GLOBAL PREVALENCE OF TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM) IN PARTICIPANTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)

Therapeutic Area:	Rare Diseases
Protocol Number:	B3461087
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NCT#	04424914

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	20 Dec 2019	Not applicable (N/A)
Amendment 1	19 May 2020	• **Coversheet:** **Revision:** Addition of EudraCT number. **Rationale:** Required for EU submissions. • **Section 1.1 Synopsis; Section 3 Objectives and Endpoints** **Current protocol** CCI [redacted] CCI [redacted]**; Appendix 2 Abbreviations** CCI [redacted] **Revision:** CCI [redacted] **Rationale:** Stress echo not being performed in study. • **Section 1.1 Synopsis; Section 3 Objectives and Endpoints** CCI [redacted] CCI [redacted] **Revision: Additional language** CCI [redacted] • **Section 1.3 Schedule of Activities** **Revision:** Editorial revisions for clarity in biospecimen collections. **Rationale:** Easier reading.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		Section 1.3 Schedule of Activities, and Section 7.1.4 Follow Up Visit 1 **Current protocol:** Visit day for Follow-Up Visit 1 is 7 Days post last study visit (± 5 days) **Revision:** Visit day for Follow-Up Visit 1 is *14* Days post last study visit (± *10* days) **Rationale:** The visit day and window for Follow-Up Visit 1 extended to permit required testing and analysis to be performed and reported. • **Section 1.3 Schedule of Activities and Section 8.1.1 Screening** **Revision:** Addition of Adverse event reporting at Screening **Rationale:** Inconsistency with Section 11.1.2 • **Section 3 Objectives and Endpoints** **Revision: Additional language** Electrocardiography - e.g.: PR, RR, QRS, QT, and corrected ECG QTc Interval using the Fridericia's correction (QTcF interval), heart rate, and overall interpretation. **Rationale:** Addition of parameters to be analyzed for electrocardiography. • **Section 4.4 End of Study Definition Section 10 Statistical Considerations** **Current protocol:** A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the schedule of activities.

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		The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the trial globally. **Revision:** **PCD has been moved to Section 10. Statistical Considerations** The primary completion date (PCD) for the global prevalence estimate will be the date when all enrolled participants have either been diagnosed with ATTR-CM or found to be negative for ATTR-CM and have completed Follow-up Visit 1. Results will be reported at PCD and end of study. **Rationale:** All diagnostic assessments are obtained at Visit 1. Analyses of data can be performed after completion of these visits. Analyses of data from follow up visits will be performed at the end of the study. • **Section 5.5 Screen Failures** Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. **Revision: Additional language** *Minimal information includes screen failure details such as demography, eligibility criteria, and any SAE. Individuals who do not meet the criteria for participation in this study (screen failure) will be recorded as a screen failure but may be rescreened at a later date. Re-screened participants will be assigned a new screening number. Pfizer approval should be provided prior to re-screening a participant.*

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Document	**Version Date**	**Summary of Changes and Rationale**
		Rationale: Rewording of language for ease of reading. Participants may not be able to complete required assessments for screening within the protocol specified timing. **Section 6.2 Study Intervention** **Current protocol:** Not applicable. **Revision:** No study treatment is administered. For the purposes of this protocol, study intervention refers to requirement for scintigraphy, possible endomyocardial biopsy and biological specimens. **Rationale:** Correct inconsistency. • **Section 7.2 Participant Discontinuation/Withdrawal from the Study and Vital Status Follow-up** **Current protocol:** A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:… AND Due to assessment of vital status at Follow-Up 2, a Release of Medical Information Form will be required of all participants …. **Revision:** A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include *but are not limited to* the following: AND Due to assessment of vital status at Follow-Up *Visit 2*, a Release of Medical Information Form

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		Rationale: Participants may discontinue for other reasons not included in the list such as Adverse Event. Vital status is obtained at Follow-up Visit 2. • **Section 8.1.3 Visit 2; Section 8.2.4 TTR Genotyping** **Current protocol:** The following procedures will be completed at Visit 2. o Collect blood sample for TTR genotyping (if not done at Visit 1). o Serum/Urine test for primary (light chain) amyloidosis (if not done at Visit 1). **Revision:** Blood sample for TTR genotyping and Serum/Urine test for primary (light chain) amyloidosis were deleted from Visit 2 to be consistent with Section 1.3 Schedule of Activities (SoA). **Rationale:** Correct inconsistency in protocol. • **Section 8.1.5 Follow Up Visit 2** **Current protocol:** Participants should be followed for 28 days after the last study visit to collect any AE/SAE information. This post-study follow-up can be conducted at the study site or by telephone. **Revision:** This visit is eliminated from the study. **Rationale:** Visit schedule streamlined to eliminate possible overlap of visits and duplicate data entry and payment.

