STATISTICAL ANALYSIS PLAN

Version Number: 1.0

Protocol Title: A Phase 3, Prospective, Multicenter, Open Label, 2-Part Study of the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of ALXN2060 in Japanese Participants with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

Protocol Number: ALXN2060-TAC-302

Compound: ALXN2060 (previously AG10)

Short Title: A Phase 3 Study of ALXN2060 in Japanese Participants with Symptomatic ATTR-CM

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

VERSION HISTORY

This statistical analysis plan for Study ALXN2060-TAC-302 is based on protocol version 4.0, dated 12 Jan 2023.

SAP Version	Version Date	Change	Rationale
1.0	27 Mar 2023	Not applicable	Original version

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Date

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for analyzing data for Protocol "A Phase 3, Prospective, Multicenter, Open Label, 2-Part Study of the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of ALXN2060 in Japanese Participants with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTR-CM)." The current SAP covers Parts A and B of the study design mentioned in the protocol.

Standard data presentation instructions, along with the table, figure, and listing specifications, will be provided in the data presentation plan. Analyses related to the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) objectives of the study are specified in this SAP.

1.1. Objectives and Endpoints

Objective	Endpoints/Estimand
Primary	
Part A: • To determine the efficacy of orally administered ALXN2060 800 mg twice daily (bid) in the treatment of adult Japanese participants with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) as assessed by the 6-minute walk test (6MWT)	**Part A:** ***Distance walked during the 6MWT*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** Change from Baseline (CFB) to Month 12 in the distance walked during 6MWT **Summary measure:** Least-squares (LS) mean CFB to Month 12 in the distance walked during 6MWT **Intercurrent events (ICEs) and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE • Death – addressed based on a composite strategy: sampling with replacement within treatment group from the bottom 25% of observed CFB values in a given visit • Receiving a heart transplant or a cardiac mechanical assist device (CMAD) – treated as death and addressed based on the composite strategy specified above • All other ICEs, including Coronavirus Disease 2019 (COVID-19)-related ICEs – addressed based on treatment policy strategy: all data collected will be used, regardless; no imputation for missing value

Objective	Endpoints/Estimand
Part B: • To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by all-cause mortality (ACM) and cardiovascular (CV)-related hospitalization	**Part B:** ***ACM over a 30-month period*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** Time to ACM from the date of first initiation of study treatment to the date of death or the end of study. **Summary measure:** Estimated survival probability at Month 30 and corresponding 95% confidence interval (CI) **ICEs and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: ICE will be ignored; data will be analyzed as observed • Receiving a heart transplant or a CMAD – treated as death and addressed based on a composite strategy: ICE will be treated as death; no assessments after the ICE will be considered • All other ICEs, including COVID-19-related ICEs – addressed based on treatment policy strategy: ICE will be ignored; data will be analyzed as observed ***CV-related hospitalization over a 30-month period*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** Number of CV-related hospitalizations **Summary measure:** Number of CV-related hospitalizations per participant per year over a 30-month period **ICEs and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: CV-related hospitalizations over a 30-month period will be counted, regardless of the occurrence of the ICE • Death – addressed based on treatment policy strategy: CV-related hospitalizations over a 30-month period prior to the occurrence of death will be counted • Receiving a heart transplant or a CMAD – treated as death and addressed based on a composite

Objective	Endpoints/Estimand
	strategy: CV-related hospitalizations after ICE will be censored; observation time should be set at the beginning of the procedure • All other ICEs, including COVID-19-related ICEs – addressed based on treatment policy strategy: CV-related hospitalizations over a 30-month period will be counted, regardless of the occurrence of the ICE
Secondary	
Part A: • To evaluate the effects of ALXN2060 800 mg bid on the 6MWT	**Part A:** ***CFB to Months 6 and 9 of treatment in the distance walked during the 6MWT*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** CFB to Months 6 and 9 in the distance walked during 6MWT **Summary measure:** LS Mean CFB to Months 6 and 9 in the distance walked during 6MWT **ICEs and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE • Death – addressed based on a composite strategy: sampling with replacement within treatment group from the bottom 25% of observed CFB values in a given visit • Receiving a heart transplant or a CMAD – treated as death and addressed based on the strategy specified above • All other ICEs, including COVID-19-related ICEs – addressed based on treatment policy strategy: all data collected will be used regardless; no imputation for missing value

Objective	Endpoints/Estimand
• To evaluate the effects of ALXN2060 800 mg bid on health-related quality of life as measured by Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) in adult Japanese participants with symptomatic ATTR-CM	***CFB to Months 6, 9, and 12 of treatment in KCCQ-OS*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** CFB to Months 6, 9, and 12 in KCCQ-OS **Summary measure:** LS mean CFB to Months 6, 9, and 12 in KCCQ-OS **ICEs and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE • Death – addressed based on a composite strategy: sampling with replacement within treatment group from the bottom 25% of observed CFB values in a given visit • Receiving a heart transplant or a CMAD – treated as death and addressed based on the strategy specified above • All other ICEs, including COVID-19-related ICEs – addressed based on treatment policy strategy: all data collected will be used regardless; no imputation for missing value
• To assess the PD effects of ALXN2060 by circulating serum transthyretin (TTR) concentration as an in vivo biomarker of stabilization and using established ex vivo assays of TTR stabilization (fluorescent probe exclusion [FPE]) and to assess the correlation between TTR concentration/FPE and ALXN2060 concentration	***CFB in serum TTR concentration (an in vivo measure of TTR stabilization) and established ex vivo assays of TTR stabilization (FPE) on Days 14 and 28 and subsequent visits up to Month 12*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** CFB in serum TTR (prealbumin) level **Summary measure:** LS mean CFB in serum TTR (prealbumin) level **ICE and corresponding strategy:** addressed based on treatment policy strategy – all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE

Objective	Endpoints/Estimand
• To assess the safety and tolerability of ALXN2060 800 mg bid in adult Japanese participants with symptomatic ATTR-CM	**Safety parameters to be assessed:** • Treatment-emergent serious adverse events (SAEs) and adverse events (AEs) • AEs leading to treatment discontinuation • Abnormal physical examination findings of clinical relevance • Abnormal vital signs of clinical relevance • Abnormal electrocardiogram (ECG) parameters of clinical relevance • Changes in clinical safety laboratory parameters of potential clinical concern
Part B: • To evaluate the effects of ALXN2060 800 mg bid on the 6MWT	**Part B:** ***CFB to Months 18, 24, and 30 of treatment in the distance walked during the 6MWT*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** CFB to Months 18, 24, and 30 in the distance walked during 6MWT **Summary measure:** LS Mean CFB to Months 18, 24, and 30 in the distance walked during 6MWT **ICEs and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE • Death – addressed based on a composite strategy: sampling with replacement within treatment group from the bottom 25% of observed CFB values in a given visit • Receiving a heart transplant or a CMAD – treated as death and addressed based on the strategy specified above • All other ICEs, including COVID-19-related ICEs – addressed based on treatment policy strategy: all data collected will be used regardless; no imputation for missing value

Objective	Endpoints/Estimand
• To evaluate the effects of ALXN2060 800 mg bid on health-related quality of life as measured by KCCQ-OS in adult Japanese participants with symptomatic ATTR-CM	***CFB to Months 18, 24, and 30 of treatment in KCCQ-OS*** **Population:** adults (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** CFB in KCCQ-OS **Summary measure:** LS mean CFB in KCCQ-OS **ICEs and corresponding strategies:** • Study intervention discontinuation – addressed based on treatment policy strategy: all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE • Death – addressed based on a composite strategy: sampling with replacement within treatment group from the bottom 25% of observed CFB values in a given visit • Receiving a heart transplant or a CMAD – treated as death and addressed based on the strategy specified above • All other ICEs, including COVID-19-related ICEs – addressed based on treatment policy strategy: all data collected will be used regardless; no imputation for missing value
• To assess the PD effects of ALXN2060 as assessed by circulating serum TTR concentration as an in vivo biomarker of stabilization and established ex vivo assays of TTR stabilization (FPE) and correlation between TTR concentration/FPE and ALXN2060 concentration	***CFB in serum TTR concentration and established ex vivo assays of TTR stabilization (FPE) at Month 30*** **Population:** adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type) **Study intervention:** ALXN2060 800 mg bid **Variable:** CFB in TTR (prealbumin) level **Summary measure:** LS mean CFB in TTR (prealbumin) level **ICE and corresponding strategy:** addressed based on treatment policy strategy – all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE.

