STATISTICAL ANALYSIS PLAN
ALN-TTRSC02-003

Protocol Title:	HELIOS-B: A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Short Title:	HELIOS-B: A Study to Evaluate Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Study Drug:	Vutrisiran (ALN-TTRSC02)
Protocol Date:	Original protocol: 22 August 2019 Amendment 1: 28 May 2020 Amendment 2: 18 February 2021 Amendment 3: 13 May 2022 Amendment 4: 22 March 2023 Amendment 5: 12 February 2024
SAP Date:	Original SAP: 30 April 2021 Amendment 1: 15 February 2024 Amendment 2: 30 May 2024
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200

APPROVAL SIGNATURE PAGE

This document has been authored and signed electronically on the final page by the following:

PPD

Director, Biostatistics

Alnylam Pharmaceuticals, Inc.

This document has been approved and signed electronically on the final page by the following:

PPD

Senior Vice President, Clinical Research

Alnylam Pharmaceuticals, Inc.

PPD

Vice President, Biostatistics

Alnylam Pharmaceuticals, Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
6-MWT	6-minute walk test
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
ATTR	Amyloid transthyretin
BMI	Body mass index
CEC	Clinical events committee
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DB	Double blind
DMC	Data monitoring committee
CCI	[redacted]
eCRF	Electronic case report form
CCI	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
hATTR	Hereditary ATTR
HF	Heart failure
HLT	High level term
HR	Hazard ratio
ICH	International Council for Harmonisation
IRT	Interactive response technology
ISR	Injection site reaction
JFM	Joint frailty model
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire-Overall Summary

Abbreviation	Definition
LFT	Liver function test
LS	Least square
LV	Left ventricular
LVAD	Left-ventricular assist device
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MLE	Maximum likelihood estimates
MMRM	Mixed effects model repeated measures
MNAR	Missing not at random
CCI [redacted]	[redacted]
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OLE	Open Label Extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PMM	Pattern mixture model
CCI [redacted]	[redacted]
PT	Preferred term
Q1, Q3	First quartile, third quartile
q3M	once every 3 months
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TTR	Transthyretin

Abbreviation	Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of normal
wtATTR	Wild type ATTR

1. INTRODUCTION

This statistical analysis plan (SAP) details comprehensive specifications of the efficacy, safety, pharmacodynamic (PD), and pharmacokinetic (PK) data summaries and statistical analyses in support of the clinical study report (CSR) for Study ALN-TTRSC02-003 (HELIOS-B). Changes to planned analyses specified in the final SAP made after database lock will be documented with justification in the CSR.

Table, figure, and listing mock shells and specifications are contained in separate documents.

Unless otherwise specified, statistical analyses will be conducted using SAS software Version 9.4 or newer.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vutrisiran in approximately 600 patients with transthyretin (TTR) amyloidosis (ATTR amyloidosis) with cardiomyopathy. Approximately 20% of the study population is anticipated to have hereditary ATTR (hATTR) amyloidosis with cardiomyopathy and 80% to have wild type ATTR (wtATTR) amyloidosis with cardiomyopathy.

At study entry, patients are either:

- Not on tafamidis (tafamidis-naïve; see protocol for definition); or
- On tafamidis (currently receiving tafamidis) (Note: must be on-label use of commercial tafamidis per an approved cardiomyopathy indication and dose in the country of use).

The study consists of 4 periods (Figure 1):

1. **Screening Period:** Up to 45 days during which patients will undergo screening assessments to determine eligibility.
2. **Double-Blind Period (DB Period):**
   - At the start of the DB Period (on Day 1), eligible patients will be randomized in a 1:1 ratio to receive blinded doses of 25 mg of vutrisiran or placebo administered as a subcutaneous (SC) injection once every 3 months (q3M; every 12 weeks ±7 days) for up to 36 months.
   - An individual patient's DB Period visits will end after they complete their Month 36 visit, or 30 months after the last patient is randomized, whichever comes first. As such, a patient's last visit during the DB Period may vary from 30 to 36 months after enrollment.
     – The variable length of the DB Period will mean that some patients will not have a Month 33 and/or Month 36 visit. For patients whose last visit in the DB Period was Month 30 (Week 132), Day 1 in the OLE Period will occur 144 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the

DB Period was Month 33 (Week 144), Day 1 in the OLE Period will occur 156 weeks (±7 days) after enrollment in the DB Period. For patients whose last visit in the DB Period was Month 36 (Week 156), Day 1 in the OLE Period will occur on the same day (since study drug is not administered as part of the Month 36 DB visit).

– The period of DB exposure, defined as the duration prior to first exposure to open-label treatment, will be 144 to 156 weeks (33 to 36 months).

- The primary analysis will be conducted after the last patient has completed the period of DB exposure or otherwise discontinued.

3. **Open Label Extension (OLE) Period:**

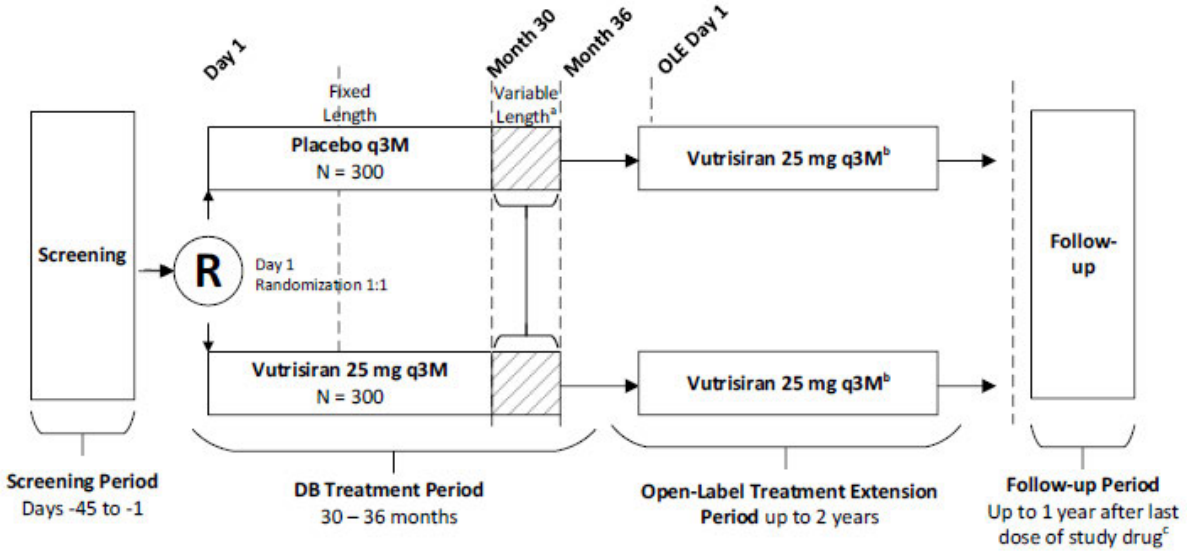
   The study has been amended (Protocol Amendment 4) to include an OLE Period in lieu of the Open-Label Randomized Treatment Extension Period (previously introduced with Protocol Amendment 3). In the OLE Period, all patients will receive the vutrisiran 25 mg q3M regimen for up to 2 years. Patients initially randomized to CCI in the OLE Period (under Amendment 3) will transition to receive open-label doses of 25 mg q3M vutrisiran administered as SC injections at their next scheduled dosing visit.

4. **Follow-Up Period:**

   Following completion of the OLE Period or completion of the DB Period for patients who do not continue into the OLE period or early treatment discontinuation in DB or OLE, patients will be followed up to 1 year after their last dose of study drug (up to 18 months for women of child-bearing potential).

Refer to Protocol Section 3.1 for more details.

Figure 1: Study Design



Abbreviations: DB=double-blind; OLE=open-label extension; q3M=every 3 months; CCI ; SC=subcutaneous.

Abbreviations: DB=double-blind; OLE=open-label treatment extension; q3M=every 3 months; SC=subcutaneous.

[a] An individual patient's DB Period visits will end after they complete their Month 36 Visit, or 30 months after the last patient is randomized, whichever comes first. As such, a patient's last visit during the DB Period may vary from 30 to 36 months after enrollment (refer to Protocol Section 3.1).

[b] The dosing schedule under Amendment 4 is 25 mg vutrisiran every 12 weeks. Upon entry into the OLE Period (OLE Day 1), all eligible patients will receive open-label doses of 25 mg q3M vutrisiran administered as SC injections. Patients initially randomized to receive CCI vutrisiran under Amendment 3 will transition to receive 25 mg q3M vutrisiran at their next scheduled dosing visit (24 weeks after their last dose of CCI vutrisiran).

[c] Following completion of the OLE Period (or completion of the DB Period for patients who do not continue into the OLE Period; or their last dose of vutrisiran for patients who discontinue study drug early), patients will commence follow-up visits as outlined in Protocol Section 3.1. For women of child-bearing potential, the duration of the Follow-up Period will be up to 18 months from their last dose of study drug.

2.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of vutrisiran compared to placebo on reducing all-cause mortality and CV events	• Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure [HF] visits) in the overall population • Composite outcome of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits) in the vutrisiran monotherapy subgroup (defined as the group of patients not on tafamidis at study baseline)
Secondary	
To evaluate the efficacy of vutrisiran compared with placebo treatment on: • Functional capacity • Patient-reported health status and health-related quality of life • All-cause mortality • Severity of clinical heart failure symptoms	The following secondary endpoints will be defined in both the overall population and the vutrisiran monotherapy subgroup: • Change from baseline in 6-MWT • Change from baseline in the KCCQ-OS • All-cause mortality • Change from baseline in NYHA Class
Exploratory	
CCI [redacted]	• CCI [redacted]

Objectives	Endpoints
• CCI	• CCI
Pharmacodynamics and Pharmacokinetics	
• To characterize the PD effect of vutrisiran on TTR • To characterize plasma PK of vutrisiran • To assess presence of antidrug antibodies (ADA) against vutrisiran	• Change from baseline in serum TTR levels • Plasma PK exposure parameters • Frequency and titers of ADA
Safety	

Objectives	Endpoints
• To evaluate the safety and tolerability of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy	• Frequency of AEs

2.3. Study Procedure

Schedule of Assessments is included in Tables 1 and 2 in the Protocol.

2.4. Randomization Methodology

Using the interactive response technology (IRT), patients will be randomized 1:1 to the vutrisiran or placebo arm. Randomization will be stratified by:

- Baseline tafamidis use (yes vs. no)
- ATTR disease type (hATTR vs. wtATTR amyloidosis with cardiomyopathy)
- NYHA Class I/II **and** age < 75 years at baseline vs. all other

2.5. Blinding

Randomization schedule is maintained by the IRT vendor which has controlled access. During the DB Period, investigators, study personnel, and the Sponsor will remain blinded to treatment assignment and any clinical laboratory results that could potentially unblind them, including TTR levels, vitamin A levels, PK data, and ADA, until after the database lock for the primary analysis.

An independent external data monitoring committee (DMC) and an independent external biostatistics group supporting the DMC, and Sponsor and contract research organization personnel responsible for unblinded Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to regulatory agencies will have access to patient-level treatment assignment on a need-to-know basis.

Any unplanned unblinding occurring during the DB Period will be documented and reported in the CSR. During the OLE period, vutrisiran will be administered in an open-label fashion. Details about the specifics of the blinding aspects throughout the entire study are available in the Randomization and Blinding Plan.

2.6. Determination of Sample Size

Enrollment (randomization) of 600 patients was planned [redacted]

3. ANALYSIS POPULATIONS

The populations (analysis sets) are defined as follows:

- Full Analysis Set (FAS): All randomized patients who received any amount of study drug. Primary efficacy analyses will be based on the FAS. Patients in the FAS will be analyzed according to the treatment to which they were randomized.
- Vutrisiran Monotherapy Subgroup FAS (mono-FAS): All patients who were not on tafamidis at the study baseline in the FAS. Patients will be analyzed according to the treatment to which they were randomized.
- Safety Analysis Set (SAF): All patients who received any amount of study drug. Safety analyses will be based on the SAF. Patients will be analyzed according to the treatment received. Patients who were randomized to placebo group but received any amount of vutrisiran during the DB period will be grouped into the vutrisiran arm.
- Vutrisiran Monotherapy Subgroup Safety Analysis Set (mono-SAF): All patients who were not on tafamidis at the study baseline in the SAF. Patients will be analyzed according to the treatment received.
- PK Analysis Set: All patients who received at least 1 full dose of study drug and have at least 1 post dose blood sample for PK parameters and have evaluable PK data. Patients will be analyzed according to the first treatment received.

- PD Analysis Set: All patients who received at least 1 full dose of study drug and have an evaluable baseline and at least one evaluable postbaseline sample for TTR assessment. Patients will be analyzed according to the first treatment received.
- All Vutrisiran Treated Set: All patients who received any amount of vutrisiran during the study, including patients who took vutrisiran during the DB period and patients who first took placebo during the DB period and switched to vutrisiran during the OLE period.
- Vutrisiran Monotherapy Subgroup All Vutrisiran Treated Set: All patients who were not on tafamidis at the first dose of Vutrisiran in All Vutrisiran Treated Set.

