post-Baseline value – Baseline value). For the purpose of tabulations, the unscheduled post-Baseline values generally will be excluded unless otherwise noted.

Completion of study

The completion of study is defined as an answer of "Yes" to the question "Did the subject complete the study (including the 7-14 day follow-up visit)?" on the form of End of Study in the CRF.

Completion of treatment

The completion of treatment is defined as an answer of "Yes" to the question "Did the subject complete the treatment period?" on the form of End of Treatment in the CRF.

Prior and Concomitant Medications

Prior medications will be any medication with a start date before the date of the first study drug dose.

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

Treatment-Emergent Adverse Events

An adverse event (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 study drug or if it was present before the first dose of study drug but increased in severity during the treatment period. Events which occur more than thirty days after the last dose of study drug will not be considered treatment emergent. Adverse Events will be considered treatment-emergent if they have missing or partial start dates for which it cannot be determined after imputation rules applied (see below) whether the AE started before or after the first dose of study drug.

Adverse Events with Outcome of Death

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

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

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

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

Treatment-related Adverse Events

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

Study Day 1

The first day of study drug administration.

Study Day

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

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

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

Analysis Visit window

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

[redacted]

[redacted]

Overall percent stabilization of ≥ 75%, defined as a subject having a stabilization greater than or equal to 75% at greater than or equal to 75% of their valid measures, will be summarized for both [redacted]

Overall percent stabilization of ≥ 90%, defined as a subject having a stabilization greater than or equal to 90% at greater than or equal to 90% of their valid measures, will be summarized for both [redacted]

Overall percent stabilization of ≥ 99%, defined as a subject having a stabilization greater than or equal to 99% at greater than or equal to 99% of their valid measures, will be summarized for both [redacted]

9.0 Analysis Sets

9.1 Full Analysis Set

The full analysis set will include all randomized subjects, and will be used for disposition, demographics and other study conduct summaries. The full analysis set will summarize by randomized treatment.

9.2 Safety

The safety analysis set will consist of all subjects receiving at least one dose of study drug (including placebo) and will be used to summarize all safety data. The safety analysis set will summarize by actual treatment.

9.3 PK Analysis Set

The PK analysis set will consist of all subjects receiving at least one dose of AG10 and have at least one quantifiable post-baseline concentration and will be used to summarize all PK data. The PK analysis set will summarize by actual treatment.

9.4 PD Analysis Set

The PD analysis set will consist of all subjects receiving at least one dose of study drug (including placebo), and have at least one post-baseline PD assessment, and will be used to summarize all PD data. The PD analysis set will summarize by actual treatment.

10.0 Interim Analyses

No interim analyses are planned for this study.

11.0 Data Review

11.1 Data Handling and Transfer

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

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

Additional details can be found in the [redacted] Data Management Plan for this study.

11.2 Data Screening

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

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

12.0 Statistical Methods

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

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

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

12.1 Subject Disposition

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

12.2 Important Protocol Deviations

Per [redacted] processes, important protocol deviations data will be entered into our Clinical Trials Management System (CTMS). The [redacted] study team and the sponsor will conduct on-going reviews of the deviation data

from CTMS and the resulting set of evaluable subjects throughout the study, adjusting the deviation criteria as seems appropriate.

The important protocol deviation list will be identified prior to unblinding and listed.

12.3 Treatments

12.3.1 Extent of Study Drug Exposure

Exposure to study drug (e.g. at least 1 dose administered), number of subjects with missed doses (Day 1 - Day 14, Day 15 – Day 28, overall), and total number of tablets administered will be summarized by treatment group for the safety analysis set.

Total number of tablets each subject takes is calculated as the sum of the number of tablets taken at each time point (AM, PM) from Day 1 through Day 28 (± 3 days).

Study drug dosing information will be presented by subject in data listings.

12.3.2 Concomitant Medications

Prior/concomitant medications will be coded by World Health Organization Drug Dictionary 2018MAR01 DDE+HD B3(Enhanced + Herbal) and will be summarized by Anatomic Therapeutic Classification (ATC) class and preferred name. The analysis will be performed using the full analysis set.

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

12.4 Demographic and Baseline Characteristics

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

General medical history will be coded by MedDRA version 21.0 or later, as applicable at time of analysis and will be presented by subject listing only.

12.5 PK Analyses

Blood samples for the determination of plasma AG10 and [redacted] will be collected on Days 1, 14, and 28 at pre-dose, and 0.5, 1, and 2 hrs post-dose.

Plasma concentrations of AG10 and [redacted] will be determined using [redacted] methods validated (AG10) and qualified [redacted] with respect to accuracy, precision, linearity, sensitivity, and specificity at [redacted].

Plasma AG10 and [redacted] concentrations will be used for calculation of appropriate AG10 and [redacted] PK parameters by population PK analysis. The population PK analysis will be performed by an outside vendor contracted by Eidos.

Plasma concentrations of AG10 and [redacted] will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration time points. Excluded subjects will be included in the concentration listings but will be excluded from the summary

statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration listings and footnoted accordingly.

Mean and individual plasma concentration-time profiles will be presented on linear and semi-log scales. Linear mean plots will be presented with SD.

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

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

12.6 PD Analyses

[redacted]

[redacted]

[redacted]

[redacted] Overall percent stabilization, defined the number of time points where a subject has ≥75%, ≥ 90% and ≥99% stabilization, as defined in Section 8.0, will be summarized by both [redacted]. Additionally, a summary of subjects who reached certain thresholds (10%, 25%, and 50%) of percent increase in [redacted] by Day 28 will be provided.

12.7 Safety Analyses

The safety population will be used for all safety analyses.

12.7.1 Adverse Events

Only TEAEs will be included in the summary tables.

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

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

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

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

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

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

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

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

12.7.2 Deaths and Serious Adverse Events

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

- TEAEs with an outcome of death
- Serious TEAEs

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

12.7.3 Clinical Events

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

Additionally, the time to the first clinical event will be described via Kaplan-Meier estimates using the Safety Set. The 25%, median, and 75% quartiles will be presented. A Kaplan-Meier plot and a by-subject listing will also be provided.

12.7.4 Laboratory Data

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

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

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

12.7.5 Vital Signs

Descriptive summaries of observed values and changes from baseline will be provided for vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and temperature) by visit.

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

Descriptive summaries of observed values and changes from baseline will be provided for ECGs (mean heart rate, aggregate RR interval, aggregate PR interval, aggregate QRS duration, aggregate QT interval, aggregate QTcB interval, and aggregate QTcF interval) by visit. Post-baseline abnormal ECG results assessed by cardiologist will be summarized by count and percentages.

Descriptive summaries of observed values for the following echocardiogram parameters will be provided:

LV Ejection Fraction

LV end diastolic volume

LV end systolic volume

LA volume

RV fractional area change

Interventricular wall thickness

PLAX posterior wall thickness

LV mass

Tricuspid annular plane sys excursion

E/Em lateral ratio

Peak RV-RA gradient

Myocardial Contraction Fraction

LV global longitudinal strain

LA longitudinal average peak strain

LV stroke volume index

ECG, echocardiogram, physical examination, and urine pregnancy test data will be listed.

13.0 Validation

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

14.0 References

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ATC	Anatomic Therapeutic Classification
ATTR	TTR amyloidosis
ATTR-CM	TTR cardiomyopathy
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
[redacted]	[redacted]
IRT	Interactive Response Technology System
[redacted]	[redacted]
PK	Pharmacokinetic
PD	Pharmacodynamic
PT	Preferred Term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTR	transthyretin