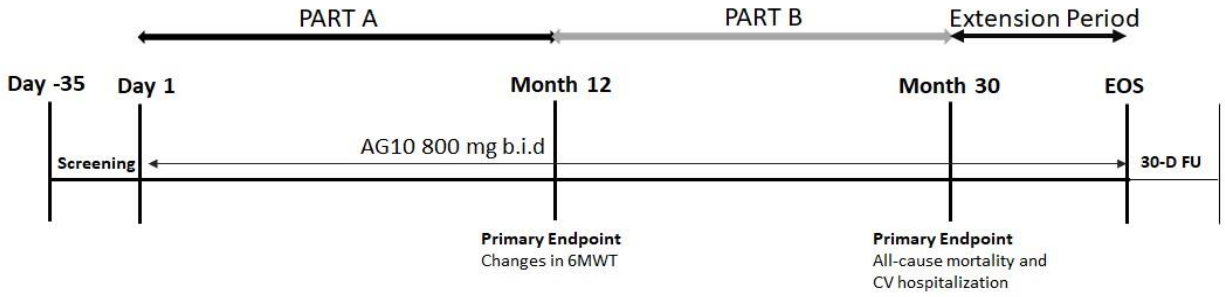
Objective	Endpoints/Estimand
• To assess the safety and tolerability of ALXN2060 800 mg bid administered for 30 months to adult Japanese participants with symptomatic ATTR-CM	**Safety parameters to be assessed:** • Treatment-emergent SAEs and AEs • AEs leading to treatment discontinuation • Abnormal physical examination findings of clinical relevance • Abnormal vital signs of clinical relevance • Abnormal ECG parameters of clinical relevance • Changes in clinical safety laboratory parameters of potential clinical concern
Exploratory	
• To determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by ACM and CV-related hospitalization (only Part A)	ACM and CV-related hospitalization over a 12-month period (only Part A)
• To explore the population PK of ALXN2060 and its metabolites under the 800 mg orally administered bid dosing regimen	Exploration of PK over 30 months for ALXN2060 and its metabolite
• To evaluate the effects of ALXN2060 800 mg bid on circulating biomarkers of myocardial wall stress and microvascular ischemia in Japanese participants with symptomatic ATTR-CM	CFBs over Month 30 in N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and troponin I (TnI)
• To evaluate the effects of ALXN2060 800 mg bid on European Quality of Life Health 5-item Questionnaire Dimensions 5 Levels (EQ-5D-5L) in Japanese participants with symptomatic ATTR-CM	CFB in EQ-5D-5L over Month 30
• To evaluate the effects of ALXN2060 800 mg bid on cardiac magnetic resonance imaging (MRI)-derived measures of cardiac structure, function, and tissue characterization in Japanese participants with symptomatic ATTR-CM (only at selected sites and consenting participants)	CFB to Months 12, 24, and 30 in cardiac MRI parameters (only at selected sites and consenting participants)
Extension Period	
• To assess the safety of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period	• Safety parameters same as the Intervention Period (Part A and Part B) are assessed in the Extension Period
• To evaluate the long-term efficacy of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period	• Efficacy endpoints same as the Intervention Period excluding cardiac MRI parameters are evaluated during the Extension Period

Objective	Endpoints/Estimand
• To assess the PD effects of ALXN2060 during the Extension Period	• PD parameters (serum TTR concentration and TTR stabilization [FPE]) same as the Intervention Period are assessed in the Extension Period
• To characterize PK of ALXN2060 in Japanese participants with symptomatic ATTR-CM during the Extension Period	• Exploration of PK in the Extension Period for ALXN2060 and its metabolite

1.2. Study Design

This is a Phase 3, prospective, multicenter, open-label, 2-part study to evaluate the efficacy, safety, tolerability, PK, and PD of ALXN2060 800 mg bid administered orally in adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM. The study schema is presented in Figure 1.

Figure 1: Study Design



Abbreviations: 6MWT = 6-minute walk test; 30-D FU = 30-day follow-up; bid = twice daily; CV = cardiovascular; EOS = end of study intervention

Eligible Japanese participants with symptomatic ATTR-CM (either mutant or wild type) will be enrolled based on inclusion/exclusion criteria. In order to assess the efficacy of ALXN2060 800 mg bid as monotherapy, participants with ATTR-CM will be eligible to be enrolled as long as they were untreated with Tafamidis for at least 14 days prior to the first dose of ALXN2060.

A Screening Period of up to 28 ± 7 days will confirm the participants' diagnosis of ATTR-CM and suitability for a long-term investigation. This period will also cover the requirement of the last dose of Tafamidis administered at least 14 days prior to the first ALXN2060 dose.

Following enrollment and Screening, participants will receive ALXN2060 800 mg bid for 12 months (Part A). Following the last visit (Month 12) of Part A, participants will continue the study in Part B, which will last for an additional 18 months (30 months from Day 1). All participants will continue to receive oral treatment with ALXN2060 800 mg bid.

Following the completion of Month 30 assessments in Part B, participants will be offered the opportunity to continue into the Extension Period, which will last until ALXN2060 is approved or for up to 24 additional months, whichever occurs first. Participants will continue to receive oral treatment with ALXN2060 800 mg bid.

A participant is considered to have completed the study if he/she has completed both Part A and Part B of the study, including the last scheduled procedure shown in the Schedule of Activities in

Section 1.3 of the protocol. The end of study for each participant is defined as his/her last visit in the study. The end of study is defined as the last participant's last visit in the study.

2. STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be performed.

The success criterion for Part A is defined as the lower bound of the 95% CI of the change in 6MWT from Baseline to Month 12 > -60 m.

The success criterion for Part B is defined as the estimated survival probability at Month 30 being greater than that for placebo participants in Study AG10-301. The success criterion for Part B is based on ACM only because it is considered more clinically important than CV-related hospitalizations.

3. SAMPLE SIZE DETERMINATION

A total of 22 Japanese participants are planned for enrollment in this study. The primary endpoint in Part A is the CFB to Month 12 in the distance achieved in the 6MWT, which is an important indicator to investigate functional improvement.

Assuming similarity with the Tafamidis ATTR-ACT study (Maurer et al, 2018), where the mean change in 6MWT distance from Baseline to Month 12 in placebo group was estimated as -60 m, which could be considered as the minimum threshold for the changes to be clinically relevant for this study, and assuming that the mean change (SD) from Baseline to Month 12 in ALXN2060 group was -25 (50) m, an estimated sample size of 19 will provide over 80% power for the lower limit of a 95% CI of CFB to Month 12 in 6MWT to be over -60 m.

The primary endpoints in Part B are ACM and CV-related hospitalization over a 30-month period. A sample size of 19 will have over 80% probability of showing consistency between this study and Study AG10-301 with respect to the 2 primary endpoints in Part B, based on simulations.

Considering a missing rate of 10% to 15% for 6MWT at Month 12, the target sample size of 22 is set for this study.

4. ANALYSIS SETS

Analysis Set	Description
Screened Set	All consented participants.
Enrolled Set	All consented participants meeting eligibility criteria.
Full Analysis Set (FAS)	All participants who have received at least 1 dose of ALXN2060.
Per-protocol Set (PPS)	All FAS participants without major protocol deviations that may affect the primary efficacy endpoint.
Safety Set (SS)	All participants who have received at least 1 dose of ALXN2060. Since this is a single-arm study, SS and FAS are identical.
Pharmacokinetic Analysis Set	All participants who have received at least 1 dose of ALXN2060 and who have at least 1 evaluable ALXN2060 concentration.
Pharmacodynamic Analysis Set	All participants who have received at least 1 dose of ALXN2060 and who have evaluable PD data.