4. GENERAL STATISTICAL CONSIDERATIONS

Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the following descriptive summary statistics: number of patients (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

The day of the first dose of study drug administered is defined as Day 1. The Study Day of a time point of interest is calculated as follows.

If on or after Day 1, Study Day = date of interest – date of the first dose of study drug + 1

If prior to Day 1, Study Day = date of interest – date of the first dose of study drug

There is no Day 0. For example, the day before the first study drug dosing is defined as Day -1.

For laboratory parameters, if there are multiple assessments on the same day, the average will be calculated. Assessment results reported with mathematic symbol (e.g., >, <,) will be replaced by the numeric value without mathematic symbol.

For 6-MWT, only assessments confirmed as valid by the Colorado Prevention Center (6-MWT site training and oversight vendor) will be included in analyses.

For efficacy analysis, heart transplant and LVAD placement will be treated as death, unless noted otherwise.

In general, all analyses will be presented by treatment groups in the overall population, vutrisiran monotherapy subgroup and background tafamidis subgroup. All listings will include all data collected during the entire study for all randomized patients. Due to large file size, listings will not be generated for individual KCCQ/CCI [redacted], mBMI, CCI [redacted], vital signs, and ophthalmology.

4.1. Analyses for the Entire Study

The study design includes a 33-36 months of DB period and an OLE period. The primary objective is to evaluate the efficacy and safety of vutrisiran compared with placebo during the DB period. In addition, the long-term efficacy of vutrisiran will be evaluated during the entire study period and the long-term safety of vutrisiran will be evaluated during the entire vutrisiran treatment period.

Two pivotal trials in ATTR-CM, including ATTR-ACT and ATTRibute-CM, indicated that therapeutics with upstream mechanisms of action (MoAs) take ~18 months to manifest benefit on mortality. CCI

[redacted]

The different analysis periods, analysis population, data inclusion strategies and description of treatment arms are summarized in Table 1.

Table 1: Summary of Analysis Periods

Analysis Period	Analysis Population	Data Inclusion	Treatment arm description
During the DB period	FAS, mono-FAS SAF, mono-SAF PD/PK Analysis Set	Including all data during the DB period	Placebo; vutrisiran.
During the DB + 6 months OLE period	FAS, mono-FAS (for analysis of outcome endpoints only)	Including all data during the DB period and within 6 months of the first OLE dose	Placebo; vutrisiran.
During the Study	FAS, mono-FAS	Including data during the entire study, integrating the DB and OLE periods	Placebo; vutrisiran.
During vutrisiran treatment [1]	All Vutrisiran Treated Set Mono All Vutrisiran Treated Set	Including data after the first dose of vutrisiran (taken during DB or OLE)	Placebo/vutrisiran; vutrisiran/vutrisiran; total

[1] For placebo patients crossing over to vutrisiran, baseline tafamidis subgroup will be redefined using the tafamidis use status prior to the first dose of vutrisiran.

4.2. Analysis Cutoff and Database Lock

The study has two planned analyses: the Primary Analysis and the Final Analysis.

The Primary Analysis will be performed after the last patient has completed the period of DB exposure or otherwise discontinued. As the study will be ongoing with patients in the OLE period or safety follow-up period, the study database will be locked with all data up to a prespecified cutoff date quality controlled (approximately when the last patient enrolled into OLE), i.e., data in the electronic data capture system will be cleaned and frozen and external laboratory data will be cleaned and quality controlled (and quality assured, where appropriate). Details regarding the database lock process are documented in the study Data Management Plan.

For the Primary Analysis, data on or prior to the prespecified cutoff date will be included. Survival follow-up data after the cutoff date will be kept in the dataset to determine the survival status of patients at the time of cutoff. For assessments with starting/ending dates (e.g., AEs, medications etc.), the starting date will be compared with the cutoff date.

The Final Analysis will be conducted after the study is completed, i.e., all patients have either discontinued or completed all periods of the study.

4.3. Baseline Definition

Baseline definitions will be defined separately for analyses during the DB Period, the entire study period, and the vutrisiran treatment period.

DB period analyses and entire study period analyses

For efficacy parameters, baseline will be defined as the last non-missing value available on or before the date of the first dose of study drug, unless otherwise specified. For 6-MWT, if a patient walked for ≤4 minutes at Day 1 visit, the screening visit will be used as baseline.

For PD parameters (TTR, Vitamin A), baseline will be defined as the average of all records prior to the date and time of first dose.

For laboratory parameters (including cardiac biomarkers) and vital signs, baseline will be defined as the last non-missing value prior to the date and time of the first dose of study drug. Only central laboratory (PP) results will be used, unless otherwise specified. For troponin I, the local laboratory results for site 171 patients will be used as baseline for these patients in absence of pre-dose central laboratory results.

CCI [redacted]

Vutrisiran treatment period analyses

For patients who received vutrisiran in the DB period, their baseline in the vutrisiran treatment period will be the same as that in the DB period.

For patients who received placebo in the DB period, their baseline in the vutrisiran treatment period will be defined as the last non-missing value prior to the first dose in the OLE period, unless otherwise specified.

4.4. Randomization Stratification Factors

Stratification factors are recorded in both the IRT and the clinical database. In statistical analyses which adjust randomization stratification factors in the model, the stratum assignment will reflect the values as recorded in the clinical database. In the presence of stratification errors, the stratification used in analysis may not match that in the IRT. A comparison of the number and percentage of patients in each randomization stratification factor in IRT versus the clinical database will be summarized by randomized treatment arm and overall, for all randomized patients. Data recorded in IRT and clinical database will be listed as well.

4.5. Analysis Windowing Rules

In the study, each patient has variable length of the DB periods, i.e., 33-36 months, depending on the enrollment time. For the analysis of all-cause mortality in different analysis periods, the Survival Follow-up Time is calculated as time from the first dose of study drug to the last Survival Follow-up date, following the windowing rules summarized as in Table 2. For the analysis of composite outcome all-cause mortality and CV events in different analysis periods, the Event Follow-up Time is calculated as time from the first dose of study drug to the last Event Follow-up date, following the windowing rules summarized as in Table 3.

For all longitudinal efficacy assessments, if a scheduled post-baseline assessment is not performed, another assessment performed within the Visit Window will be grouped with the scheduled assessment for analysis (Table 4 and Table 5). If there are two or more such assessments within a Visit Window, the assessment closest to the Target Visit Day will be used as the analysis value for that visit. If there are multiple visits with the same distance from the Target Visit Day, the earliest visit will be selected.

Table 2: Definition of Last Survival Follow-up Date in the Analysis of All-cause Mortality for Different Analysis Periods

Analysis Period	Patients who enter OLE	Patients who do not enter OLE
During the DB period	First dose of OLE	Earlier of last known alive/death date and first DB dose date + 1120 days
During the DB + 6 months OLE period	Earlier of last known alive/death date and the first OLE dose date + 183 days	Earlier of last known alive/death date and first DB dose date + 1303 days
During the Study	Last known alive/death date	

Note: Dates after analysis cutoff date will be replaced by the cutoff date. 1120 days are calculated as 36 months (156 weeks) plus 4 weeks. 1303 days are calculated as 1120 days plus 6 months (e.g., 183 days).

Table 3: Definition of Last Event Follow-up Date in the Analysis of Composite Outcome for Different Analysis Periods

Analysis Period	Patients who enter OLE	Patients who do not enter OLE
During the DB period	First dose of OLE	Earliest of last known alive/death date, study discontinuation date, and first DB dose date + 1120 days
During the DB + 6 months OLE period	Earliest of last known alive/death date, study discontinuation date, last dose date + 365 days and the first OLE dose date + 183 days	Earliest of last known alive/death date, study discontinuation date, and first DB dose date + 1303 days
During the Study	Earlier of last known alive/death date and study discontinuation date	

Note: For patients who died within 30 days of study discontinuation date, the study discontinuation date will be set as the death date. Dates after analysis cutoff date will be replaced by the cutoff date. 1120 days are calculated as 36 months (156 weeks) plus 4 weeks. 1303 days are calculated as 1120 days plus 6 months (e.g., 183 days).

Table 4: Analysis Visit Windows for Longitudinal Efficacy Endpoints in the DB period

Analysis Visit Label	Target Day	Visit Window (days, inclusive)				
		6-MWT, KCCQ, NYHA, CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]
Month 3 (Week 12)	85	N/A	CC [redacted]	[43, 126]	CC [redacted]	[redacted]

Analysis Visit Label	Target Day	Visit Window (days, inclusive)				
		6-MWT, KCCQ, NYHA, CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]
Month 6 (Week 24)	169	[85, 252]	N/A	[127, 210]	CCI [redacted]	CCI [redacted]
Month 9 (Week 36)	253	N/A	N/A	[211, 294]	CCI [redacted]	CCI [redacted]
Month 12 (Week 48)	337	[253, 420]			CCI [redacted]	
Month 18 (Week 72)	505	[421, 630]			CCI [redacted]	CCI [redacted]
Month 24 (Week 108)	757	[631, 840]				
Month 30 (Week 132)	925	[841, 1016]				

Table 5: Analysis Visit Windows for Longitudinal Efficacy Endpoints in the OLE period

Analysis Visit Label	Target Day	Visit Window (days, inclusive)	
		KCCQ, CCI [redacted], NYHA Class, CCI [redacted]	CCI [redacted]
OLE Day 1	1	N/A	N/A
OLE Month 6 (Week 24)	169	[85, 252]	[85, 210]
OLE Month 9 (Week 36)	253	N/A	[211, 294]
OLE Month 12 (Week 48)	337	[253, 420]	[295, 420]
OLE Month 18 (Week 72)	505	[421, 588]	
OLE Month 24 (Week 96)	673	[589, 756]	

Note: the target day and visit windows for OLE period is relative to the first dose date in OLE period.

For PD and safety parameters, the reported eCRF visits will be used for by-visit analysis. Only scheduled assessments will be included in by-visit summaries of these parameters.

4.6. Multiple Comparisons/Multiplicity Procedure

The overall Type I error rate for the two primary endpoints and secondary endpoints will be controlled at a 2-sided 0.05 significance level using a prespecified multiplicity testing procedure as described in Figure 2. Each primary and secondary endpoint defined in the vutrisiran monotherapy subgroup and overall population is considered as a family, e.g., 6-MWT in vutrisiran monotherapy subgroup and overall population. There are 5 families in total. The primary endpoint family and the first three secondary endpoint families will be tested using a truncated Hochberg test with a truncation fraction of 0.96, and the last secondary endpoint family will be tested using a regular Hochberg test. This Hochberg-based gatekeeping procedure was

based on an extension of the general mixture methodology [Dmitrienko 2011; Dmitrienko 2013]. The details of this multiple testing procedure are described below.

Step 1 (primary endpoint family)

The two primary endpoints will be tested at a 2-sided 0.05 significance level using the truncated Hochberg testing procedure with a truncation faction of 0.96.

i. If the larger of two p-values is ≤0.049, reject both null hypotheses and continue to Step 2a.

ii. If the larger p-value is >0.049 and the smaller p-value is ≤0.025, reject the null hypothesis corresponding to the smaller p-value and continue to Step 2b.

iii. If the larger p-value is >0.049 and the smaller p-value is >0.025, accept both null hypotheses and stop the testing procedure.

Step 2 (6-MWT family)

The overall significance level used in the 6-MWT family is determined by the number of significant tests in Step 1.

Step 2a: If both null hypotheses are rejected in Step 1, test following the same steps i, ii, and iii as for the primary endpoint family.

Step 2b: If only one null hypothesis is rejected in Step 1, only test the 6-MWT defined in the same population as the corresponding rejected null hypothesis in Step 1.

i. If the p-value is ≤0.001, reject the null hypothesis and continue to test the next secondary endpoint defined in the same population.

ii. If the p-value is >0.001, accept the null hypothesis and stop the testing.

For the KCCQ-OS and all-cause mortality families, the Step 3 and Step 4 are the same as that described in Step 2. For the NYHA class family, the Step 5 is described as below.

Step 5 (NYHA class family)

Step 5a: If both null hypotheses are rejected in Step 4, then the two NYHA class endpoints will be tested as follow.

i. If the larger of two p-values is ≤0.05, reject both null hypotheses.

ii. If the larger p-value is >0.05 and the smaller p-value is ≤0.025, reject the corresponding null hypothesis of the smaller p-value.

iii. If the larger p-value is >0.05 and the smaller p-value is >0.025, accept both null hypotheses.