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		• **Section 8.2.6** **Current protocol:** If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range. **Revision:** If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values *using Fridericia's formula* are in the acceptable range. **Rationale:** Clarification that Fridericia's formula should be used to evaluate QTc. • **Section 8.2.15** Physical Examination and Height and Weight Measurement **Revision: Additional language** Units of inches for height and pounds for weight added. **Rationale:** To collect the value as determined by the clinical site without the need for a calculation. • **Section 8.1.6 Follow Up Visit 3** **Current protocol:** This visit will occur 6 months after diagnosis or at time of early discontinuation. **Revision:** This visit becomes Follow-Up Visit 2 and will occur 6 months after *Follow-up Visit 1* or at time of early discontinuation. **Rationale:** Correct inconsistency in protocol and accommodate the removal of a follow

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		up visit. • **Section 8.2.6 Echocardiography** **Current protocol:** Echocardiography (2D Doppler) will be performed for all participants at Screening. The assessment of end diastolic interventricular septal thickness for study entry will be based on the echocardiogram performed at the Screening visit as interpreted by the independent central laboratory. If the Screening echocardiographic recording is not clear enough to accurately determine the end diastolic interventricular septal wall thickness it must be repeated. **Revision:** Echocardiography (2D Doppler) will be performed for all participants at Screening. The assessment of end diastolic interventricular septal thickness *and left ventricular ejection fraction* for study entry will be based on the echocardiogram performed at the Screening visit as interpreted by the independent central laboratory. If the Screening echocardiographic recording is not clear enough to accurately determine the end diastolic interventricular septal wall thickness *and left ventricular ejection fraction,* it must be repeated. **Rationale:** Both assessments are required for eligibility. • **Section 8.2.5 Testing for Light Chain Amyloid** **Current protocol:** Specifications for testing samples are provided in the study laboratory

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		manual. Elderly participants with reduced renal function may experience elevations in levels of free kappa light chains and free lambda light chains with no change in the kappa/lambda ratio. Participants with elevated serum/urine levels of free kappa light chain, free lambda light chain and a serum free kappa/lambda ratio indicative of light chain amyloidosis (monoclonal gammopathy of unknown significance [MGUS]) will require confirmatory test using mass spectrometry or immunohistochemistry with electron microscopy or scintigraphy. Samples will be collected for all participants, but only analyzed for those with scintigraphy Grades 1-3. **Revision:** Specifications for testing samples are provided in the study laboratory manual. *Blood specimen for measuring the ratio of kappa to lambda light chains with the serum free light chain assay and testing for immunofixation electrophoresis of serum and urine will be obtained from all participants, but only analyzed for those with scintigraphy Grades 1-3. Participants with serum or urine test result indicative of monoclonal gammopathy of undetermined significance (MGUS) will require a confirmatory biopsy performed locally.* **Rationale:** Exclusion criteria for ruling out Light chain amyloid in clinical practice has been updated. Definition of MGUS has been corrected and edited for easier reading.

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		CCI [redacted]

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		CCI [redacted] • **Section 8.2.17. Body Mass Index/Modified Body Mass Index** **Revision: Additional language** *Height and weight collected at Screening will be used for this calculation.* **Rationale:** Provide clarification that assessments collected for the study are to be used for calculation. • **Section 9.2. Banked Specimens for Biomarkers** **Current protocol:** Additional Banked Biospecimens collected at Visit 1 in this study are: 10 mL whole blood Prep R1 optimized for RNA; Prep B1 optimized for plasma. 10-mL urine (Prep M2). **Revision:** • *2.5mL whole blood (Prep R1 optimized for RNA);* • 10-mL whole blood (Prep B1 optimized for plasma); • 10-mL urine (Prep M*4*). **Rationale:** • Blood volumes for the Prep R1 specimen has been updated and Prep R1 and Prep B1 are separated for clarity. The total blood volume is ~104 mL as noted in Section 9.1. Sections 9.4 & 9.5

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		have been reworded for clarity. Substance of information has not changed.