5. STATISTICAL ANALYSES

5.1. General Considerations

All analyses will be performed using Statistical Analysis Software® (SAS®) release, version 9.4 or higher (SAS Institute, Inc., Cary, NC, USA), or other validated statistical software.

Continuous variables will be summarized using descriptive statistics, including number of observations and mean, SD, median, minimum, and maximum values. The 25th and 75th percentiles of the continuous variables will be provided when deemed appropriate. Categorical variables will be summarized by frequency counts with the number and percentage of participants.

All data and all outcomes derived from the data will be presented in detailed data listings or summary tabulations. Graphical displays may also be provided when appropriate.

Medical history information and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 25.1 or higher).

The severity of AEs will be assessed by using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0, published 27 Nov 2017).

Medications will be mapped to a generic term using the World Health Organization Drug Dictionary of Mar 2022 or later.

5.1.1. Definition of Baseline

Unless otherwise specified, baseline is defined as the last available assessment prior to the start of the first dose of the study intervention. If any baseline laboratory analyte is evaluated at both the local and the central laboratories, then the central laboratory results will be used for analysis.

5.1.2. Derivation of Study Day

The date of first dose of study intervention will be considered Study Day 1, and the day before the first dose of study intervention will be Study Day -1. There is no Study Day 0.

Study days will be calculated as follows only when the full assessment date is known (ie, partial dates will have missing study days):

For days on or after the first dose of study intervention:

- Date of Assessment – Day of First Dose of Study Intervention + 1.

For days before the first dose of study intervention:

- Date of Assessment – Date of First Dose of Study Intervention.

5.1.3. Analysis Visit Windows

The analysis visit windows for 6MWT, Kansas City Cardiomyopathy Questionnaire (KCCQ), and EQ-5D-5L are defined in Table 1. The analysis visit windows for ECG, laboratory assessments, and physical examinations are defined in Table 2. Similarly, the analysis visit windows for New York Heart Association (NYHA) class assessments are defined in Table 3.

The analysis visit windows pertaining to the Extension Period will be described in a separate SAP.

Results presented by visit will use the visit record data closest to the scheduled (target) visit day. If 2 visits occur equidistant from the scheduled (target) visit day, the most recent visit record date (ie, later of the 2 visits) will be used.

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

Day 1 = First Dose Date			
		Analysis Window Study Day	
Visit	Target Study Day	Low	High
Baseline	≤ 1	< 1	1
Month 6	183	2	228
Month 9	274	229	319
Month 12	365	320	410
Month 18	548	411	594
Month 24	731	595	867
Month 30	913	868	958

Abbreviations: 6MWT = 6-minute walk test; EQ-5D-5L = European Quality of Life Health 5-item Questionnaire Dimensions 5 Level; KCCQ = Kansas City Cardiomyopathy Questionnaire

Table 2: Analysis Visit Windows for ECG, Laboratory Assessments, and Physical Examinations

Day 1 = First Dose Date			
		Analysis Window Study Day	
Visit	Target Study Day	Low	High
Baseline	≤ 1	< 1	1
Day 14	14	2	21
Day 28	28	22	59
Month 3	91	60	136
Month 6	183	137	228
Month 9	274	229	319
Month 12	365	320	410
Month 15	457	411	502
Month 18	548	503	593
Month 21	639	594	684
Month 24	731	685	776
Month 27	822	777	867
Month 30	913	868	958

Abbreviation: ECG = electrocardiogram

Table 3: Analysis Visit Windows for NYHA Class Assessment

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

Abbreviation: NYHA = New York Heart Association

5.2. Study Participants

The number and percentage of participants in the following disposition categories will be summarized using the FAS:

- Participants in each analysis set
- Participants who completed the study intervention
- Participants who discontinued the study intervention along with the reasons for discontinuation
- Participants who completed the study
- Participants who discontinued the study along with the reasons for discontinuation

A listing of participants will be provided for the following:

- Participants who failed the screening
- Participants included or excluded in the given analysis sets along with the reasons for exclusion from the respective analysis sets
- Participants who discontinued the study intervention
- Participants who discontinued the study

5.3. Primary Endpoints Analysis

The primary analysis set for the efficacy analyses will be the FAS. The primary efficacy endpoints will also be analyzed on the PPS.

5.3.1. Primary Efficacy Endpoint in Part A - CFB to Month 12 in the Distance Walked During the 6MWT

5.3.1.1. Definition of Endpoint

The CFB will be calculated as the difference between the distance walked during the 6MWT at the respective months and the distance walked during the 6MWT at Baseline.

To determine the baseline, at least 2 6MWTs will be conducted > 24 hours to ≤ 3 weeks apart prior to the first dose of ALXN2060. The walking distance must be ≥ 150 m, and the distance walked must be within 15% on 2 tests on different days. If 1 of the first 2 tests is not ≥ 150 m or the first 2 test results are not within the 15% of distance walked, a third test must be conducted ≤ 3 weeks of the first test. If the third test is still not ≥ 150 m or within 15% of 1 of the first 2 tests, the participant will not be eligible for participation.

If the participant has a need for a walking aid (eg, cane) or supplemental oxygen at Baseline, it must be consistently used at each subsequent 6MWT throughout the study.

The baseline 6MWT is the average of the total distance walked by participant for the 2 qualifying 6MWTs that meet all the protocol-defined criteria. In case there are > 1 pair of qualifying 6MWTs, the pair of 2 qualifying 6MWTs with the most similar distance (ie, the smallest distance in percent change between the 2 tests) walked will be utilized to calculate the baseline value. Participants who prematurely discontinue the study will have the 6MWT administered at the time of their discontinuation.

5.3.1.2. Estimand

The primary study objective is to determine the efficacy of orally administered ALXN2060 800 mg bid in the treatment of adult Japanese participants with symptomatic ATTR-CM as assessed by the 6MWT.

The primary estimand attributes are as follows:

a. Population: adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type).
b. Study intervention: ALXN2060 800 mg bid.
c. Variable: CFB to Month 12 in the distance walked during 6MWT.
d. Summary measure: LS mean CFB to Month 12 in the distance walked during 6MWT.
e. ICEs and corresponding strategies: ICEs and their corresponding strategies are summarized in Table 4.

Table 4: ICEs and Corresponding Strategies for 6MWT

ICE	Strategy Addressing the ICE and Its Description
Study intervention discontinuation	Treatment policy strategy: all available postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE
Death	Composite strategy: sampling with replacement within treatment group from the bottom 25% of observed change from Baseline values in a given visit[a]
Receiving a heart transplant or a CMAD	Composite strategy: ICE will be treated as death; sampling with replacement within treatment group from the bottom 25% of observed change from Baseline values in a given visit[a]
All other ICEs, including COVID-19-related ICEs	Treatment policy strategy: all data collected will be used regardless; no imputation for missing value.

[a] Due to the small sample size in this study, sampling with replacement using the bottom 25% values will ensure some randomness in the values that will be used in the imputation.

Abbreviations: 6MWT = 6-minute walk test; CMAD = cardiac mechanical assist device; COVID-19 = Coronavirus Disease 2019; ICE = intercurrent event

5.3.1.3. Main Analytical Approach

Observed 6MWT distance values will be utilized if available, regardless of ICEs such as treatment discontinuation, initiation of prohibited medications, and other protocol deviations. Missing data due to reasons other than death or receiving a heart transplant or a CMAD will be handled by MMRM without imputation. For missing data following death or receiving a heart transplant or a CMAD, the imputation will be performed by sampling with replacement from the bottom 25% of observed (nonmissing) CFB values at a given visit. The MMRM model will include visits up to Month 12 and will be adjusted by baseline 6MWT measures and visits. An unstructured covariance matrix will be used to model the within-participant variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous first-order autoregressive covariance structure, and compound symmetry will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Actual mean values and mean CFBs in the distance walked during the 6MWT will be summarized by visit. LS mean CFB and associated 95% CI will also be presented by visit. In addition, the LS mean (SE) of CFB in 6MWT will be plotted over time.