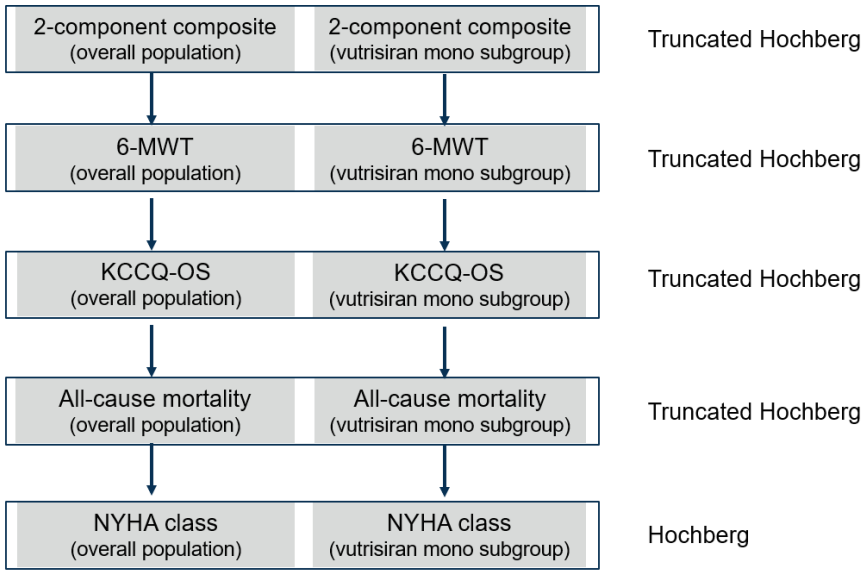
Step 5b: If only one null hypothesis is rejected in Step 4, only the NYHA class defined in the same population as the corresponding rejected null hypothesis in Step 4 will be tested.

i. If the p-value is ≤0.001, reject the null hypothesis.

ii. If the p-value is >0.001, accept the null hypothesis.

CCI [redacted]

Figure 2: Multiplicity testing procedure for testing primary and secondary endpoints



4.7. Handling of Missing Data

No imputation will be done for early dropout patients for the primary analysis of the composite outcome endpoint. For longitudinal endpoints including 6-MWT and KCCQ-OS, the primary analyses will be based on mixed effects model repeated measures (MMRM) which implicitly impute missing values assuming missing at random (MAR). The only exception is missing due to death and unable to walk due to progression of ATTR amyloidosis (for 6-MWT only). For NYHA class, the missing due to death will also be imputed as class IV, and missing due to other reasons will be imputed via multiple imputation. Data handling strategies for these aforementioned intercurrent events and other intercurrent events in the primary analysis of 6-MWT, KCCQ and NYHA class are detailed in Section 5.7.2.1 and Section 5.7.2.3, respectively. Sensitivity analysis of the composite outcome endpoint will be conducted using Multiple Imputation (MI) to handle missing data, as described in Section 5.7.1.4.4. Sensitivity analyses for 6-MWT and KCCQ-OS will be conducted based on a pattern mixture model (PMM) which assume missing not at random (MNAR), as described in Section 5.7.2.1.3.

Since baseline NT-proBNP will be used as a covariate in the statistical models, for one patient with missing baseline NT-proBNP, the baseline value will be imputed with Week 12 visit data.

4.8. Categorization of Death, Hospitalizations and Urgent HF Visits

The details about the adjudication process for hospitalizations and urgent HF visits were specified in the Clinical Events Committee (CEC) Charter. Specifically, the CEC will adjudicate all non-elective (urgent/emergency/unscheduled) cardiovascular (CV) and non-cardiovascular (non-CV) hospitalizations/emergency department visits and all urgent, unscheduled office or outpatient visits for heart failure (urgent HF visits) occurring after randomization. Elective (scheduled/non-urgent/non-emergency) CV hospitalizations and non-CV hospitalizations are not events of special interest in this trial. However, these will also be reviewed by the CEC to ensure

that potential non-elective hospitalizations have not been missed. All deaths will be adjudicated, including those that are collected after a subject permanently discontinues the study (e.g., publicly available death records).

Investigators also record their assessment of each inpatient admission or urgent/unscheduled healthcare visit on the eCRF. Hospitalizations and urgent HF visits based on the Investigator's assessment are defined as follows:

- Hospitalizations are defined as non-elective hospitalizations or visits (excluding home visits) requiring overnight stay (i.e., discharge date at least one day after admission date). The exact times of admission/discharge are not collected in the eCRF; therefore, the 24-hour stay criteria cannot be applied. For each hospitalization, the investigator provides their classification of CV versus non-CV.
- Urgent HF visits are defined as non-elective visits (including home visits) that are not classified as hospitalizations based on the above definition, but meet the following criteria:
  - Heart failure is the primary reason for the visit per the Investigator.
  - IV diuretics administered during the visit.

CCI [redacted]

CCI [redacted]

CCI [redacted]

5. PRIMARY STATISTICAL ANALYSES

The primary objective of this study is to evaluate the efficacy and safety of vutrisiran compared with placebo. Analyses described in this section focus on this objective.

5.1. Patient Disposition

The number and percentage of patients in the following categories will be summarized by randomized treatment arm and overall:

- Randomized

- Treated
- Completed Month 30 (Week 132) visit
- Completed the DB Period
- Discontinued treatment in the DB period and primary reason for treatment discontinuation
- Discontinued study in the DB period and primary reason for study discontinuation
- Entered the OLE period
- Discontinued treatment in the OLE period and primary reason for treatment discontinuation
- Discontinued study in the OLE period and primary reason for study discontinuation

The number and percentage of patients enrolled by country and site will also be summarized.

5.2. Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized using the FAS.

Age at randomization, height, weight, and body mass index (BMI) will be summarized using descriptive statistics. Age group (<65; ≥65 - <75; ≥75), sex, race, ethnicity, and region (US; Europe; rest of world) will be summarized by presenting the frequencies and percentages of patients in each category.

The following baseline disease characteristics will be summarized by presenting the numbers and percentages of patients in each category:

- ATTR disease type [hATTR; wtATTR]
- Baseline tafamidis use [Yes; No]
- NYHA Class [I; II; III]
- NYHA Class I/II and age < 75 years [Yes; No]
- ATTR amyloidosis disease stage [1; 2; 3]
- CCI [redacted]
- Previous HF hospitalization [Yes; No]
- NT-proBNP (≤3000; >3000 ng/L)

The age at symptom onset and the time in years since hATTR or wtATTR diagnosis will be summarized, overall and by ATTR disease type, using descriptive statistics. For those who previously used tetramer stabilizers, the time from discontinuation of tetramer stabilizer to the start of study drug will be summarized using descriptive statistics. For patients in the baseline tafamidis subgroup (per the clinical database), the time from the start of tafamidis therapy to the start of study drug will be summarized using descriptive statistics.

The number and percent of patients with each ATTR disease type and with each genotype (for hATTR patients) will be summarized by country and treatment arm.

5.3. Medical History

Medical history and prior procedures reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or newer. Unique patients who report medical history events will be summarized by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). Other medical history data including cardiac medical history, neuropathy history, historical surgeries/procedures in the past 12 months and historical inpatient admissions or urgent healthcare visits in the past 12 months will also be summarized. Medical history data will be summarized using the FAS and presented in data listings as well.

5.4. Protocol Deviations

Protocol deviations will be classified by medical review prior to database lock, and protocol deviations will be identified in the protocol deviation file. A major protocol deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being (ICH E3. Guideline: Structure and content of Clinical Study Reports Questions & Answers (R1). 2012).

The Sponsor or designee will be responsible for identifying and reporting the protocol deviations into the protocol deviation file. This file will include a description of each protocol deviation and whether each deviation is classified as major. The file also contains an identifier about if a protocol deviation is related to COVID-19 pandemic. The file will be reviewed and finalized prior to database lock.

Major protocol deviations will be summarized for all randomized patients. All protocol deviations, major protocol deviations, and those related to COVID-19 will be listed.

5.5. Study Drug Exposure and Compliance

Exposure to study drug in months and the number of doses of study drug received will be summarized using the Safety Analysis Set for the DB period. Summaries of the numbers and percentages of patients with no missing doses, and the number of missing doses per patient will also be provided.

The last date of exposure to study drug during the DB period is defined as the earliest of the following dates:

- Last dose date + 83 days (the dosing interval is 84 days)
- Analysis cutoff date
- End of study date
- OLE Day 1 Dose date (start of OLE period)

Duration of exposure (month) is defined as: (the last date of exposure to study drug – date of the first dose +1)/30.4375. Dose interruptions and compliance are not taken into account for duration of exposure. Study drug exposure data collected in the electronic case report form (eCRF) of study drug administration will be listed.

5.6. Prior and Concomitant Medications/Procedures

Medications will be coded using the World Health Organization Drug Dictionary (March 2019 or later); and procedures will be classified by the MedDRA coding system (version 23.0 or later).

Medications will be classified as prior and/or concomitant. Prior medications are those medications with start date prior to the first dose of study drug, regardless of medication end date. If the medication end date is before the date of first dose of study drug, the medication will be summarized as prior medication regardless of whether the start date is missing or not. Concomitant medications are medications, other than the study drug, that have a start date on or after the date of first dose of study drug, as well as medications that started before the date of first dose of study drug and are ongoing after the first dose of study drug (or have an imputed end date after the first dose of study drug) and through the first dose in the OLE period for patients who entered OLE, or the earlier of (84 days after the last dose of study drug, early study discontinuation) for patients who discontinued DB treatment for the outputs during the DB period. Unique patients who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class (or level 2 if not available) and PT. Summaries will be provided for prior and concomitant medications separately using Safety Analysis Set.

Similarly, procedures will be classified as prior and/or concomitant. Unique patients who report procedures during the DB period will be summarized by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT).

When there are partial or missing dates, imputed dates will be used to determine 1) if a medication/procedure is prior or concomitant, and 2) duration of exposure to select medications/procedures, as needed. Imputed dates will not be presented in the listings. The imputation rule is documented in Appendix 9.7.

For patients who are not on baseline tafamidis, tafamidis drop-in after the date of the first dose of study drug will be summarized, including but not limited to: number and percent of patients with drop-in as well as descriptive statistics for the time from the first dose of study drug to the tafamidis drop-in.

For patients who are taking tafamidis at baseline, tafamidis disease progression signs and symptoms prior to the baseline will be summarized.

CCI [redacted]

5.7. Efficacy Analyses

Efficacy endpoints will be analyzed using the FAS and mono-FAS. As an important subgroup, efficacy endpoints will also be analyzed in the background tafamidis subgroup. Therefore, unless otherwise specified, all efficacy analyses will be presented by treatment groups in the overall population, vutrisiran monotherapy subgroup and background tafamidis subgroup. The vutrisiran monotherapy subgroup and background tafamidis subgroup analyses are based on subgroup data only. In general, the same statistical model will be used for analyzing the efficacy endpoint for overall population, the vutrisiran monotherapy subgroup and the background tafamidis subgroup,

with the exception that in the analysis of the overall population, baseline tafamidis use will be used as an additional covariates or stratification factor.

For covariates used in the statistical models, unless noted otherwise, the categorizations will be based on ATTR disease type (hATTR vs. wtATTR), NYHA Class (I/II vs. III), age group (<75 vs. >=75) and baseline NT-proBNP group (<=3000 ng/L, >3000 ng/L). CCI [redacted]

For composite endpoints, mean cumulative function (MCF) plots by treatment groups will be generated. For longitudinal endpoints, least square mean (+/- SEM) over time by treatment groups will be plotted. For time to event endpoints, Kaplan-Meier (KM) plots by treatment groups will be generated.

5.7.1. Primary Endpoints

5.7.1.1. Definition of Estimand

For the primary objective of evaluating the efficacy of vutrisiran compared with placebo on the composite outcome of all-cause mortality and recurrent CV events, the estimand is defined as follows:

- **Target patient population:**
  - **Overall population:** Patients with hATTR or wtATTR amyloidosis with cardiomyopathy regardless of use of tafamidis.
  - **Vutrisiran monotherapy subgroup:** Patients with hATTR or wtATTR amyloidosis with cardiomyopathy who are tafamidis naïve.
- **Treatment condition:**
  - **Overall population:** Vutrisiran or placebo administered as a subcutaneous injection 25mg q3M (once every 12 weeks) with or without concomitant use of tafamidis.
  - **Vutrisiran monotherapy subgroup:** Vutrisiran or placebo administered as a subcutaneous injection 25mg q3M (once every 12 weeks) without concomitant use of tafamidis.
- **Endpoint**: Composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent HF visits).
- **Population-level summary:** Hazard ratio (HR) for the composite outcome between the vutrisiran and placebo arms.
- **Intercurrent events (ICE) strategies:** Intercurrent events include treatment and study discontinuation, tafamidis drop-in (applicable to vutrisiran monotherapy subgroup only), selected prohibited medications, CCI [redacted], heart transplantation and LVAD placement, and events due to COVID-19, etc. They require different handling strategies, which are described in Table 6 below.