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Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 2	20 Aug 2020	• **Coversheet** **Revision:** NCT number added. • **General** Editorial revisions. • **Section 1.1 Synopsis** **Objectives and Endpoints** **Secondary endpoints:** **Current protocol:** CCI **Revision:** CCI **Rationale:** Study simplified to improve feasibility. • **Tertiary endpoints:** **Current protocol:** •Electrocardiogram - e.g.: PR, RR, QRS, QT, and corrected ECG QTc Interval using the Fridericia's correction (QTcF interval), heart rate, and overall interpretation. •TTR concentration. **Revision:** 6-MWT added. ECG and TTR concentration were eliminated from protocol therefore will not be included in analysis. **Rationale:** Study simplified to improve feasibility • **Number of Participants** **Current protocol:** The empirical estimate for the prevalence of ATTR-CM in HFpEF participants is approximately 10%. The study will enroll approximately 2500 HFpEF participants within whom it is expected to detect 250 ATTR CM

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Document	**Version Date**	**Summary of Changes and Rationale**
		participants. Enrollment will be stopped if 250 ATTR CM participants are identified before 2500 HFpEF are enrolled. No formal sample size calculation was performed. A sample size of 2500 HFpEF participants would be adequately large to impact treatment guidelines and yield an estimate for the global prevalence of ATTR CM in HFpEF participants with a precision of ±2.5%. **Revision:** The empirical estimate for the prevalence of ATTR-CM in HFpEF participants is approximately 10%. The study will enroll approximately *2000* HFpEF participants within whom it is expected to detect *200* ATTR CM participants. Enrollment will be stopped if *200* ATTR CM participants are identified before *2000* HFpEF are enrolled. No formal sample size calculation was performed. A sample size of *2000* HFpEF participants would be sufficient to inform treatment guidelines and yield an estimate for the global prevalence of ATTR CM in HFpEF participants with a precision of ±2.5%. **Rationale:** Sample size was decreased to 2000 which is adequate to meet prevalence precision. • **Statistical Analysis** **Revision:** Visit 2 will be deleted from Safety Analysis. **Rationale:** Study simplified to improve feasibility.

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Document	**Version Date**	**Summary of Changes and Rationale**
		• **Section 1.4 Schedule of Activities** **Current protocol:** Echo and NT-Pro-BNP performed at Screening; Biopsy performed at Visit 2; ECG, 6-MWT; blood collection for cardiac troponin I &T, creatinine, albumin, TTR concentration, blood and urine for banked biospecimens; mBMI, eGFR obtained at visit 1. **Revision:** Visit 2 was deleted; footnote **a** revised to: *Echo performed if previous echo was > or = 6 months prior to screening visit. If echo was performed within 6 months prior to screening and results are available, the echo can be used for study and does not need to be repeated. NT-Pro-BNP will be collected at Visit 1.* **The following assessments were deleted:** *ECG, TTR concentration, banked biospecimens. Subsequent diagnosis testing was added to table.* **Rationale:** Study simplified to improve feasibility. • **Section 3 Objectives and Endpoints** **Secondary endpoints:** CCI [redacted] CCI [redacted]

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Document	**Version Date**	**Summary of Changes and Rationale**
		CCI [redacted] • **Section 4.1 Overall Design** **Current protocol:** The study will enroll approximately 2500 participants. **Revision:** The study will enroll approximately *2000* participants. **Rationale:** Sample size was decreased to 2000 which is adequate to meet prevalence precision. • **Section 5.1 Inclusion Criteria** **Current protocol:** #5. Willing and able to undergo scintigraphy and biopsy (if Grade 1 scintigraphy); #6. NT-ProBNP ≥600 pg/ml. **Revision**: #5. Willing and able to undergo scintigraphy; #6 NT-Pro-BNP criterion eliminated **Rationale:** Endomyocardial biopsy requirement eliminated from protocol. Study simplified to improve feasibility; NT-Pro-BNP criterion eliminated for enrollment.