All ICEs will be handled as described in Table 4.

5.3.2. Primary Efficacy Endpoint in Part B - ACM Over a 30 Month Period

5.3.2.1. Definition of Endpoint

ACM will be assessed as time from the date of first initiation of study treatment to the date of death. Participants who are alive at the end of the study will be censored at the last date the participants are known to be alive. Mortality will also be reported as AEs.

5.3.2.2. Estimand

The primary estimand attributes are as follows:

a. Population: adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type).
b. Study intervention: ALXN2060 800 mg bid.
c. Variable: time to ACM from the date of first initiation of study treatment to the date of death or the end of study.
d. Summary measure: Estimated survival probability at Month 30 and corresponding 95% confidence interval.
e. ICE and corresponding strategies: ICEs and their corresponding strategies are summarized in Table 5.

Table 5: ICEs and Corresponding Strategies for ACM

ICE	Strategy Addressing the ICE and Its Description
Study intervention discontinuation	Treatment policy strategy: ICE will be ignored; data will be analyzed as observed.
Receiving a heart transplant or a CMAD	Composite strategy: ICE will be treated as death (event); no assessments after the ICE will be considered.
All other ICEs, including COVID-19-related ICEs	Treatment policy strategy: ICE will be ignored; data will be analyzed as observed.

Abbreviations: ACM = all-cause mortality; CMAD = cardiac mechanical assist device; COVID-19 = Coronavirus Disease 2019; ICE = intercurrent event

5.3.2.3. Main Analytical Approach

Time to ACM will be calculated as (date of death – date of first initiation of study treatment + 1) / 365.25, rounded to 1 decimal place. Participants who are alive at the end of the study will be censored at the last date the participants are known to be alive.

ACM will be assessed using time-to-event analysis. The number and percentage of participants with events will be presented. The number and percentage of participants censored will also be presented.

In the event of a participant's death, the complete date of death, including the day, month, and year, and the cause of death will be obtained. If the date of death is missing or partially missing, the imputation rules as described in Appendix 1, Section 6.1.1 will be applied.

Kaplan-Meier analysis of ACM will be provided as point estimates at Months 12 and 30, along with 95% CIs. The Kaplan-Meier curve will also be plotted.

All ICEs will be handled as described in Table 5.

5.3.3. Primary Efficacy Endpoint in Part B - CV-related Hospitalizations Over a 30-Month Period

5.3.3.1. Definition of Endpoint

CV-related hospitalization is defined as the number of CV-related hospitalizations per participant per year over a 30-month period. CV-related hospitalizations will also be reported as AEs and will be reviewed and adjudicated by an independent Clinical Events Committee (CEC).

5.3.3.2. Estimand

The primary estimand attributes are as follows:

a. Population: adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type).
b. Study intervention: ALXN2060 800 mg bid.
c. Variable: number of CV-related hospitalizations.
d. Summary measure: number of CV-related hospitalizations per participant per year over a 30-month period.
e. ICEs and corresponding strategies: ICEs and their corresponding strategies are summarized in Table 6.

Table 6: ICEs and Corresponding Strategies for CV-related Hospitalizations

ICE	Strategy Addressing the ICE and Its Description
Study intervention discontinuation	Treatment policy strategy: CV-related hospitalizations over a 30-month period will be counted, regardless of the occurrence of the ICE.
Death	Treatment policy strategy: CV-related hospitalizations over a 30-month period prior to the occurrence of death will be counted.
Receiving a heart transplant or a CMAD	Composite strategy: ICE will be treated as death; CV-related hospitalizations after ICE will be censored; observation time should be set at the beginning of the procedure.
All other ICEs, including COVID-19-related ICEs	Treatment policy strategy: CV-related hospitalizations over a 30-month period will be counted regardless of the occurrence of the ICE.

Abbreviations: CMAD = cardiac mechanical assist device; COVID-19 = Coronavirus Disease 2019; CV = cardiovascular; ICE = intercurrent event

5.3.3.3. Main Analytical Approach

The CV-related hospitalizations as reviewed and adjudicated by an independent CEC will be determined as the total number of CV-related hospitalizations per year during the duration of study participation over a 30-month period for each participant. The cumulative frequency of CEC-adjudicated CV-related hospitalization will be estimated using a negative binomial regression analysis with no covariates but an offset term equal to log of each participant's study duration included in the model. If the number of participants with 0 CV-related hospitalization is high, a 0 inflated negative binomial model will be performed to provide further assurance of the results. The CV-related hospitalization per person per year will be presented with 95% CI.

The duration of study participation (years) over a 30-month period will be determined for each participant as (date of Month 30 visit – date of first initiation of study treatment + 1) / 365.25, rounded to 1 decimal place.

All ICEs will be handled as described in Table 6.

5.3.3.4. Handling of Missing Month 30 Visit

If a participant misses the Month 30 visit due to any reason and is known to be alive beyond the Month 30 visit, then the target Month 30 visit date will be used for the given participant to derive the duration of study participation over a 30-month period.

If a participant dies before the scheduled Month 30 visit, then the date of death will be used to determine the duration of study participation. If a participant discontinues from the study before the scheduled Month 30 visit and the survival status could not be tracked, then the date of study discontinuation will be used to determine the duration of study participation.

5.4. Secondary Endpoints Analysis

All the secondary endpoint analyses will be performed using the FAS.

The secondary endpoints in Part A are the following:

2. CFB to Months 6 and 9 in the distance walked during the 6MWT
3. CFB to Months 6, 9, and 12 in KCCQ-OS
4. CFB in serum TTR concentration (an in vivo measure of TTR stabilization) and established ex vivo assays of TTR stabilization (FPE) on Days 14 and 28 and subsequent visits up to Month 12

The secondary efficacy endpoints in Part B are the following:

1. CFB to Months 18, 24, and 30 of treatment in the distance walked during the 6MWT
2. CFB to Months 18, 24, and 30 of treatment in KCCQ-OS
3. CFB in TTR concentration and established ex vivo assays of TTR stabilization at Month 30

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

a. Population: adult (≥ 20 to ≤ 90 years of age) Japanese participants with symptomatic ATTR-CM (either mutant or wild type)
b. Study intervention: ALXN2060 800 mg bid
c. Variable: CFB in in the distance walked during 6MWT, CFB in KCCQ-OS, CFB in serum TTR (prealbumin) level
d. Summary measure: LS mean CFB in the distance walked during 6MWT, LS mean CFB in KCCQ-OS, LS mean CFB in serum TTR (prealbumin) level
e. ICEs for CFB in 6MWT and CFB in KCCQ-OS and their corresponding strategies are summarized in Table 4. For CFB in serum TTR level, ICEs will be addressed using the treatment policy strategy (ie, participants' postbaseline measurements will be used in analyses as available, regardless of the occurrence of the ICE)

5.4.1. Secondary Endpoint - CFB to Months 6 and 9 (Part A), to Months 18, 24, and 30 (Part B) of Treatment in Distance Walked During the 6MWT

5.4.1.1. Main Analytical Approach

Actual mean values and mean CFBs in the distance walked during the 6MWT will be summarized by visit. All available values will be utilized, regardless of ICEs such as treatment discontinuation, initiation of prohibited medications, and other protocol deviations. The actual mean values will be plotted over time.

The CFB in the distance walked during the 6MWT will be analyzed using an MMRM model similar to that described in Section 5.3.1.3. Missing data due to reasons other than death or receiving a heart transplant or a CMAD will be handled by MMRM without imputation. For missing data following death or receiving a heart transplant or a CMAD, the imputation will be performed by sampling with replacement from the bottom 25% of observed (nonmissing) CFB values at a given visit. LS mean CFB and associated 95% CI will also be presented by visit. In addition, the LS mean (SE) of CFB in 6MWT will be plotted over time. For Part A, the MMRM model will include all visits up to Month 12. For Part B, the MMRM model will include all visits up to Month 30. All ICEs will be handled as described in Table 4.