Table 6: Intercurrent Event Strategies for the Primary Analysis of Primary Endpoints

Intercurrent Event	Primary analysis of composite endpoint Strategy with Rationale
Treatment and study discontinuation	Following treatment discontinuation, patients may opt to remain on the study for CV events data collection. Patients who discontinue study will no longer report CV events but will be followed up for vital status. In the CCI, the follow-up duration needs to be the same for CV events and deaths, therefore deaths collected after study discontinuation will be excluded from the CCI but will be included in the component analysis of all-cause mortality. Treatment policy strategy in the component analysis of all-cause mortality: all deaths collected will be included in the analysis, including deaths after treatment and study discontinuation. Treatment policy strategy for treatment discontinuation in the analysis using CCI: CV events and deaths after the treatment discontinuation and prior to study discontinuation will be included in the analysis. Hypothetical strategy for study discontinuation in the analysis using CCI: Deaths after study discontinuation will not be included in the model.
Initiation of alternative therapies: • Tafamidis drop-in in the vutrisiran monotherapy subgroup • CCI • Prohibited medications including inotersen, commercial patisiran and vutrisiran	Treatment policy strategy: CV events and deaths after the initiation of these alternative therapies will be included in the analysis. Initiation of tafamidis after randomization is permitted per protocol. However, a high rate of tafamidis drop-in and differential drop-in rates between two treatment arms will confound the estimate of treatment effect, which (if occurring) will be assessed by additional analyses (see Section 5.7.5).
Deaths and CV events related to COVID-19	Treatment policy strategy: CV events and deaths related to COVID-19 will be included in analysis.
Heart transplantation and LVAD placement	Composite variable strategy: Heart transplantation and LVAD placement will be treated as CV-related death.

5.7.1.2. Primary Analysis

The primary endpoint of all-cause mortality and recurrent CV events CCI

CCI [redacted]

The primary analysis will include events occurring during the DB period. For each patient, the Event Follow-up time will be calculated as the time from the first dose of study drug to the last Event Follow-up date (Table 3). Deaths collected after study discontinuation are not included in the analysis.

5.7.1.3. Component Analysis

The primary endpoint includes 2 components: all-cause mortality and recurrent CV events. The following will be summarized: the number of all-cause mortality (including death, heart transplant, and LVAD), the number of CV events (including CV hospitalization, indeterminate hospitalization, and urgent HF visit), the number and percentage of patients with at least one event. Vital status data after study discontinuation is not included in the above mortality component descriptive summary.

Inferential analyses for the component of all-cause mortality will include the vital status data collected after study discontinuation. The same statistical methods as that for the secondary endpoint of all-cause mortality (Section 5.7.2.2) will be used.

Inferential analyses for the component of recurrent CV events will be based on Poisson regression model with covariates including treatment, ATTR disease type, NYHA Class, age group, and baseline NT-proBNP as covariates, adjusting for the event follow-up time (i.e., including this duration as an offset). The overall population analysis will also include baseline tafamidis use and treatment-by-baseline tafamidis use interaction as covariates.

Recurrent CV events will be also analyzed using a joint frailty model (JFM) [Rondeau 2007] as a sensitivity analysis. For the JFM, the same covariates will be included for both the sub-model for recurrent CV events and the sub-model for all-cause mortality: treatment, ATTR disease type, NYHA Class, age group and baseline NT-proBNP group. The overall population analysis will also include baseline tafamidis use as a covariate. The baseline hazard functions for both recurrent CV events and all-cause mortality are approximated by piecewise constant functions. Details of the JFM methodology and implementation are provided in Appendix 9.6 .

5.7.1.4. Sensitivity Analyses and Additional Analyses

Several sensitivity analyses will be conducted to evaluate the robustness of the primary analysis method and the impact of missing CV event data due to early study discontinuation. An additional analysis for the primary endpoint using CV events per investigator assessment instead of CEC will also be conducted using the primary analysis approach (Section 5.7.1.4.2).

5.7.1.4.1. Win Ratio Analysis

The composite outcome endpoint of all-cause mortality and recurrent CV events will be analyzed using a win ratio method [Dong 2018], stratified by baseline NT-proBNP group. The overall population analysis will also be stratified by baseline tafamidis use. The win ratio statistic is

calculated from the ranking of each possible vutrisiran-placebo pair based on survival time and the frequency (count) of CV events in a hierarchical order. In this analysis, all-cause mortality is given higher importance than the frequency of CV events. Vital status collected after study discontinuation will be used in the ranking procedure. The point estimate of the win ratio as well as 95% CI and p-value will be generated. Details of this method are provided in Appendix 9.2.

5.7.1.4.2. Analyses Based on Alternative Definitions of the Composite Outcome

Three separate analyses of the composite outcome of all-cause mortality and recurrent CV events will be performed based on alternative definitions of all-cause mortality or CV events as outlined in Table 7 below. The same model from the primary analysis will be applied.

Table 7: Alternative Definitions of one Component of the Composite Outcome for Three Separate Analyses

Component to be redefined	Alternative Definition of Component
All-cause mortality	Heart transplant and left-ventricular assist device (LVAD) placement are not included in all-cause mortality. Patients will be censored at the date of such procedure or at the censoring date described in Section 4.5, whichever is earlier.
CV events	In addition to the CV events defined in the primary analysis, CCI [redacted] CCI [redacted]
CV events	Using CV events per investigator assessment instead of CEC

CCI [redacted]

5.7.1.4.4. Analysis Based on Imputing CV Events after Study Discontinuation

A two-stage multiple imputation (MI) process that follows the procedure for monotone missing data [Rubin 1987] will be used to assess the sensitivity of the primary analysis for any missing CV events due to early study discontinuation. Missing CV events will not be imputed after death. The imputation will be done for up to the last survival follow-up date in the DB period as defined in Table 2 for patients who discontinued the study. For each imputed dataset, the same LWYY model as the primary analysis will be applied. The results will be combined using Rubin's rule [Rubin 1987]. Details of the two-stage MI approach are provided in Appendix 9.3.

CCI [redacted]

5.7.1.4.6. Summary of Sensitivity analyses

The rationale and difference in handling ICEs comparing with the primary analysis approach are summarized for each sensitivity analysis in the following table.

Sensitivity analysis	**Differences from the primary analysis in assumptions or handling approach for ICEs and Rationales**
Win ratio analysis (Section 5.7.1.4.1)	CCI [redacted]
HT or LVAD placements are not treated as death (Section 5.7.1.4.2)	In the primary analysis, Composite variable strategy is used for intercurrent event of HT or LVAD placement, which treats them as death. In this sensitivity analysis, Hypothetical strategy is used to censor patients at the time of HT/LVAD placement.
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
Analysis based on imputing CV Events after study discontinuation (Section 5.7.1.4.4)	In the primary analysis, patients who discontinued study not due to death, HT or LVAD placement are censored at the last event follow up date during the DB period (defined in Table 3). In this sensitivity analysis, CV events are imputed after the study discontinuation to assess the impact of missing CV event due to early study discontinuation.
CCI [redacted]	CCI [redacted]

5.7.2. Secondary Endpoints

This section defines the estimands and analysis methods for the secondary endpoints. In the estimands, the first two elements "Target Patient Population" and "Treatment Condition" are the same as the primary endpoints and will not be repeated in the descriptions.

5.7.2.1. 6-MWT and KCCQ-OS

The scoring algorithm for the KCCQ-OS is included in Appendix 9.8 .

5.7.2.1.1. Definition of Estimand

For the objective of evaluating the efficacy of vutrisiran compared with placebo on 6-MWT and KCCQ-OS after 30 months of treatment, the estimands are defined as follows:

- **Endpoint**: Change from baseline in 6-MWT/KCCQ-OS at Month 30 (Week 132)
- **Population-level summary:** The Least Square (LS) mean difference in the change from baseline in 6-MWT/KCCQ-OS at Month 30 between the vutrisiran and placebo arms.
- **Intercurrent events (ICE) strategies:** Intercurrent events include treatment discontinuation, death, progression of ATTR amyloidosis, initiation of alternative therapies, and COVID-19 infection. They require different handling strategies, described in Table 8 below.

Table 8: Intercurrent Event Strategies for the Primary Analysis of 6-MWT and KCCQ-OS

Intercurrent Event	Strategy with Rationale
Treatment discontinuation	Treatment policy strategy: Intercurrent event is ignored; 6-MWT/KCCQ-OS assessments obtained after treatment discontinuation will be included in analysis.
Death (including heart transplant and LVAD placement)	CCI [redacted]

Intercurrent Event	Strategy with Rationale
Unable to walk due to progression of ATTR amyloidosis (applicable to 6-MWT only)	Composite variable strategy: The missing 6-MWT change will be imputed using the same approach as death.
Initiation of alternative therapies: • Tafamidis drop-in in the vutrisiran monotherapy subgroup • CCI [redacted] • Prohibited medications including inotersen, commercial patisiran and vutrisiran	Treatment policy strategy: Intercurrent event is ignored; 6-MWT/KCCQ-OS assessments obtained after the initiation of alternative therapies will be included in analysis.
COVID-19 infection	Treatment policy strategy: Intercurrent event is ignored; 6-MWT/KCCQ-OS assessments after COVID-19 infections will be included in analysis.

5.7.2.1.2. Primary Analysis

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

5.7.2.1.3. Sensitivity Analysis

An alternative estimand is to estimate the changes from baseline and treatment effects at scheduled visits for patients who were alive at the visits. The analysis will be based on the same MMRM model as the primary analysis with different ICE handling strategy for death. Missing data due to death will not be imputed with worst outcome and will be assumed as MAR. For 6-MWT, missing due to unable to walk due to progression of ATTR amyloidosis will still be imputed with worst outcome, the same as in the primary analysis.

A sensitivity analysis using PMM will also be performed to assess the robustness of the primary MMRM results to the possible violation of the MAR missingness assumption. The PMM accommodates situations where the missingness mechanism may be MNAR. Unlike the primary analysis, this sensitivity analysis imputes the missing data based on different missing patterns. More details on the PMM are provided in Appendix 9.4.

5.7.2.2. All-Cause Mortality

5.7.2.2.1. Definition of Estimand

For the objective of evaluating the efficacy of vutrisiran compared with placebo on all-cause mortality, the estimand is defined as follows:

- **Endpoint**: time from the first dose to death from any cause (including heart transplantation and LVAD placement)
- CCI [redacted]
- **Intercurrent events (ICE) strategies:** The ICE handling strategies are described in Table 9 below.

Table 9: Intercurrent Event Strategies for All-cause Mortality in Different Analyses

Intercurrent Event	Secondary endpoint all-cause mortality: primary analysis (over 42 months)	Secondary endpoint all-cause mortality: additional analysis including data during the study	Component analysis of all-cause mortality for the primary endpoint (over 36 months)
Study discontinuation	Treatment policy strategy		
Cross-over to vutrisiran in the OLE period (placebo patients)	Hypothetical strategy: for both vutrisiran and placebo arms, all vital status data during the DB period and within	Treatment policy strategy: ICE ignored; all data included in analysis	Hypothetical strategy: data censored at the first OLE dose date

Intercurrent Event	**Secondary endpoint all-cause mortality: primary analysis (over 42 months)**	**Secondary endpoint all-cause mortality: additional analysis including data during the study**	**Component analysis of all-cause mortality for the primary endpoint (over 36 months)**
	the first 6 months of OLE period will be included in the analysis. Data after 6 months of the first dose in OLE will be censored.		
Initiation of alternative therapies (other than cross-over)	Treatment policy strategy		
Deaths related to COVID-19	Treatment policy strategy		
Heart transplantation and LVAD placement	Composite variable strategy: treated as CV-related death.		

5.7.2.2.2. Primary Analysis

CCI [redacted]

5.7.2.2.3. Additional Analysis

CCI [redacted]

CCI

Month 30 and Month 33 survival rates will be analyzed using the Cochran-Mantel-Haenszel (CMH) method, stratified by baseline NT-proBNP group and baseline tafamidis use (for the overall population only). Common risk difference with corresponding CIs and p-values will be reported. Since not all patients will have 36 months of survival follow-up by the time of primary analysis data cut, Month 36 survival rate will not be analyzed.

Time to CV-related death (including deaths with CV and indeterminate causes, heart transplants, and LVAD placement) will be analyzed.

The analysis of all-cause mortality will also be conducted including data collected during the study (including data after 6 months of the first dose in OLE). The overall HR and p value will be estimated using similar methods as for the primary analysis.

5.7.2.3. NYHA Class

5.7.2.3.1. Definition of Estimand

For the objective of evaluating the efficacy of vutrisiran compared with placebo on NYHA Class change from baseline after 30 months of treatment, the estimand is defined as follows:

- **Endpoint**: Proportion of patients with stable or improved NYHA class at Month 30 (Week 132)
- **Population-level summary:** Difference in proportion of patients with stable or improved NYHA class at Month 30 comparing vutrisiran with placebo .
- **Intercurrent events (ICE) strategies:** For ICEs of treatment discontinuation, initiation of alternative therapies and COVID-19 infection, the treatment policy strategy will be used, i.e., NYHA class collected after these ICEs will be included in analysis. For ICEs of death (including heart transplant and LVAD placement), the composite variable strategy will be used, i.e., the NYHA class after death will be imputed as NYHA class IV.

5.7.2.3.2. Primary Analysis

The change from baseline in NYHA class at Month 30 will be dichotomized into two categories: stable/improved vs. worsened. Missing data not due to death will be imputed using multiple imputation assuming MAR, with details provided in Appendix 9.5. Each dataset will be analyzed using CMH method stratified by baseline NT-proBNP. The overall population analysis will also be stratified by baseline tafamidis use. The common risk difference and standard error from all datasets will be combined by Rubin's rule to get the estimates of treatment difference, 95% CI and p value for the proportion of being stable or improved.