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Document	**Version Date**	**Summary of Changes and Rationale**
		• **Section 5.2 Exclusion Criteria** **Current protocol:** **#2.** Presence or history of ischemic heart disease affecting at least 1 of the main coronary arteries. **Revision:** Prior clinical history of myocardial infarction, CABG or multi-vessel obstructive coronary disease (>50% stenosis of ⩾2 epicardial coronary arteries). **Rationale:** To focus criterion on the medical to the aged HFpEF population and their associated comorbidities. • **Section 6.2 Study Intervention** **Current protocol:** For the purposes of this protocol, study intervention refers to requirement for scintigraphy, possible endomyocardial biopsy and biological specimens. **Revision:** For the purposes of this protocol, study intervention refers to requirement for scintigraphy and biological specimens. **Rationale:** Endomyocardial biopsy requirement eliminated from protocol. Study simplified to improve feasibility. • **Section 8.1 Procedures** **Current protocol:** The total blood sampling volume for individual participants in this study is approximately 104 mL. • **Revision:** The total blood sampling volume for individual participants in this study is approximately 63 mL. **Additional language:**

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		Protocol-specified safety laboratory tests may be performed at a local laboratory if the study participant is unable to visit the study site, where allowable by law or local guidance. Local laboratory reference ranges need to be documented. • **Rationale:** Some blood tests have been eliminated. Remote visits are permitted for consistency with local COVID-19 guidance. • **Section 8.1.1 Screening Visit** **Current protocol:** Echocardiography; NT-ProBNP ≥600 pg/ml. • **Revision:** Echocardiography *(unless obtained ± 6 months prior to Screening Visit and results are available)*; NT-ProBNP inclusion eliminated and assessment moved to Visit 1. **Rationale:** Study simplified to improve feasibility. • **Section 8.1.2 Visit 1** **Current protocol:** •Single 12-lead ECG- perform ECG prior to any blood collection or blood pressure measurements. **Revision:** NT-Pro-BNP has been moved from Screening to Visit 1. ECG, TTR concentration and banked biospecimens have been deleted. **Rationale:** Study simplified to improve feasibility. • **Section 8.1.3 Visit 2** **Revision:** Section deleted.

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		Rationale: Endomyocardial biopsy is no longer required therefore visit deleted. • **Section 8.1.4 Follow-up 1 Visit** **Current protocol:** Participants will be informed of their diagnosis and collect any AE/RRI information within 14 days of their last study visit. For participants with either a scintigraphy grade 0 OR grade 2 or higher, Follow-up Visit 1 will occur 14 days after Visit 1. For participants who require a biopsy, Follow-up Visit 1 will occur 14 days after Visit 2. **Revision**: Participants will be informed of their diagnosis and collect any AE/RRI information within 14 days (+10 days) *of study visit 1*. **Rationale:** Endomyocardial Biopsy is no longer required so Visit 2 has been eliminated. • **Section 8.1.5 Follow-up 2 Visit** **Current protocol:** Participants diagnosed with ATTR-CM will be contacted to assess current medications and vital status (alive/dead). **Revision:** *Participants with scintigraphy of grade 1 or higher* will be contacted to assess current medications and vital status . *Participants with scintigraphy grade 1 will be asked if they have undergone a biopsy or other testing as follow up to their scintigraphy since their last visit. Data will be collected on method of diagnosis and whether it confirmed the presence of ATTR-CM. This post study follow up can be conducted remotely.*

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		This will occur 6 months after the Follow-up 1 Visit (+/- 30 days) or at early study discontinuation. **Rationale:** Endomyocardial biopsy is no longer required in the protocol. Collection of available diagnosis information on participants with scintigraphy grade 1. • **Section 8.2.1.1 Endomyocardial biopsy** **Revision:** Section deleted. **Rationale:** Study simplified to improve feasibility. • **Section 8.2.2 Echocardiogram** **Current protocol:** Echocardiography (2D Doppler) will be performed for all participants at Screening. Each echocardiogram will be sent to an independent central laboratory that will conduct a centralized review of the results for determination of eligibility. The central reading of the Screening echocardiogram must be completed prior to participant enrollment. The assessment of end diastolic interventricular septal thickness and left ventricular ejection fraction for study entry will be based on the echocardiogram performed at the Screening visit as interpreted by the independent central laboratory. **Revision:** Echocardiography (2D Doppler) will be performed for all participants at Screening *unless one has been obtained within 6 months prior to Screening Visit and results are available. The assessment of end diastolic*