5.4.2. Secondary Endpoint - CFB to Months 6, 9, and 12 (Part A), to Months 18, 24, and 30 (Part B) of Treatment in KCCQ-OS

5.4.2.1. Definition of Endpoint

The KCCQ-OS values will be calculated from the answers on the KCCQ electronic case report form according to the scoring instructions provided by Outcomes Instruments, LLC (revision 27 Mar 2001). The scoring algorithm adjusts for missing answers to questions by calculating means of questions answered. The algorithm also specifies the minimum number of responses required to calculate each summary score. More details are provided in Appendix 3.

5.4.2.2. Main Analytical Approach

Summary statistics of the actual mean values and mean CFBs in KCCQ-OS will be presented by visit. All available values will be utilized, regardless of ICEs such as treatment discontinuation, initiation of prohibited medications, and other protocol deviations.

Analysis of the KCCQ-OS will utilize the same analytical approach as that used for CFB in 6MWT. Missing data due to reasons other than death or receiving a heart transplant or a CMAD will be handled by MMRM without imputation. For missing data following death or receiving a heart transplant or a CMAD, the imputation will be performed by sampling with replacement from the bottom 25% of observed (nonmissing) CFB values at a given visit. Least square means will be displayed for each postbaseline study visit to summarize treatment effects over time. For Part A, the MMRM model will include all visits up to Month 12, while the MMRM model for Part B will include all visits up to Month 30.

Summary statistics of the 7 domain scores, the Total Symptom Score, and the Clinical Summary Score will also be presented by visit. All ICEs will be handled as described in Table 4.

5.4.3. Secondary Endpoint - CFB in Serum TTR Concentration (an in vivo measure of TTR stabilization) and Established Ex Vivo Assays of TTR Stabilization (FPE) on Days 14 and 28 and Subsequent Visits up to Month 12 (Part A), at Month 30 (Part B)

5.4.3.1. Main Analytical Approach

Actual mean values and mean CFBs over time in serum TTR concentration and the established ex vivo assays of TTR stabilization (FPE) will be summarized. LS mean CFB and associated 95% CI for the treatment group and visits will also be presented, derived from an MMRM model with visits and baseline serum TTR as a covariate. Other covariates may be included as needed. The same technique used in Section 5.3.1.3 to model the within-participant variance-covariance errors will be utilized. Part A analysis will include CFB to Days 14 and 28 and subsequent visits up to Month 12, while Part B analysis will include CFB of all visits up to Month 30.

All ICEs will be handled using the treatment policy strategy (ie, participants' postbaseline measurements will be used in the analysis as available, regardless of the occurrence of the ICE).

5.5. Exploratory Endpoints Analysis

5.5.1. Exploratory Endpoint in Part A - ACM and CV-related Hospitalization Over a 12-month Period

ACM will be assessed using a time-to-event analysis similar to that performed in Section 5.3.2. The number and percentage of participants with events will be presented, as well as the number and percentage of participants censored. A Kaplan-Meier analysis of ACM will be provided as point estimates at Month 12, along with 95% CIs. The Kaplan-Meier curve will also be plotted.

CV-related hospitalizations over a 12-month period will be analyzed similarly as in Section 5.3.3 and will be determined as the total number of CV-related hospitalizations per year during the duration of study participation over a 12-month period for each participant. The cumulative frequency of CEC-adjudicated CV-related hospitalization will be estimated using a negative binomial regression analysis with no covariates but an offset term equal to log of each participant's study duration included in the model. If the number of participants with 0 CV-related hospitalization is high, a 0 inflated negative binomial model will be performed to provide further assurance of the results. The CV-related hospitalization per person per year will be presented with 95% CI.

5.5.2. Exploratory Endpoint - CFB over Month 30 in NT-proBNP and TnI

5.5.2.1. Main Analytical Approach

Actual values, CFBs, and percent CFBs in NT-proBNP and TnI will be summarized by time point up to Month 30. All available values will be utilized, regardless of ICEs such as treatment discontinuation, initiation of prohibited medications, and other protocol deviations. Missing data due to reasons other than death or receiving a heart transplant or a CMAD will be handled by MMRM without imputation. For missing data following death or receiving a heart transplant or a CMAD, the imputation will be performed by sampling with replacement from the bottom 25% of observed (nonmissing) CFB values at a given visit. LS mean CFB and associated 95% CI will be

presented, derived from an MMRM model with baseline NT-proBNP/TnI value and visits as covariates. Other covariates may be included as needed. The same technique used in Section 5.3.1.3 to model the within-participant variance-covariance errors will be utilized. The MMRM model will include all visits up to Month 30. Additional exploratory analyses may be performed if deemed necessary.

All ICEs will be handled as described in Table 4.

5.5.3. Exploratory Endpoint - CFB in EQ-5D-5L Over Month 30

5.5.3.1. Definition of Endpoint

The EQ-5D-5L instrument includes 2 parts. In the first part, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), with each dimension having 5 levels of function (1 = no problem, 2 = slight problem, 3 = moderate problem, 4 = severe problem, and 5 = extreme problem).

The second part is a respondent's self-rating of current health status on a European Quality of Life visual analog scale with endpoints labeled "best health you can imagine" (best imaginable health state, score of 100) and "worst health you can imagine" (worst imaginable health state, score of 0).

The scores from the 5 dimensions will be used to calculate a single index value, known as a utility score. EQ-5D index value will be created as follows:

- Assign the level codes 1, 2, 3, 4, and 5 to each level of the 5 dimensions (as described above).
- Create a health state for each participant-time point combination. A health state is a combination of the 5-level code (1-level code for each dimension). The dimensions are ordered as described above (eg, health state 12543 indicates "no problems walking, slight problems washing or dressing myself, unable to do my usual activities, severe pain or discomfort, moderately anxious or depressed").
- Assign an index value to each health state, where the EQ-5D health state is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The algorithm is based on the valuation of EQ-5D health states using the UK time trade-off method (TTO)-based value set.

5.5.3.2. Main Analytical Approach

Frequency tabulations of the EQ-5D-5L dimensions will be provided. Actual values and CFBs in European Quality of Life visual analog scale and index values will be summarized by time point up to Month 30.

All available values will be utilized, regardless of ICEs such as treatment discontinuation, initiation of prohibited medications, and other protocol deviations. Missing data due to reasons other than death or receiving a heart transplant or a CMAD will be handled by MMRM without imputation. For missing data following death or receiving a heart transplant or a CMAD, the imputation will be performed by sampling with replacement from the bottom 25% of observed (nonmissing) CFB values at a given visit. LS mean CFB and associated 95% CI will be

presented, derived from an MMRM model with visits and baseline EQ5D-5L values as covariates. The analysis will utilize an MMRM model with all visits up to Month 30. Other covariates may be included as needed. The same technique used in Section 5.3.1.3 to model the within-participant variance-covariance errors will be utilized.

All ICEs will be handled as described in Table 4.

5.5.4. Exploratory Endpoint - CFB up to Months 12, 24, and 30 in Cardiac MRI Parameters

The cardiac MRI parameters will include structural measures, functional measures, and tissue characterization for participants at selected sites who consented. Actual values and CFBs up to Months 12, 24, and 30 in the following cardiac MRI parameters may be summarized if sufficient data are available. A listing will be presented by participant.

- Left ventricular mass
- Left ventricular end diastolic volume
- Left ventricular end systolic volume
- Stroke volume
- Left ventricular ejection fraction
- Tricuspid annular plane systolic excursion
- Mitral annular plane systolic excursion
- Left atrial area
- Right atrial area
- Native T1
- Extracellular volume
- Strain
- Late gadolinium enhancement

5.6. Efficacy Analyses During Extension Period

All efficacy endpoints except for cardiac MRI parameters will be analyzed during the Extension Period. Further details will be elaborated in a separate SAP.

5.7. Pharmacokinetic Analyses

5.7.1. Exploration of PK Over 30 Months for ALXN2060 and Its Metabolite

PK and PD analyses specified in this section will be performed using the respective Pharmacokinetic Analysis Set and Pharmacodynamic Analysis Set.