Descriptive summary will be provided, including the number of percentage of patients with improving, stable, and worsening in NYHA class at each visit, and the shift from baseline to Month 30 in NYHA class.

5.7.2.3.3. Sensitivity Analysis

The change from baseline in NYHA class will be treated as a continuous variable and analyzed using MMRM model. The model includes treatment, baseline NYHA class, baseline NT-proBNP, visit, and treatment-by-visit interaction as fixed effect terms. The overall population analysis will also include baseline tafamidis use and treatment-by-baseline tafamidis use interaction as fixed effect terms. The ICEs handling is the same as that for the primary analysis approach.

5.7.3. Exploratory Endpoints

CCI

CCI

CCI

CCI

CCI [redacted]

5.7.4. Evaluation of Subgroups

All analysis and summary results are presented by baseline tafamidis use subgroups, with vutrisiran monotherapy subgroup defined as an analysis population and background tafamidis defined as a key subgroup. Additionally, subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by baseline characteristics as listed in the following table.

Subgroup	**Overall population**	**Vutrisiran Monotherapy subgroup**
Baseline tafamidis use (yes; no)	Yes	N/A
Age group (<75; ≥75)	Yes	Yes
ATTR disease type (hATTR; wtATTR)	Yes	Yes
NYHA class (I/II; III)	Yes	Yes
Baseline NT-proBNP (≤2000; >2000 ng/L)	Yes	Yes

Subgroup analyses will be performed for the composite endpoint of all-cause mortality and recurrent CV events, 6-MWT, KCCQ-OS, all-cause mortality, NYHA class, and recurrent CV events in both the overall population and vutrisiran monotherapy subgroup. The analyses will be conducted based on the subgroup data only.

- Composite endpoint of all-cause mortality and recurrent CV events:

Composite endpoint of all-cause mortality and recurrent CV events will be analyzed by LWYY model including treatment and baseline NT-proBNP as covariate. For subgroup analysis in the overall population, the model will also be stratified by baseline tafamidis use.

- Change from baseline in 6-MWT and KCCQ-OS:

  Change from baseline in 6-MWT and KCCQ-OS will be analyzed by MMRM model with baseline value as a covariate, and treatment, visit, treatment-by-visit interaction as fixed effects. For subgroup analyses in the overall population, the model will also include baseline tafamidis use as a fixed factor.

- CCI [redacted]

- Change from baseline in NYHA class:

  The binary outcome (stable or improved vs. worsened in NYHA Class at Month 30) will be analyzed by a CMH method stratified by baseline NT-proBNP. For subgroup analysis in the overall population, the model will also be stratified by baseline tafamidis use.

- Recurrent CV events:

  The frequency of CV events will be analyzed by Poisson regression including treatment and baseline NT-proBNP as covariates. For subgroup analysis in the overall population, the model will also include baseline tafamidis use as a covariate.

Forest plots will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

5.7.5. Additional Analyses

An alternative estimand is to assess vutrisiran compared to placebo in the vutrisiran monotherapy subgroup without concomitant use of tafamidis.

- For the composite outcome endpoint, events collected beyond 9 months of tafamidis drop-in will be censored. The same LWYY model as for the primary analysis will be applied.
- For 6-MWT and KCCQ-OS, assessments after tafamidis drop-in will be excluded from the MMRM analysis. Missing data due to death and unable to walk due to progression of ATTR amyloidosis (for 6-MWT only) will not be imputed.

For continuous efficacy endpoints, descriptive statistics will be provided for actual value and change from baseline by visit; descriptive statistics for percentage change from baseline by visit may also be provided, as appropriate.

5.8. Pharmacodynamic Analyses

The PD parameters for this study include serum TTR and vitamin A. For all post-baseline TTR data, only post-baseline TTR assessments collected within 84 days (inclusive) after last dose of

study drug will be summarized. Assessments more than 84 days after last dose of vutrisiran will be presented in listings and individual patients plots only. If a patient who received placebo for the first dose but received any amount of vutrisiran due to dispense errors, the patient will still be grouped as placebo but the data after receiving vutrisiran will be censored.

Summary tables will be provided for observed values, changes, and percentage changes from baseline for each scheduled time point by treatment arm for TTR and vitamin A.

The following parameters, derived using all available serum samples for measurement of TTR and vitamin A levels within the specified windows (including unscheduled), will be summarized using descriptive statistics:

- Maximum percentage reduction in serum TTR and vitamin A over the DB period
- Mean percentage reduction in serum TTR and vitamin A over the DB period
- Mean percentage reduction in serum TTR (trough) during steady state from Month 6 to 30

Subgroup analysis for maximum, mean percentage reduction in serum TTR and mean percentage reduction in serum TTR (trough) during steady state described above will be provided for:

- Age (<75; ≥75)
- Sex (male; female)
- Race (white; black; all other)
- ATTR disease type (hATTR; wtATTR)
- baseline tafamidis use (yes; no)
- NYHA Class (I/II; III)
- Body weight (<65 kg; ≥ 65 kg)
- ADA status (positive; negative)

All PD data will be displayed in data listings.

5.9. Pharmacokinetic Analyses

5.9.1. Study Variables

For vutrisiran, plasma concentrations of vutrisiran will be summarized. Concentration values that are below the lower limit of quantification will be set to zero for analysis.

- Day 1, Week 36, Week 72 (Month 18), Week 132 (Month 30): Predose levels and observed concentration 4-hour postdose (Cp [4 hr]) for vutrisiran

5.9.2. Statistical Methods

Descriptive statistics for plasma concentration will include the number of patients, mean, SD, coefficient of variation, geometric mean, geometric mean coefficient of variation, median, minimum, and maximum. Descriptive statistics and graphical displays of the plasma concentrations of vutrisiran will be presented by nominal sampling day (or week).

Population PK and exposure-response modeling may be performed and will be reported separately, as applicable.

5.10. Anti-Drug Antibody Analyses

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at any time during the DB Period, as well as treatment-emergent ADA during the DB Period will be summarized. Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, as defined below:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer >4x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

The ADA titer results for patients with confirmed positive ADA and treatment-emergent ADA results will also be summarized using descriptive statistics.

For patients with confirmed positive ADA results, spaghetti plots for the serum TTR (ELISA) over time and the plasma concentration of vutrisiran over time will be presented and compared with those with negative ADA results. Effect of positive ADA on efficacy and safety may also be explored.

ADA data and patients with confirmed positive ADA results will be presented in data listings.

5.11. Safety Analyses

For AEs, CMs, procedures, laboratory parameters, vital signs and body weight, and ECG, summaries will be based on data from the date of first dose of study drug through the first dose in the OLE period for patients who entered OLE, or through 84 days after the last dose of study drug for patients who discontinued or completed DB treatment.

For by-visit summaries of safety parameters, only scheduled visits and central laboratory data will be used. For derivation of worst postbaseline values and abnormalities, all available assessments (i.e., scheduled and unscheduled) will be used. For the selected laboratory parameters (such as LFTs), two sets of deviations will be used to determine the worst postbaseline values. One set will be solely using central laboratory data and the other set will make use of both central and local laboratory data.

No inferential safety analysis is planned.

5.11.1. Adverse Events

AEs will be classified by the MedDRA coding system (version 23.0 or later) and displayed in tables and data listings using SOC and PT, unless otherwise specified.

Analyses of AEs will be performed for those events that are considered treatment-emergent, defined as any AE occurring or worsening on or after the first dose of study drug and through the first dose in the OLE period for patients who entered OLE, or the earlier of (84 days after the last dose of study drug, early study discontinuation) for patients who discontinued DB treatment, or

any study drug-related AE. Events with a fully or partially missing onset date will be imputed according to the imputation rule defined in Appendix 9.7 before determining treatment-emergent or not.

Unless otherwise specified, AEs will be summarized by the numbers and percentages of patients reporting a given AE, as well as number of AEs and event rates per 100 patient-years.

An overall table of TEAEs will include:

- any AE
- any AE related to study drug
- any serious adverse event (SAE)
- any SAE related to study drug
- any severe AE
- any severe AE related to study drug
- any AE leading to treatment discontinuation
- any drug-related AE leading to treatment discontinuation
- any AE leading to study drug interruption
- any treatment-related AE leading to study drug interruption
- any AE leading to study discontinuation
- any drug-related AE leading to study discontinuation
- any AE leading to death including those not treatment emergent but deaths occurred after the end of study visit are not included.

Tabulations by SOC and PT will be produced for the following:

- AEs
- Treatment-related AEs
- Severe AEs
- SAEs
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption
- AE leading to study discontinuation
- AEs over time

Tabulations by SOC and PT will be produced for AEs with a higher frequency (≥5% or ≥10%) in either treatment group.

Tabulations by PT will be produced for the following:

- AEs

- Treatment-related AEs
- SAEs

AEs and AEs related to treatment will also be summarized by severity. A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence or the most related occurrence, respectively. An AE with missing severity will be assumed to be severe. An AE with missing study drug relatedness will be assumed to be related. For number of AEs and event rates per 100 patient-years, multiple occurrences of the same AE in a patient will be counted multiple times for that patient.

Adverse events mapping to the Standardized MedDRA query (SMQ) Drug Related Hepatic Disorder will be summarized by SOC and PT. Other SMQs or AE groupings may be evaluated.

Injection site reaction (ISR) events will be summarized. The number and percentage of patients reporting at least one ISR, the number and percentage of patients reporting at least one severe or serious ISR, and the numbers and percentages of patients with different ISR symptoms will be summarized, together with number of events and event rates per 100 patient-years.

AE and SAE summary tables (by SOC and PT) will be separately generated for each of the subgroups below:

- Age group [<75; ≥75 at randomization]
- ATTR disease type [hATTR; wtATTR]
- NYHA Class [I/II; III]
- Sex (Male; Female)
- Race (White; Black; All other)
- Region (US; Europe; Rest of world)

All AEs will be presented in patient data listings. Listings of all deaths, SAEs, AEs leading to treatment discontinuation or study withdrawal, and AEs mapping to the SMQs as described above will be listed. A listing of ISRs will be presented.

5.11.2. Laboratory Data

Clinical laboratory values will be expressed in standard units. Missing laboratory data will not be imputed.

For each continuous clinical laboratory parameter (including hematology, serum chemistry, liver function tests (LFTs), coagulation, and urinalysis), descriptive statistics will be presented for the actual values, change from baseline, and percentage change from baseline by visit, or average of multiple records per visit will be presented. These by-visit tables for the DB period will use the central laboratory data only.

For hematology and serum chemistry, summary tables of potentially clinically significant abnormalities will be provided. The results may also be graded according to the National Cancer Institute CTCAE Version 5.0 or above. A shift summary of baseline to maximum postbaseline CTCAE grade may be presented during the DB period, as appropriate. For shift and summary of

abnormalities in worst post-baseline tables, the central laboratory data will be used. For the selected laboratory parameters (such as LFTs), the abnormalities tables and figures using both central and local laboratory data will be presented as applicable.

CCI [redacted]

All laboratory data will be provided in data listings. Laboratory results with CTCAE grade 3 or higher will be presented in a separate listing with proper flags. Local laboratory data, if available, will also be flagged.

Liver Function Tests

A frequency table and a shift table will be produced to summarize the number and percentage of patients in each of the below categories at any postbaseline time point.

- Alanine aminotransferase (ALT): >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20× upper limit of normal (ULN),
- Aspartate aminotransferase (AST): >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALT or AST: >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- Alkaline phosphatase (ALP): ≤1, >1 & ≤1.5, > 1.5×ULN,
- Total Bilirubin: ≤1, >1 & ≤1.5, >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN,
- Total Bilirubin > 2×ULN concurrent with ALT or AST > 3×ULN

In separate figures, the peak total bilirubin (as multiple of ULN) at any time postbaseline will be plotted against the peak ALT, peak AST and the peak AST or ALT (as multiple of ULN) at any time postbaseline.

A spaghetti plot for patients who had worst ALT >3×ULN or worst total bilirubin >2×ULN will be provided. A listing for all patients with abnormal liver function tests, defined as an ALT >3×ULN, AST >3×ULN, or total bilirubin >2×ULN at any time point, will also be provided.

Selected laboratory tests (e.g., ALT, AST, total bilirubin, ALP, creatinine, CCI) will be presented over time graphically (e.g., box plot).

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

5.11.4. Vital Signs and Weight

For vital signs and body weight, descriptive statistics for actual values and change from baseline by visit will be provided for each variable during the DB period. A frequency table of abnormalities in vital signs will be provided.

5.12. Interim Analysis

No interim analysis is planned.

5.13. COVID-19 Related Summaries

Additional data are collected to characterize the impact of the COVID-19 pandemic on general study conduct and disposition, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidance (FDA and EMA guidance on clinical trial during COVID-19 pandemic, 2020; FDA and EMA statistical consideration guidance during COVID-19 pandemic, 2020).

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries. Impact on study participation due to COVID-19, including missing visits, visit location changes, study drug dosing changes and missing doses, will be summarized descriptively.

Deaths, hospitalizations, urgent HF visits due to COVID-19 will be summarized and presented in data listings. Summaries of missing 6-MWT/KCCQ-OS assessments due to the COVID-19 will be presented.

An overall summary of AEs mapping to a COVID-19 custom query will be presented. AEs mapping to the COVID-19 custom query will be summarized by HLT and PT. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint. AEs mapping to the COVID-19 custom query will also be presented in a data listing.

6. OTHER STATISTICAL ANALYSES

6.1. During Vutrisiran Treatment Period

The long-term safety of vutrisiran will be characterized by the analysis of All Vutrisiran treated Set for the vutrisiran treatment period (Section 4.1). The analysis will include all data on or after the first dose of vutrisiran during either the DB or OLE period:

- For patients who receive vutrisiran in the DB period, data from the DB and OLE periods will be integrated.
- For patients who receive placebo in the DB period and receive at least one dose of vutrisiran in the OLE period, only data after the first dose of vutrisiran in the OLE will be included.

Where applicable, baseline will be defined as described in Section 4.3. Summaries will be presented by placebo/vutrisiran, vutrisiran/vutrisiran, and total for the All Vutrisiran treated Set.

Duration of drug exposure will be defined as last vutrisiran dose date – first vutrisiran dose date + 1, with last vutrisiran date defined as the earliest of the following dates:

- Last vutrisiran dose date + treatment-specific window (83 days if last vutrisiran dose received is 25 mg q3M; CCI [redacted]
- Analysis cutoff date
- End of study date

AE and ISR summaries described in Section 5.11.1 will be provided for vutrisiran-emergent adverse events, defined as treatment-emergent adverse events occurring on or after the first dose of vutrisiran treatment through a treatment-specific window following the last dose of vutrisiran (83 days if last vutrisiran dose received is 25 mg q3M; CCI [redacted] Potentially clinically significant postbaseline abnormalities and shift from baseline to the worst postbaseline status for laboratory, vital signs, and ECG parameters, ADA, concomitant medications, and overall study drug exposure, during the vutrisiran treatment period will be summarized.

6.2. During the Study Period

Clinical efficacy, cardiac biomarker, and PD parameters will be summarized descriptively by visit throughout the entire study, to characterize the long-term effect of vutrisiran. For clinical efficacy and cardiac biomarker parameters, the visits will be presented as described in Table 4 and Table 5. For PD parameters, summary tables will be provided for observed values, changes, and percentage changes from DB period baseline for each scheduled time point.

The summary and MCF plot of composite all-cause mortality and recurrent CV events during the study will be provided. The MCF plots of recurrent CV events during the study will also be provided. The summary and KM plot for all-cause mortality during the study will also be generated.

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8. AMENDMENT HISTORY

8.1. Changes in SAP Amendment 1 compared to original SAP

The original SAP was developed based on the original protocol and the SAP Amendment 1 is developed for Protocol Amendment 5. The changes to the study design and endpoints are documented in the protocol amendment history and are not repeated in this SAP.

In addition to updates that are required to address the changes in the protocol amendment, the SAP Amendment 1 also includes more details previously not discussed in the original SAP, e.g., for the primary endpoint, details for defining CV events and windowing rules are added.

Some changes to analysis methods are made following regulatory feedback or based on new learnings. A few select changes and rationales are listed in the below table.

Summary of changes	Rationales
CCI	CCI
CCI	Updates were made following FDA's feedback.
Updated the ICEs handling strategy for the primary endpoints: • For death and CV events related to COVID: changed from hypothetical strategy to treatment policy strategy. • For selected prohibited concomitant medications: changed from hypothetical strategy to treatment policy strategy; added commercial vutrisiran to the list. • For treatment discontinuation: kept treatment policy for the analysis of all-cause mortality component and changed treatment policy to hypothetical strategy for the	The global COVID-19 pandemic has ended. There was a very small number of deaths and CV events related to COVID-19. Therefore, treatment policy strategy will be used. For selected prohibited concomitant medications, vutrisiran received global approval for polyneuropathy while the study is ongoing. The commercial drug was added as a prohibited medication.

Summary of changes	Rationales
composite endpoint, i.e., CV events and deaths collected after last dose date in DB period plus 12 months will be excluded in analysis.	Treatment policy strategy will be used following FDA's feedback. It was observed that the CV events reporting becomes sparse after patients discontinue treatment for more than one year which could reflect uncertainties with the data collection. In addition, patients likely seek other rescue medication which will confound the treatment effect estimate.
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
For the primary endpoint, removed two sensitivity analyses for the primary endpoints: • Broad definition: Hospitalizations adjudicated as non-CV that had myocardial infarction or stroke as a contributing reason are included as CV events, in addition to those defined in the primary analysis. • Narrow definition: Hospitalizations adjudicated as being indeterminate are not counted as CV events. Only hospitalizations adjudicated as CV hospitalizations will be included along with urgent HF visits.	As of November 2023, only one additional event will be included based on the broad definition, and there were few indeterminate hospitalizations. Given the small number of events, such sensitivity analyses are not considered useful.
Details on win ratio analysis are added to the appendix	To address FDA's feedback on win-ratio analysis rank algorithm.
Additional details on how to impute different patterns are added to the appendix for PMM	Updates made following FDA's feedback on using retrieved dropouts for imputation

8.2. Changes in SAP Amendment 2 compared to Amendment 1

Changes in SAP amendment 2 compared to amendment 1 are summarized in the following table.

Summary of changes	**Rationales**
Updated multiplicity control method for the primary and secondary endpoints: changing Hochberg to truncated Hochberg	Truncated Hochberg testing procedure allows partial alpha to be passed down to test the secondary endpoints if only one primary endpoint hits statistical significance.
Estimand for primary endpoint: • Updated wording of target population definition • Changed the ICE handling strategy from hypothetical to treatment policy for treatment discontinuation	To clarify the target population definition and reflect FDA's feedback.
CCI	CCI
CCI	CCI

	CCI [redacted]
CCI [redacted]	CCI [redacted]
Updated the primary analysis from logistic regression (reporting odds ratio) to CMH test (reporting difference in proportion) for secondary endpoint of NYHA class; the same update applied to the subgroup analysis for NYHA class	Odds ratio is a conditional treatment effect estimation, and often inconsistent with marginal estimation. The risk difference is a commonly used population quantity for binary data analysis.
For MMRM analysis, added a GROUP=treatment option in REPEATED statement	To allow for heteroscedasticity between treatment groups
CCI [redacted]	CCI [redacted]
Updated the missing CV event imputation algorithm to sample the event rate from the Poisson regression model using PROC MCMC.	Updated the sampling method to account for variability.
Updated the upper bound for Month 30 windowing rule in Table 4 from 1015 days to 1016 days	To include additional assessments

Added a table to summarize the list of subgroups; removed subgroup analysis for all-cause mortality using CMH method	To clarify the list of pre-specified subgroup analysis.
Added a table to summarize the rationales for sensitivity analyses of the primary endpoint in Section 5.7.1.4	To clarify the rationales and ICE handling for each sensitivity analysis

9. APPENDICES

CCI [redacted]

CCI [redacted]

9.2. Stratified Win Ratio

CCI [redacted] The vutrisiran monotherapy subgroup analysis will be stratified by baseline NT-proBNP group (<=3000 ng/L, >3000 ng/L). The overall

population analysis will also be stratified by baseline tafamidis use (yes vs. no). This method makes within-stratum pairwise comparisons for all possible vutrisiran/placebo patient pairs based on the 2 components (all-cause mortality, recurrent CV events) in a hierarchical order. Within a stratum, each vutrisiran patient will be compared with each placebo patient using a two-step procedure specified below, with the "winner" assigned a score of +1 and the "loser" assigned a score of "-1" for each pair. In case of a tied pair, no winner is chosen for that pair, a score of 0 is assigned to the pair of patients.

Step 1: Compare all-cause mortality over the common survival follow-up times for two patients

- During the common survival follow-up times for two patients, if one patient is alive and the other is deceased, the alive patient is assigned a score of +1 and the deceased patient is assigned a score of -1.
- If both patients are alive or deceased exactly on the same day, proceed to Step 2.

Step 2: Compare frequency of CV events over the common event follow-up times for two patients

- During the common event follow-up times for two patients, the patient with fewer CV events is assigned a +1 score and the other patient with more CV events is assigned a score of -1.
- If the numbers of CV events are the same, the two patients are tied and assigned a score of 0.

The survival data (including death, heart transplantation and LVAD placement) collected after study discontinuation will be used for calculating the survival duration and for the first step of pairwise comparison described above.

The point estimate of the stratified win ratio (WR) is defined as

$$\boldsymbol{WR} = \frac{\sum_{m=1}^{M} n_t^{(m)}/N^{(m)}}{\sum_{m=1}^{M} n_c^{(m)}/N^{(m)}}$$

Where M is the number of strata, $n_t^{(m)}$ and $n_c^{(m)}$ are the number of vutrisiran/placebo pairs in stratum m in which the vutrisiran patient is the winner and in which the placebo patient is the winner, respectively, and $N^{(m)}$ is the total number of patients in stratum m.

[Dong 2018] note that the logarithm of the stratified win ratio is asymptotically normally distributed with mean $\upsilon_{\log(WR)}$ and variance $\sigma^2_{\log(WR)}$. The point estimate of the logarithm of the stratified win ratio, $\hat{\upsilon}_{\log(WR)}$, is the logarithm of the stratified win ratio statistic defined above. The variance estimate, $\hat{\sigma}^2_{\log(WR)}$, is calculated from equation (8) of their paper under the null hypothesis of the same treatment effect in the vutrisiran and placebo groups.

Then $\hat{z} = \frac{\hat{\upsilon}_{\log(WR)}}{\sqrt{\hat{\sigma}^2_{\log(WR)}}}$ follows a standard normal distribution, from which the p-value is readily obtained.

The 95% confidence interval for the logarithm of the stratified win ratio is constructed as

$$\hat{\upsilon}_{\log(WR)} \pm 1.96 * \sqrt{\hat{\sigma}^2_{\log(WR)}}$$

The limits of this confidence interval for the logarithm of the stratified win ratio will then be exponentiated to construct the 95% confidence interval for the stratified win ratio.

SAS Sample Code to Determine Winner/Loser for Stratified Win Ratio Method

Generate 'WR' dataset containing winner/loser indicator from 'pairs3' dataset for each pair by stratum. 'DTH(V|P)=1' means (Vutrisiran|Placebo) patient died for the common survival follow-up time. 'NHOSP(V|P)' stands for the number of cv events for (Vutrisiran|Placebo) patient during the common event follow-up time.

```
*Calculate win and lose categories;
data WR;
set pairs3;
      length WINCAT $100;
      if DTHV = 1 and DTHP = 0 then WINCAT = "A. Placebo patient won at Step
      1";
      if DTHV = 0 and DTHP = 1 then WINCAT = "B. Vutrisiran patient won at
      Step 1";
      if DTHV = DTHP and NHOSPV > NHOSPP then WINCAT = "C. Placebo patient
      won at Step 2";
      if DTHV = DTHP and NHOSPV < NHOSPP then WINCAT = "D. Vutrisiran patient
      won at Step 2";
      if DTHV = DTHP and NHOSPV = NHOSPP then WINCAT = "T. Patient pair
      tied";
      if SUBSTR(WINCAT, 1, 1) in ("A", "C") then WINSCORE = -1;
      if SUBSTR(WINCAT, 1, 1) in ("B", "D") then WINSCORE = 1;
      if SUBSTR(WINCAT, 1, 1) = "T" then WINSCORE = 0;
run;
```

SAS Sample Code to derive estimates and confidence interval for Stratified Win Ratio Method

See lbps_a_1397007_sm1516.sas in the supplemental of [Dong 2018] for the derivation of stratified win ratio estimates and confidence interval.