5.7.2. Pharmacokinetic Sampling

Blood samples will be collected at the following time points to determine plasma concentrations of ALXN2060 and its active metabolite, ALXN2060 acyl glucuronide (ALXN2060-AG):

- Day 1, Day 14, and every 3-month study visits during Parts A and B: predose
- Day 28: predose and at 1 hour postdose
- Month 1 and every 3-month after the Extension Period: predose
- Early discontinuation

5.7.3. Handling of Below the Limit of Quantification Values/Missing Values

For ALXN2060 and its metabolite concentration summaries, values below the limit of quantification will be set to 0. Missing values will not be imputed.

5.7.4. PK Data Presentation Conventions

Data on ALXN2060 and its metabolite concentration will be summarized using the following descriptive statistics: number of participants (N), number of participants with available data (n), arithmetic mean, SD, arithmetic coefficient of variation, geometric mean (GM), GM of coefficient of variation, median, minimum, and maximum.

The following conventions will be applied to presentations and summaries of ALXN2060 and its metabolite:

- For continuous variables, all mean and median values are formatted to 1 more decimal place than the measured value. SD values are formatted to 2 more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.

5.7.5. PK Concentration Analyses

Plasma concentrations of ALXN2060 and ALXN2060-AG versus time data will be presented in a data listing by participant. Plasma concentration data will be summarized separately by analyte, nominal month/day, and time point using descriptive statistics. When calculating the GM, values of 0 will be discarded.

Individual trough concentration observed at the start of the dosing interval (C_{trough}; predose) plasma concentration versus study day/month profiles will be presented similarly. The time to reach steady state will be graphically assessed by plotting mean plasma C_{trough} concentration

versus month/study day in both linear and semilogarithmic scales. In addition, time to steady state may be evaluated using stepwise testing for linear trend.

5.7.6. PK Parameter Analyses

As data permit, C_{trough} (predose) will be calculated for ALXN2060 and ALXN2060-AG using SAS version 9.4 or higher.

Additional plasma PK parameters may be calculated if deemed appropriate.

PK parameters derived from plasma concentrations of ALXN2060 and ALXN2060-AG will be presented in data listings and will be summarized by analyte and nominal month/study day using descriptive statistics.

5.7.7. Population PK Analyses

The details of the proposed population PK/exposure-response analyses for this study will be documented in a separate modeling and simulation SAP. The results of the population PK/exposure-response analyses will be reported separately from the clinical study report.

5.7.8. PD Analyses

Observed values and CFBs in serum TTR concentration and the established ex vivo assays of TTR stabilization will be summarized by visit using descriptive statistics. Observed values and CFBs will also be presented graphically.

5.7.9. PK-PD Correlation

The PK-PD relationship between ALXN2060 and ALXN2060-AG plasma concentration and TTR stabilization (percentage of occupancy) measured by FPE may be explored. Individual FPE values will be plotted against the corresponding ALXN2060 and ALXN2060-AG plasma concentrations. Individual serum TTR concentration will also be plotted against the corresponding ALXN2060 and ALXN2060-AG plasma concentrations.

5.8. Safety Analyses

All safety analyses will be conducted on the SS, unless otherwise noted. All safety data will be provided in participant listings. No formal hypothesis testing is planned. Safety data include the following:

- Treatment-emergent adverse events (TEAEs)
- SAEs
- Clinical laboratory tests (hematology, chemistry, urinalysis, pregnancy, and special laboratory tests)
- Vital signs, including respiratory rate, pulse rate, blood pressure, and weight
- Physical examination
- Twelve-lead ECG, including rate, rate ranges, and diagnostic statements

AEs will be coded using the MedDRA coding dictionary version 25.1 or higher and presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). Participant incidence of each SOC and unique PT will be tabulated, including all TEAEs, related versus unrelated TEAEs, TEAEs resulting in discontinuation of study treatment, TEAEs by toxicity grade, and treatment-emergent SAEs. Note that only AEs that occur on or after the date of signing the informed consent form are entered into the AE database. "Treatment-emergent AEs" are defined as AEs with an onset on or after the first study date but on or before 30 days after the last study intervention.

AEs and SAEs will be assessed for intensity by the Investigator using categories from National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, published 27 Nov 2017. Analyses of laboratory, vital sign, and ECG outcomes will include mean CFBs, as well as shifts (eg, normal to abnormal) from Baseline, and the incidence of abnormal values.

5.8.1. Extent of Exposure

The number of participants exposed to the study intervention and the duration of exposure to study intervention will be summarized.

The duration (month) of exposure to study intervention will be calculated as (date of last exposure to treatment – date of first dose + 1) / 30.4375, regardless of dose interruptions or dose reductions. Noninteger values will be rounded to 1 decimal place.

5.8.2. Adverse Events

AEs occurring on or after the first treatment date (ie, treatment-emergent as described in Appendix 1, Section 6.1.2) will be tabulated and presented. For simplification, AEs/SAEs refer to treatment-emergent AEs/SAEs. Additional details are outlined in Appendix 1, Section 6.1.2.

5.8.2.1. Pretreatment AEs

Pretreatment AEs are defined as AEs that occur on or after the signing the informed consent but before the first treatment date. Pretreatment AEs will be presented in a listing.

5.8.2.2. Overall Summary of AEs

An overall summary of AEs, SAEs, and nonserious AEs will be presented. The number of events (E) and the number and percentage of participants with events (n, %) will be shown by the relationship of events to study intervention (ie, related versus not related).

The AEs resulting in study intervention withdrawal and the toxicity grades of the AEs (Grade 1 through Grade 5) will be summarized similarly.

These statistics will be prepared separately for all AEs and SAEs. In addition, the number and percentage of participants who died on study will be presented.

5.8.2.3. AEs and SAEs by SOC and PT

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT. Participants are counted once in each SOC and PT. Percentages will be based on the total number of participants in the SS. SOCs will be listed in alphabetical order and PT will be listed in order of frequency of occurrence within the SOC.

Additional summary tables stratifying AEs by age, gender, and race will also be provided. SAEs will be summarized similarly.

5.8.2.4. AEs and SAEs by SOC, PT, and Relationship

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT as described above by relationship (related versus not related). If a participant has > 1 occurrence of an AE, the strongest relationship to study intervention will be used in the summary table. If relationship to study intervention is missing, the AE will be assumed to be related. SAEs will be summarized similarly.

The number of TEAEs by System Organ Class, Preferred Term, and relationship, without taking into account the highest relationship, will be analyzed. A similar analysis will be conducted for treatment-emergent SAEs.

5.8.2.5. AEs and SAEs by SOC, PT, and Toxicity Grade

The number of AEs and the number and percentage of participants with events will be presented by SOC and PT as described above by toxicity grade (Grade 1 through Grade 5). If a participant has > 1 occurrence of an AE, the highest grade will be used in the summary table. SAEs will be summarized similarly.

The number of TEAEs by System Organ Class, Preferred Term, and severity, without taking into account the highest severity, will also be analyzed. A similar analysis will be conducted for treatment-emergent SAEs.

5.8.2.6. Deaths, Other SAEs, and Other Significant AEs

AEs leading to death, AEs leading to withdrawal of study intervention, and AEs resulting in the modification of the study intervention, including interruption and reduction, will also be presented by SOC and PT as described above.

Listings for the SAEs and deaths will be produced.

5.8.3. Clinical Laboratory Assessments

Descriptive statistics by time of assessment will be presented for each laboratory parameter. CFBs at each visit and worst postbaseline value will be summarized. Shifts from Baseline at each visit and from Baseline to worst postbaseline values will also be summarized. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges supplied by the central laboratory. Frequencies of abnormal values will be presented in tabular form. All the laboratory values will be listed. For purposes of analyses, laboratory results based on standardized units will be used. If a result begins with a "<", then the result will be imputed by the numeric part divided by the square root of 2. If a result begins with a ">," then the result will be imputed by the numeric part.