The following is a sample code to derive the win ratio estimate for each stratum:

```
data wr_stra;      set wr_stra;
       stratum = 1;
        win_trt = &nt_s1.; win_con = &nc_s1.; total = &n_s1.;
        theta_KL0 = (win_trt + win_con)/(2*total);
        winratio = win_trt/win_con;
        output;
        stratum = 2;
        win_trt = &nt_s2.; win_con = &nc_s2.; total = &n_s2.;
        theta_KL0 = (win_trt + win_con)/(2*total);
        winratio = win_trt/win_con;
        output;
        stratum = 3;
        win_trt = &nt_s3.; win_con = &nc_s3.; total = &n_s3.;
        theta_KL0 = (win_trt + win_con)/(2*total);
        winratio = win_trt/win_con;
        output;
```

```
        stratum = 4;
        win_trt = &nt_s4.; win_con = &nc_s4.; total = &n_s4.;
        theta_KL0 = (win_trt + win_con)/(2*total);
        winratio = win_trt/win_con;
        output;
  label win_trt = 'Number of winners for Treatment group'
        win_con = 'Number of winners for Control group'
        theta_KL0 = 'Theta K0/L0'
        winratio = 'Win ratio';
  keep stratum win_trt win_con theta_KL0 winratio total;
run;
```

9.3. Multiple imputation for CV events

A two-stage multiple imputation (MI) process, following the procedure for monotone missing data [Rubin 1987], will be used to assess the sensitivity of primary analysis for any missing CV events due to early study discontinuation. Missing CV events will not be imputed after all-cause mortality events (death, heart transplant or LVAD placement). The imputation will be up to the last survival follow-up date in DB period for patients who discontinued study earlier but are still alive at the last survival follow-up date in DB period. For patients who discontinued study early but subsequently died during the DB period, the missing CV events between the study discontinuation date and death date will be imputed. There are four types of patients summarized in below table:

Type	Status during the DB period	Imputation for CV events
1	Patients who complete the DB period	No imputation
2	Patients who discontinued study due to death (including heart transplant and LVAD placement)	No imputation
3	Patients who discontinued study (not due to death) and died after study discontinuation	Imputing CV events from study discontinuation to death
4	Patients who discontinued study (not due to death) and were alive at the end of DB period	Imputing CV events from study discontinuation to the last survival follow-up date in DB period

The follow-up duration of 33 to 36 months will be divided into two intervals: 0 to 18 months and beyond 18 months. The imputation will be done by treatment arm and baseline tafamidis status group, sequentially for two intervals and separately for patients who died versus alive within the same interval. The two stage MI process are described as following:

Interval 1 (0-18 months):

- **Stage 1: Sampling for CV event rates**

  The CV event rates will be sampled separately from the Poisson regression model for patients who were alive or died in the interval, by treatment arm and baseline tafamidis status group. The model for sampling will include frequency of CV events during interval 1 (through study discontinuation date) as response variable, and baseline NT-proBNP as a covariate while adjusting for the event follow-up time

during interval 1. The SAS PROC MCMC procedure will be used for the sampling. With the simulated samples of parameters of intercept and coefficient of covariate from the PROC MCMC Poisson regression model, the samples of CV event rates for Period 1 can be obtained for each patient with the corresponding baseline NT-proBNP within each group.

- **Stage 2: CV event time imputation for individual patients (type 3 or 4)**

  The imputation will be done separately for patients who were alive and who died during the interval.

  – **For patients who discontinued study in Interval 1 and were alive 18 months (either type 3 or 4):**

    For each patient, the event times after study discontinuation will be generated from random samples from the exponential distribution based on the sampled CV event rate in stage 1. Event times within Interval 1 will be kept and those after 18 months will be discarded.

  – **For patients who discontinued study and died in Interval 1 (type 3):**

    For each patient, the event times after study discontinuation will be generated from random samples from the exponential distribution based on the sampled CV event rate in stage 1 Event times before the patient's death will be kept and those after death will be discarded.

Interval 2: 18-33/36 months

- **Stage 1: CV event rate estimation**

  The CV event rates will be sampled separately from the Poisson regression model for patients who were alive or died in the interval, by treatment arm and baseline tafamidis status group. The model for sampling will include frequency of CV events during Interval 2 (through study discontinuation date) as response variable, and the observed number of CV events in Interval 1 and baseline NT-proBNP as covariates while adjusting for the event follow-up time during interval 2. With the simulated samples of parameters of intercept and coefficients of covariates from the sampling Poisson regression model, the samples of CV event rates for Period 2 can be obtained for each patient using the patient's baseline NT-proBNP and the total number of CV events during Interval 1 (observed and imputed).

- **Stage 2: CV event time imputation for individual patients (type 3 or 4)**

  – **For patients who discontinued study in either Interval 1 or Interval 2 and were alive during Interval 2 (type 4):**

    For patients who discontinued study in Interval 1, the entire Interval 2, i.e., from 18 months to the last survival follow-up date in the DB period, will be imputed. For patients who discontinued study in Interval 2, only the interval from the study discontinuation to the last survival follow-up date in the DB period will be imputed. The imputation steps are similar as Interval 1.

- **For patients who discontinued study in either Interval 1 or Interval 2 and died in Interval 2 (type 3):**

  For each patient, The imputation steps are similar as above.

The above 2-stage MI process will be repeated for 500 times, e.g., 500 imputed datasets. For each imputed dataset, the same LWYY model as the primary analysis will be applied. The results will finally be combined using Rubin's rule [Rubin 1987].

Sample SAS Code:

Stage 1 (CV event rate estimation model):

Poisson model will be used to fit CV event data and will then be used to impute the missing data. The "OFFSET" in the linear model implemented by PROC GENMOD is the adjustment for the event follow up time in the interval (those who entered the interval but did not complete through).

```
proc sort data=tot; by flg_dthevt_p1 trt01p tafabsl; run;

proc mcmc data=tot outpost=mcmc_p1 nmc=500 propcov=quanew nbi=2000
mintune=500 seed=7;
   ods select PostSumInt;
   array data[2] 1 logbnp;
   array beta[2] alpha beta_logbnp;
   parms alpha beta:;
   prior alpha beta: ~ normal(0, prec = 1e-6);
   call mult(data, beta, mu);
   model nevt_p1 ~ poisson(exp(mu+logdur_p1));
   by flg_dthevt_p1 trt01p tafabsl;
run;
```

where variable 'nevt_p1' is the number of cv events during Interval 1, 'logdur_p1' is the log transformation of the event follow up time in Interval 1.

For Interval 2, the model covariates will also include 'ncv1' as an additional model term for the number of the cv events occurring during the Interval 1.

Stage 2 (event time imputation model):

The macro below can be used to perform the multiple imputation to generate the predicted missing event time.

```
data aftersample;
    /* Set the seed for reproducibility */
    call streaminit(1234);
        set needimput;
 /* Generate random event times until cumulative time reaches the end of the
interval */
```

```
        time = 0;
        cumulative_time = 0;
        event_count = 0;

        /* Loop until cumulative time reaches the end of the interval */
           do while (cumulative_time < gapfu);
            /* Generate random event time from exponential distribution */
            time = rand("Exponential", 1/rate);
           /* Update cumulative time */
            cumulative_time + time;

            /* Output the result for each event */
            if cumulative_time < gapfu then do;
               event_count + 1;      output;
               end;
        else do;
               time = .;  cumulative_time = gapfu; output;
               end;
        end;
run;
```

The dataset 'needimput' will contain all the subjects that will be imputed. The variable 'rate' will be their individual sampled monthly event rate, which is exp ($intercept + \sum coefficient * covariates$) where coefficients are samples drawn from the PROC MCMC procedure for each iteration to account for variation. (Note, for interval 2, covariates will also include the imputed event count in interval 1). The variable 'gapfu' represents the relative duration in months for which the event needs to be imputed for the patient in that interval.

Once imputed event times are generated, they will be stacked with the observed data to serve as a complete data to feed into PROC PHREG for conducting the LWYY analysis. The observed data for patients without imputation will be counted through the last event follow-up date (defined in Table 3), while the observed data for patients with imputation will be counted through last survival follow-up date (defined in Table 2). The results then will be combined using Rubin's rule [Rubin 1987]:

```
proc mianalyze data=final;
      modeleffects estimate;
      stderr stderr;
      where parameter = 'trt01pn';
      ods output ParameterEstimates=mi_result;
run;
```

9.4. Pattern Mixture Model

Patients are classified into four patterns for missing 6-MWT/KCCQ-OS data during the DB period:

1. Patients who died (including HT and LVAD placement) or unable to walk due to progression of ATTR amyloidosis (including hospitalization due to ATTR amyloidosis; applicable to 6-MWT only) before Month 30 visit: the missing change from baseline values at a postbaseline visit will be imputed as sampling with replacement from the worst 10% of observed change from baseline values from all patients at the same visit

and in same treatment group and same baseline tafamidis group, capped by the worst possible change for the patient (i.e. 0 – baseline value).

2. Patients in the vutrisiran arm who are not in Pattern 1 and have missing visits within 126 days of the last dose of vutrisiran: the missing change from baseline values are considered MAR and will be imputed using multiple imputation (MI) estimated from vutrisiran patients with non-missing data collected on treatment (i.e., data on visits within 126 days from last dose) in the same baseline tafamidis group. The window of 126 days is chosen as 1.5× the dosing interval of 84 days.
3. Patients in the vutrisiran arm who are not in Pattern 1 and have missing visits that are more than 126 days after the last dose of vutrisiran:
    a. If there are sufficient (i.e., at least 10) retrieved dropouts at Month 30 in the same baseline tafamidis group, i.e., vutrisiran patients who discontinued treatment but still had assessment that are more than 126 days after the last dose, the missing data will be imputed using data from these retrieved dropouts.
    b. If there are insufficient retrieved dropouts, missing change from baseline values will be assumed to be MNAR and imputed (using data from placebo patients in the same baseline tafamidis group) using the copy reference (CR) approach.
4. Patients in the placebo arm who are not in Pattern 1 and have missing data for other reasons:
    a. If there are sufficient (i.e., at least 10) retrieved dropouts at Month 30 in the same baseline tafamidis group, i.e., placebo patients who discontinued study treatment but still had assessment that are more than 126 days from the last dose, the missing data will be imputed using data from these retrieved dropouts.
    b. If there are insufficient retrieved dropouts, missing change from baseline values will be considered as MAR and imputed using MI estimated from all placebo patients in the same baseline tafamidis group.

Imputed change from baseline from any of the above methods will be capped by the worst possible change of the patient (0 – baseline value).

Details of MI:

For patients in Pattern 1, the imputation details are described above. For patients in Pattern 2 and Pattern 4b, all missing data for the placebo arm and missing data for the vutrisiran arm during the on-treatment period (ie, assessments within 126 days of the last dose of study drug) will be imputed using MI under the MAR assumption. Since the pattern of missing data within patients may be non-monotone, multiple imputation will be conducted separately by treatment arm and baseline tafamidis use group using the Markov Chain Monte Carlo (MCMC) method. For each treatment arm/baseline tafamidis use group, the imputation model will include type of amyloidosis (hATTR vs. wtATTR), NYHA class (I/II vs. III), age at randomization (<75 vs. ≥75), NT-proBNP (≤3000 ng/L vs >3000 ng/L), baseline value, and all post baseline change from baseline values at protocol specified visits. The input dataset DATAIN will exclude data from vutrisiran patients that were collected after treatment discontinuation (ie, more than 126 days after the last dose of study drug). Below is a sample SAS code for the multiple imputation:

```
proc mi data=DATAIN out=DATA_STEP1 seed=xxx nimpute=100;
      by treatment bltaf;
      em maxiter=300 converge=1e-4 itprint outem=outem;
      var baseline_variables base chg6m chg12m chg18m chg24m chg30m;
      mcmc chain=multiple initial=em;
run;
```

The MI procedure generates imputed values for all missing values. For patients in Pattern 1, the imputed data will be discarded and replaced by the imputed values using method described in Pattern 1 above. For vutrisiran patients, the imputed data from the on-treatment period will be kept while the imputed data after treatment discontinuation will be discarded and replaced by either the observed non-missing values (if available) or the imputed values using the CR approach described below (Pattern 3b). The imputation model is the same as that for Pattern 2 and 4.

```
proc mi data=DATA_STEP1_2 out=DATA_STEP2 nimpute=1 seed=xxx;
      by _imputation_ bltaf;
      class treatment;
      fcs nbiter=30 reg (chg30m = baseline_variables base chg6m chg12m chg18m
      chg24m);
      mnar model (chg30m / modelobs=(treatment='placebo'));
      var baseline_variables base chg6m chg12m chg18m chg24m;
run;
```

For imputation using the retrieved dropouts (Pattern 3a and 4a), the multiple imputation approach described in [Wang 2022] is adopted.

Combining Results

Missing values will be imputed 100 times to generate 100 complete datasets using the procedures described above (via MI, CR or other methods described above). An analysis of covariance (ANCOVA) model will be fit to each imputed dataset for the change from baseline in 6-MWT/KCCQ-OS at Month 30. The ANCOVA model will include baseline 6-MWT/KCCQ-OS as a covariate and treatment arm, baseline tafamidis use, treatment by baseline tafamidis use interaction, ATTR disease type, and age group as factors. For the vutrisiran monotherapy subgroup analysis, baseline tafamidis use, and treatment by baseline tafamidis use interaction will be removed from the model. The LS mean and SE estimated from the ANCOVA model fit to each imputed dataset will be combined by applying Rubin's rules,[Rubin 1996; Rubin 1987] using SAS PROC MIANALYZE to produce inferential results including the treatment difference in LS means, 95% CI for the treatment difference, and the p-value.