Baseline is defined as the last available assessment prior to the start of the first dose of the study intervention. If any baseline laboratory analyte is evaluated at both the local and the central laboratories, then the central laboratory results will be used for analysis.

The following protocol-required clinical laboratory assessments will be analyzed:

Laboratory Assessments	**Parameters**
Hematology	Hemoglobin, hematocrit, white blood cell count, platelet count, complete blood count, and differential
Chemistry	Sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, prealbumin, retinol-binding protein, free thyroxine, alkaline phosphatase, calcium, phosphorus, total and fractionated (indirect or direct) bilirubin, uric acid, thyroid-stimulating hormone, TnI, creatine kinase, creatine kinase-MB, and NT-proBNP
Urinalysis	Complete urinalysis (specific gravity, pH, glucose, protein, hemoglobin, leukocyte esterase, and nitrite). Additionally, albumin-to-creatinine ratio and a microscopic urinalysis will be performed on every specimen and will specifically look for casts, bacteria, white blood cells, epithelial cells, and red blood cells.
Pregnancy test	Highly sensitive urine test at all visits as outlined in the Schedule of Assessments in Section 1.3 of the protocol (female participants of childbearing potential only)

5.8.4. Vital Signs

Observed values and CFBs in vital signs (blood pressure, pulse rate, respiratory rate, and weight) at each visit will be summarized descriptively. A listing of vital signs will be presented by participant, vital sign, and visit.

5.8.5. Electrocardiogram

Twelve-lead ECGs will be conducted at timings specified in the SoA. The following quantitative ECG measurements will be taken:

- ECG mean heart rate (beats/min)
- PR interval (msec)

- QRS duration (msec)
- QT interval (msec)
- QT corrected for heart rate by Bazett formula (QTcB) interval (msec)
- QT corrected for heart rate by Fridericia's formula (QTcF) interval (msec)
- RR interval (msec)

Descriptive statistics by time of assessment will be presented for each ECG parameter value and for CFB values. Similar summary statistics will also be provided for QTcB and QTcF. These parameters will be derived as follows:

$$QTcB\ (msec) = QT / RR^{1/2}$$

$$QTcF\ (msec) = QT / RR^{1/3}$$

where QT is measured in milliseconds and RR is measured in seconds.

The number and percentage of participants with observed QT, QTcB, and QTcF greater than a given threshold (> 450, > 480, and > 500 msec) will be presented at each assessment visit.

The number and percentage of participants with CFB in QT, QTcB, and QTcF over predetermined cutoffs (> 10, > 30, > 60, and > 90 msec) by time point/visit will be presented. These will also be presented for the worst postbaseline values.

The number and percentage of participants with PR > 200 msec and CFB > 25% (of baseline observed value) by time point/visit will be presented. These will also be presented for the worst postbaseline values.

The number and percentage of participants with QRS duration > 120 msec and CFB > 25% (of baseline observed value) by time point/visit will be presented. These will also be presented for the worst postbaseline values.

A listing of ECG results will be presented by participant and visit.

5.8.6. Physical Examinations

The number and percentage of participants with abnormal physical examination findings will be summarized by visit and body system. A listing will also be created.

5.9. Other Analyses

5.9.1. Study Duration

Study duration in months is defined as the duration from the date of informed consent to the date of study discontinuation (date of study discontinuation – data of informed consent + 1) / 30.4375, rounded up to 1 decimal place. Study duration will be summarized for participants in the FAS. A supportive listing will be produced.

5.9.2. Treatment Compliance

Treatment compliance is defined as follows:

Compliance (%) = (number of doses received) / (total number of doses scheduled) × 100

It will be summarized in the following ways:

- Compliance (%)
- Compliance (< 80% or ≥ 80%)

5.9.3. Subgroup Analyses

No subgroup analyses are planned for this study.

5.10. Interim Analyses

No interim analysis is planned for this study. Data will be analyzed as described in Section 5, when all participants have completed Month 30 (Part B) and when the study is completed.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

6.1.1. Imputation of Missing or Partial Date of Death

In the event of a participant's death, the complete date of death, including the day, month, and year, will be obtained. If the date of the death is missing or partially missing, the following imputation rules should be applied:

Imputation Rules for Partial Death Dates (D = day, M = month, Y = year)		
Missing	**Additional Conditions**	**Imputation**
D	M and Y the same as the M and Y of the last date recorded	Last known date recorded
	M and/or Y not the same as the last known date recorded	First day of the month
D and M	Y the same as the Y of the last known date recorded	Date of the last known date recorded
	Y after the Y of the last known date recorded	Set to 01 Jan
D, M, Y	None (Date is completely missing.)	Last known date recorded

6.1.2. Adverse Events

Treatment-emergent AEs are events with start dates and start times on or after the date and time of the first study intervention dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do not indicate that it occurred prior to the first dose, then the AE is considered as treatment-emergent if the following apply:

- The start year is after the year of the first study intervention dose.
- The start year is the same as the year of the first study intervention dose.
  - The start month is missing.
  - The start month is present and is the same or after the month of the first study intervention dose.
- The start date is completely missing.

All other AEs are considered pretreatment AEs.

Percentages are based on the total number of participants in the SS.

To be able to calculate time from the first dose to AE, the following are the imputation rules for AE start dates:

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start date for AEs	D	M and Y same as M and Y of the first dose of study intervention	Date of the first dose of study intervention
		M and/or Y not same as the date of the first dose of study intervention	First day of the month
	D and M	Y same as Y of the first dose of study intervention	Date of the first dose of study intervention
		Y is after Y of the first dose	Set to 01 Jan
	D, M, and Y	None – date is completely missing	Date of the first dose of study intervention

AE duration (days) = date of stop of AE – date of start of AE + 1.

Duration will be set to "missing" if the stop date of AE is incomplete or if the AE is ongoing.

6.2. Appendix 2: Study and Participant Characteristics

6.2.1. Protocol Deviations

Major protocol deviations may have the potential to impact participants' rights, safety, or well-being or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock, and appropriate categories of the protocol deviations will be determined.

The number and percentage of participants with any important/not important protocol violations, as well as the number and percentage of participants with violations within each category, will be presented. A listing will also be provided.

All participants in the FAS, with the exclusion of any participants deemed to have a major impact on the assessment of primary efficacy endpoint, will be considered in the PPS.

6.2.2. Demographics, Disease Characteristics, and History

All demographic and baseline characteristic information will be handled in a similar fashion as in Part A SAP. Summaries and listings will utilize the FAS.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be provided for all continuous variables. Frequency counts with the number and percentage of participants in each category will be provided for all categorical variables.

6.2.2.1. Demographics

The following demographic and baseline characteristic variables will be summarized:

- Sex (male, female, undifferentiated, or unknown)
- Ethnicity (not of Hispanic, Latino/Latina, or Spanish origin; Mexican, Mexican American, or Chicano/Chicana; Puerto Rican; Cuban; another Hispanic, Latino/Latina, or Spanish origin; not reported; or unknown)
- Race (White, Black or African American, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, other Pacific Islander, not reported, unknown, or other)
- Age (years) at Baseline (continuous)
- Age (years) at Baseline (categorical; < 65 and ≥ 65, and < 78 and ≥ 78)
- Height at Baseline (centimeter)
- Weight at Baseline (kilogram)
- Body mass index at Baseline (kg/m^2)

6.2.2.2. Disease Characteristics

The following disease characteristics will be summarized:

- Time since diagnosis of ATTR-CM (years)
- Genetic status of ATTR-CM (mutation, wild type, or unknown)
- Mutation genotype (V30M, V122I, T60A, S77Y, T49A, L111M, E89Q, or other)
- Type of mutation (heterozygote, homozygote, or unknown)
- NYHA class (I, II, or III)
- Baseline NT-proBNP level (≤ 3000 pg/mL versus > 3000 pg/mL)
- Baseline estimated glomerular filtration rate (≥ 45 mL/min/1.73 m^2 versus < 45 mL/min/1.73 m^2)

Time since diagnosis of the disease will be presented as the number of years between the date of the first dose and the date of diagnosis (ie, time since diagnosis of the disease = [date of the first dose – date of diagnosis + 1] / 365.25, rounded up to 1 decimal place).

6.2.2.3. Medical/Surgical History and Baseline Physical Examination

Medical history information will be coded to the primary SOC and PT using the MedDRA (version 25.1 or higher). Medical history will be summarized by SOC and PT. Summaries will be presented as prior disease and concomitant disease, with the prior and concomitant status determined by whether the condition was active at the time of Screening. Participant listings will be presented, including medical history condition, start and end dates, and status as ongoing.

The number and percentage of participants with abnormal baseline physical examination findings will be listed and summarized by body system.

6.2.2.4. Prior and Concomitant Medications/Therapies

Medications will be mapped to a generic term using the World Health Organization Drug Dictionary of Mar 2022 or later. Prior medication is defined as any medication taken and discontinued by a participant prior to the first dose of study intervention. Concomitant medication is defined as any medications taken by a participant that overlaps with the study intervention.

The following steps will be implemented to categorize the medications:

Algorithm for Categorization of Medications (Prior or Concomitant)			
Parameter	**Value**	**Additional Conditions**	**Medication Category/Action**
Ongoing flag	Yes	Not applicable.	Concomitant
	No	Medication end date is partial or missing.	Perform the imputation on medication end date and then assign the medication category
		Medication end date is before the first dose of study intervention.	Prior
		Medication end date is on or after the first dose of study intervention.	Concomitant

Imputation Rules for Partial Dates			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
End date of medication	D	M and Y the same as the M and Y of the first dose of study intervention	Day of the later of (date of the first dose of study intervention, start date of medication)
		M and/or Y not the same as the date of the first dose of study intervention	Last day of the month
	D and M	Y the same as the Y of the first dose of study intervention	Day and month of the later of (date of the first dose of study intervention/start date of medication)
		Y is after the Y of the first dose	Day and month of the start date of medication
	D, M, and Y	None (Date is completely missing.)	Later of (date of the first dose of study intervention, start date of medication)

D = day; M = month; Y = year

6.3. Appendix 3: Instrument Scoring Details

6.3.1. European Quality of Life Health 5-item Questionnaire Dimensions 5 Levels

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

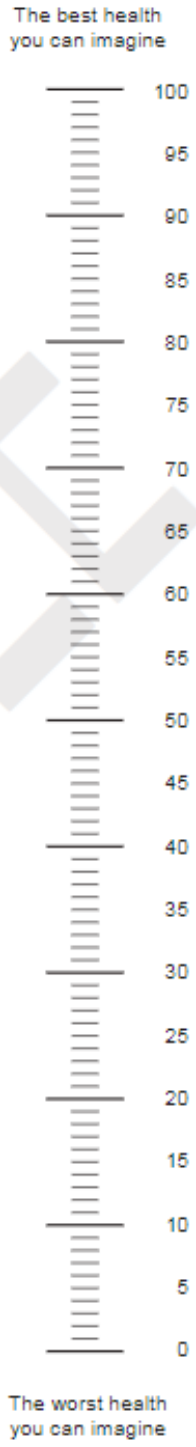
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



6.3.2. Kansas City Cardiomyopathy Questionnaire

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	**I occasionally** felt that way	**I rarely** felt that way	**I never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

The Kansas City Cardiomyopathy Questionnaire
Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. **Physical Limitation**

   - Code responses to each of Questions 1a-f as follows:

     Extremely limited = 1
     Quite a bit limited = 2
     Moderately limited = 3
     Slightly limited = 4
     Not at all limited = 5
     Limited for other reasons or did not do = <*missing value*>

   - If at least three of Questions 1a-f are not missing, then compute

     Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

     (see footnote at end of this document for explanation of meaning of "actually answered")

2. **Symptom Stability**

   - Code the response to Question 2 as follows:

     Much worse = 1
     Slightly worse = 2
     Not changed = 3
     Slightly better = 4
     Much better = 5
     I've had no symptoms over the last 2 weeks = 3

   - If Question 2 is not missing, then compute

     Symptom Stability Score = 100*[(Question 2) – 1]/4

3. **Symptom Frequency**

   - Code responses to Questions 3, 5, 7 and 9 as follows:

     <u>Question 3</u>
     Every morning = 1
     3 or more times a week but not every day = 2
     1-2 times a week = 3
     Less than once a week = 4
     Never over the past 2 weeks = 5

3. **Symptom Frequency (cont.)**

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. **Symptom Burden**

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. **Total Symptom Score**

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

6. **Self-Efficacy**

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. **Quality of Life**

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

7. **Quality of Life (cont.)**

   - If at least one of Questions 12, 13 and 14 is not missing, then compute

     Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. **Social Limitation**

   - Code responses to each of Questions 15a-d as follows:

     Severely limited = 1
     Limited quite a bit = 2
     Moderately limited = 3
     Slightly limited = 4
     Did not limit at all = 5
     Does not apply or did not do for other reasons = <*missing value*>

   - If at least two of Questions 15a-d are not missing, then compute

     Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. **Overall Summary Score**

   = mean of the following available summary scores:
   Physical Limitation Score
   Total Symptom Score
   Quality of Life Score
   Social Limitation Score

10. **Clinical Summary Score**

    = mean of the following available summary scores:
    Physical Limitation Score
    Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

- If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
  (sum of the responses to those *n-i* questions) / (*n-i*)
  not
  (sum of the responses to those *n-i* questions) / *n*

6.4. Appendix 4: Additional Details on Statistical Methods

6.4.1. Analysis Considerations Related to COVID-19

On 11 Mar 2020, coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (Cucinotta and Vanelli, 2020). This section summarizes additional analysis considerations to assess the potential impact of COVID-19 (Meyer et al, 2020). The following additional analyses will be included to assess the impact of the pandemic disruption on the study and to address pandemic-related data missingness.

1. The summary of participant disposition will include COVID-19-related discontinuations and withdrawals.
2. A summary of known COVID-19 exposure or diagnosis will be provided using the SS.
3. A summary of COVID-19-related important protocol deviations will be provided. A by-participant listing of all protocol deviations will be provided.
4. A summary of the number and percentage of participants who missed a study visit or had a modified study visit, along with the reasons (COVID-19 related or not), will be provided by visit using the SS. For participants who had a modified study visit, the method for the different assessments will be summarized.
5. Alternative data collection methods required during the pandemic may introduce additional variability. A sensitivity analysis will be performed to assess this possibility. Descriptive statistics for the primary and key secondary endpoints by visit can be calculated with the visits split into the 2 categories as either “collected as planned” or “modified.”
6. Missing data on the primary endpoint due to any COVID-19-related reasons will be handled according to the strategy for addressing the ICEs described in Section 5.

6.5. Appendix 5: Changes to Protocol-Planned Analyses

Not applicable.

6.6. Appendix 6: List of Abbreviations

Abbreviation or Acronym	Explanation
6MWT	6-minute walk test
ACM	all-cause mortality
AE	adverse event
ALXN2060-AG	ALXN2060 acyl glucuronide
ATTR-CM	transthyretin amyloid cardiomyopathy
bid	twice daily
CEC	Clinical Events Committee
CFB	change from Baseline
CI	confidence interval
CMAD	cardiac mechanical assist device
COVID-19	Coronavirus Disease 2019
C_{trough}	trough concentration observed at the start of the dosing interval
CV	cardiovascular
ECG	electrocardiogram
EQ-5D-5L	European Quality of Life Health 5-item Questionnaire Dimensions 5 Levels
FAS	Full Analysis Set
FPE	fluorescent probe exclusion
GM	geometric mean
ICE	intercurrent event
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Score
LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NT-proBNP	N-terminal pro-brain-type natriuretic peptide
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	Per-protocol Set
PT	Preferred Term
QRS	ventricular conductance time
QTcB	QT interval corrected for heart rate, Bazett's formula
QTcF	QT interval corrected for heart rate, Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software®
SOC	System Organ Class
SS	Safety Set
TEAE	treatment-emergent adverse events
TnI	troponin I
TTR	transthyretin

7. REFERENCES

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