9.5. Multiple Imputation for NYHA Class analysis

CMH method incorporating multiple imputation (MI) will be the primary analysis method for NYHA class. The change from baseline in NYHA class at Month 30 will be dichotomized into two categories: stable or improved vs. worsened. For missing due to death (including heart transplant and LVAD placement), missing NYHA class values will be imputed as Class IV. For missing not due to death, the missing NYHA class values will be assumed as MAR and multiply imputed using the MCMC procedure for each treatment and baseline tafamidis use group, with information including baseline NYHA class, type of amyloidosis (hATTR vs. wtATTR), age at randomization (<75 vs. ≥75), baseline NT-proBNP, and all postbaseline NYHA class assessments at the scheduled visits as covariates. The sample code is provided below:

```
proc mi data=DATAIN out=DATA_STEP1 seed=xxx nimpute=100 round=1;
      em maxiter=1000 converge=1e-10 itprint outem=outem;
      var baseline_variables base aval6m aval12m aval18m aval24m aval30m;
      by treatment bltaf;
      mcmc chain=multiple initial=em impute=full prior=ridge=0.75 niter=500
      nbiter=500;
run;
```

One hundred imputed datasets will be generated from the MI MCMC procedure using SAS PROC MI. Each of the imputed datasets will then be analyzed using the CMH method stratified by baseline NT-proBNP. The overall population analysis will also be stratified by baseline tafamidis use.

The resulting estimates (common risk difference and standard errors) from the 100 imputed datasets will be combined using SAS PROC MIANALYZE to produce inferential results (difference in proportion of being stable or improved, 95% CI, and the P value) [Rubin 1996]. Combined difference will be calculated as the average of the 100 complete-data estimates. A total variance estimate will be calculated as a weighted sum of within-imputation variance, which is the average of the complete-data variance estimates, and a between-imputation variance term. Complete details may be found in the SAS documentation for the MIANALYZE procedure (see Combining Inferences from Imputed Data Sets under Details: http://support.sas.com/documentation/onlinedoc/stat/131/mianalyze.pdf).

9.6. Joint Frailty Model for the Analysis of Recurrent CV Events

Joint frailty models (JFM)[Rondeau 2007] not only address the dependency among the recurrent events, but also the dependency between recurrent events and the terminal event as well as informative censoring of recurrent events due to the terminal event. They model the recurrent events with a random-effect proportional intensity model where the subject-level random-effect v_i is called the frailty parameter, which has a gamma distribution with unit mean and variance θ. The frailty parameter accounts for the heterogeneity among patients on the intensity/rate of recurrent event (and the risk of the terminal event) that cannot be explained by the covariate vector Z_i. θ=0 indicates that there is no subject-to-subject variation beyond that explained by covariate vector Z_i.

The terminal event is modeled via a random-effect proportional hazard model with the random effect being v_i^{γ} and γ indicates the strength of association between the terminal event and recurrent events. A positive value of γ indicates that risk of the terminal event is positively correlated with the intensity of recurrent events; a negative value of γ indicates that risk of the terminal event is negatively correlated with the intensity of recurrent events; and γ=0 indicates that risk of the terminal event is uncorrelated with the intensity of recurrent events. This method estimates the regression parameters α (for the terminal event) and β (for recurrent events) as well as θ and γ. $r_0(t)$ and $\lambda_0(t)$ are the baseline hazard functions for the recurrent events and the terminal event, respectively. A parametric model – piecewise constant functions – will be used to approximate the baseline hazard function for both recurrent events and the terminal event.

$$r_i(t) = v_i \exp(\beta^T Z_i)\, r_0(t)$$

$$\lambda_i(t) = v_i^{\gamma} \exp(\alpha^T Z_i)\, \lambda_0(t)$$

Simulation studies[Liu 2004; Rondeau 2007] show that when $\gamma = 0$, the JFM and reduced model (i.e., modeling recurrent events alone) give very similar regression parameter estimates and variance estimates for the recurrent events. In this case, the reduced model is acceptable. However, when $\gamma > 0$ indicating positive correlation between rate of recurrent events and death, reduced model generates biased regression parameter estimates for the recurrent events (biased towards null or underestimated effects on recurrence rate), while regression parameter estimates from JFM are practically unbiased.

Model fit criteria

Model fit for JFM will be checked via the testing of $\gamma = 0$. An insignificant result indicates little correlation between recurrent events and death which supports a reduced model.

Software implementation

The JFM model will be estimated using R package "frailtypack" version 3.5.1 ([Rondeau 2012];[Krol 2017]).

9.7. Imputation for Partial or Missing Dates

Inpatient admission or urgent/unscheduled healthcare visits:

For partial/missing dates, the imputation will be done for discharge (end) dates first, followed by admission (start) dates.

If the location of the visit is not 'inpatient admission':

End date imputation:

- If only day is missing: if the start date is complete, impute the end date as the start date, otherwise impute as the last day of the month.
- If both month and day are missing:
  - if the start date is complete, impute the end date as the start date.
  - if the start date has missing day only, impute the end date as the last day of the same month as the start date.
  - if the start date has both month and day missing, impute the end date as June 30. If this results in a date before the first dose date, set the end date to the last day of the month and year of the first dose date.
- If the date is complete missing:
  - if the start date is complete, impute the end date as start date.
  - if the start date has missing day only, impute as the last day of the same month of the start date.
  - if the start date has missing month and day, the month and day are imputed as June 30, and year is the same the start date. If this results in a date before the first dose date, set the end date to the last day of the month and year of the first dose date.

Start date imputation:

- if only day is missing and the year and month are the same as the end date, impute the missing day the same as the end date.
- if both day and month are missing, impute the missing day and month the same as the end date.
- if complete missing, impute the missing date the same as the end date.

If the location of the visit is 'inpatient admission':

End date imputation:

- If only day is missing: if the start date is complete, impute the end date as the day after the start date, otherwise, impute as the last day of the month.
- If both month and day are missing:
  - if the start date is complete, impute the end date as the day after the start date.
  - if the start date has missing day only, then impute the end date as the last day of the same month as start date.
  - if the start date has missing month and day, impute the end date as June 30, if this results in a date before the first dose date, then set to the last day of the month and year of the first dose date.
- If the date is complete missing:
  - if the start date is complete, impute the end date as the day after the start date.
  - if the start date has missing day only, impute as the last day of the same month of the start date.
  - if the start date has missing month and day, impute as the last day of the month and year as the first dose date.

Start date imputation:

- if only day is missing
  - if the start date and end date have the same month, impute the missing day as the day before the end date.
  - if the start date and end date have different months, impute as the last day of the month.
- if both day and month are missing, impute as the date before the end date.
- if complete missing, impute the missing date as the date before the end date.

Medications:

- For medications with missing month/day for start or end dates:
  - For start dates, missing month will be imputed as January and missing day will be imputed as the first day of the month.

  - For end dates, missing month will be imputed as December and missing day will be imputed as the last day of the month.

- For medications with completely missing start or end dates:
  - Missing start date will be imputed as one day prior to the first dose of study drug. If the imputed start date is after the collected end date, the end date will be used as the imputed start date.
  - Missing end date will be imputed as the earliest date of study discontinuation date, cutoff date, or death date.

Adverse events and Procedures:

Partial or missing AE or procedure end dates will not be imputed. For AE or procedure start date:

- If year is missing, set to the first dose date. If this leads to a date after the end date (when end date is available with partial or complete information), set to the end date.
- If year is not missing, but both day and month are missing:
  - If year of the start date is equal to the year of the first dose date, set to the first dose date.
  - If year of the start date is not equal to the year of the first dose date, impute the missing day and month of the start date as January 1st.
  - If the imputed date leads to a date after the end date, impute the missing day and month of the start date using the day and month of the end date.
- If only day of the start date is missing:
  - If the year of the start date is equal to the year of the first dose date, and the month of the start date is equal to the month of the first dose date, impute the missing day of start date using the day of the first dose date.
  - Otherwise, impute the missing day of the start date as 1.
  - If the above leads to a date after the end date, impute the missing day of the start date using the day of the end date.

9.8. Questionnaire Scoring

In questionnaires, if multiple responses are provided to a single-response question, the question is deemed as missing.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The Kansas City Cardiomyopathy Questionnaire is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life within a 2-week recall period.

There are 6 domain scores and 2 summary scores for the KCCQ tool, which are calculated as follows:

1. Physical Function

Code responses to each of Questions 1a-1f 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 the activity = <missing value>

If at least 3 of Questions 1a-1f are not missing, then compute

Physical function score = [(mean of the non-missing Questions 1a-1f) – 1]/4 * 100

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

The symptom stability score = [(Question 2) – 1]/4 * 100.

3. Symptom Domain

Symptom Frequency:

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

- Questions 3 and 9
  - Every morning/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
- 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

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

The symptom frequency score = (mean of S3, S5, S7, S9)*100.

Symptom Burden

Code responses to 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 = [(mean of the non-missing Questions 4, 6 and 8) – 1]/4 * 100

Total Symptom Score

Total symptom score = mean of the following available summary scores

- Symptom Frequency Score
- Symptom Burden Score

4. 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 = [(mean of the non-missing Questions 10 and 11) – 1]/4 * 100

5. 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

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

Quality of life score = [(mean of the non-missing Questions 12, 13 and 14) – 1]/4 * 100

6. Social Limitation

Code responses to each of Questions 15a-15d 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 2 of Questions 15a-15d are not missing, then compute

Social limitation score = [(mean of the non-missing Questions 15a-15d) – 1]/4 * 100

7. Overall Summary Score

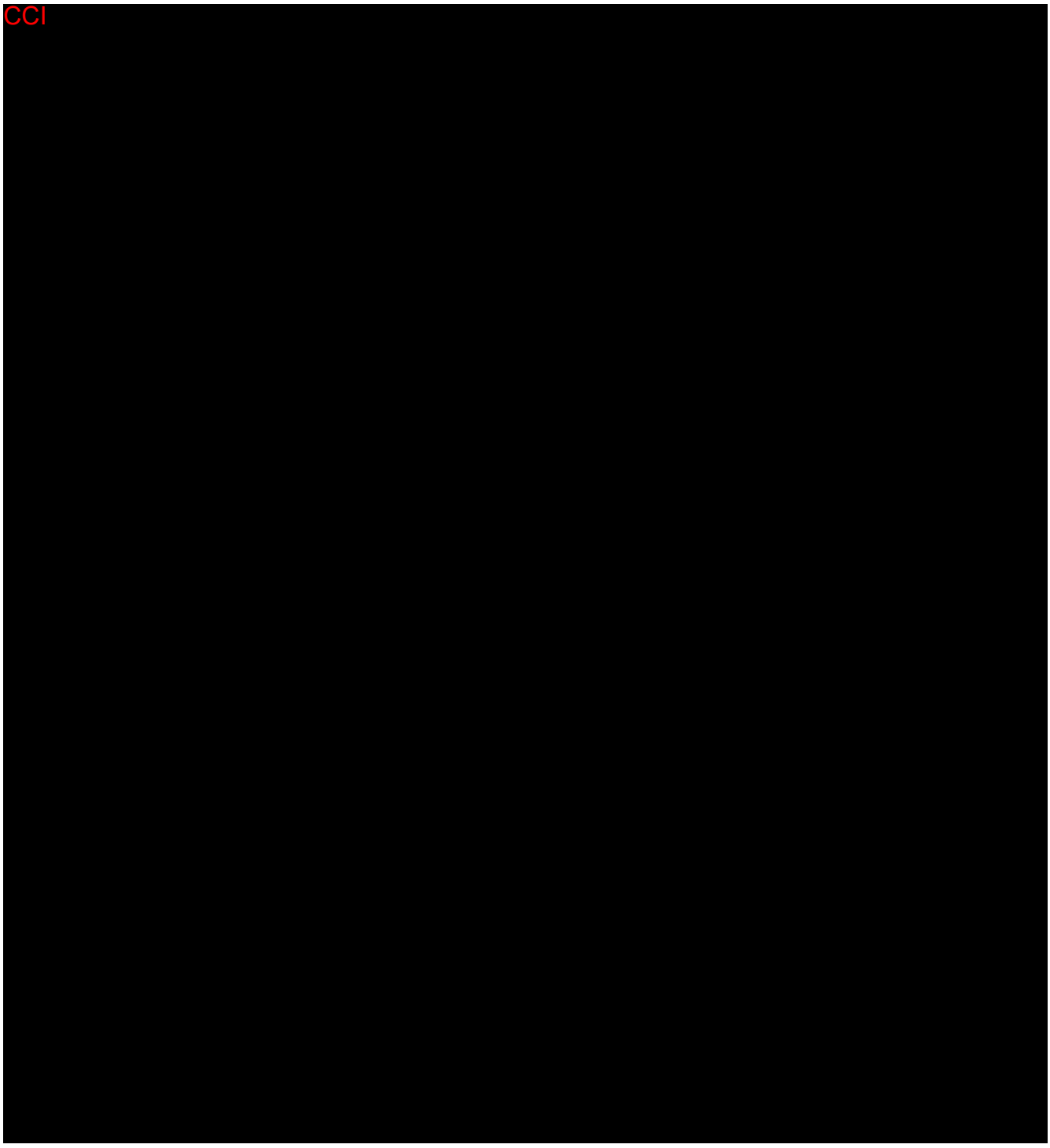
Overall summary score = mean of the following available summary scores

- Physical Function Score (Questions 1a-1f)
- Total Symptom Score (Questions 3-9)
- Quality of Life Score (Questions 12-14)
- Social Limitation Score (Questions 15a-15d)

8. Clinical Summary Score

Clinical summary score = mean of the following available summary scores

- Physical Function Score
- Total Symptom Score


CCI