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		interventricular septal thickness and left ventricular ejection fraction for study entry will be based on the echocardiogram performed at the Screening visit as interpreted locally by the site. Additional parameters to be measured: End diastolic interventricular septal wall thickness (mm), End-diastolic left ventricular posterior wall thickness (mm), Left ventricular ejection fraction (%), Left atrial diameter, anterior posterior (mm), Left atrial diameter, medio lateral (mm), Left atrial diameter, superior inferior (mm), Left ventricular end systolic diameter (mm), Left ventricular end systolic volume (mL), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (mL), E/A Ratio, E/E' Ratio. **Rationale:** Study simplified to improve feasibility. Central readings will no longer be performed. Collection of aortic valve parameters to monitor presence of aortic stenosis. • **Section 8.2.3 Cardiac Biomarkers: N Terminal Pro-Hormone Brain Natriuretic Peptide (NT-proBNP) and** CCI [redacted] **Curr** A 2.5 mL blood sample for NT-proBNP will be collected at Screening. CCI [redacted] **Revision:** A 2.5 mL blood sample for NT proBNP will be collected at *Visit 1 and analyzed locally by the investigator site.* CCI [redacted]

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		CCI [redacted] **Rationale:** Study simplified to improve feasibility. • **Section 8.2.5 TTR Genotyping** **Current protocol:** Samples will be collected for all participants, but only analyzed for those that are diagnosed with ATTR CM. The sample will be sent to a reference laboratory for complete genomic sequencing. **Revision:** Samples will be collected for all participants, but only analyzed for those with scintigraphy grades 1, 2, & 3. The sample will be sent to a reference laboratory for complete genomic sequencing *of TTR gene*. **Rationale:** Participants with scintigraphy grade 1 may not have biopsy confirmation of ATTR-CM therefore, clarification added to perform genotyping on participants with scintigraphy grades 1-3. Also, clarity provided for sequencing. • **Section 8.2.6 Electrocardiogram** **Revision:** Assessment eliminated from protocol. **Rationale:** Study simplified to improve feasibility. CCI [redacted]

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		CCI [redacted] • **Section 8.2.11 TTR Concentration** **Revision:** Section deleted. **Rationale:** Study simplified to improve feasibility. CCI [redacted] • **Section 8.2.16. Body Mass**

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		Index/Modified Body Mass Index **Current protocol:** A modified Body Mass Index (mBMI) will be calculated at Visit 1 as weight (kg)/[height (meters)]^2. The mBMI is calculated by multiplying BMI by serum albumin concentration (g/L). A blood sample (2.5 mL) will be collected at Visit 1 to measure serum albumin. Height and weight collected at Screening will be used for this calculation. **Revision:** Serum albumin test is not required in the protocol, however, if a serum albumin has been obtained within 6 months of Screening visit, data will be collected. **Rationale:** Study simplified to improve feasibility. • **Section 8.2.17 Vital Status** **Current protocol:** Participants, or their delegate, will be contacted at Follow-up 3 to determine vital status (alive or dead). **Revision:** Participants, or their delegate, will be contacted at Follow-up *2* to determine vital status. *For participants who had scintigraphy grade 1 at Visit 1, subsequent testing information will be collected.* **Rationale:** Diagnosis data collection. • **Section 8.3.1 Adverse Events** **Current protocol** Any AE that occurs from the time the participant signs the informed consent through and including 28 days following the participant's last visit

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		(Follow-up Visit 1) must be recorded. **Revision:** Any AE that occurs from the time the participant signs the informed consent through and including ***14*** days following the participant's last visit (Follow-up Visit 1) must be recorded. **Rationale:** Correct inconsistency with SoA. • **Section 9.1 Banked Biospecimens for Genetics** **Revision:** Section has been deleted **Rationale:** Study simplified to improve feasibility. • **Section 9.2 Banked Biospecimens for Biomarkers** **Revision:** Section has been deleted. **Rationale:** Study simplified to improve feasibility. • **Section 9.3 ATTR Biomarker Identification and Validation** **Revision:** Section moved to Section 8.2.4. **Rationale:** Improvement in protocol flow. • **Section 9 Statistical Considerations** **Current protocol:** The empirical estimate for the prevalence of ATTR-CM in HFpEF participants is approximately 10%. The study will enroll approximately 2500 HFpEF participants within whom it is expected to detect *250* ATTR CM participants. Enrollment will be stopped if 250 ATTR CM participants are identified before 2500 HFpEF are

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		enrolled. No formal sample size calculation was performed. A sample size of 2500 HFpEF participants would be adequately large to impact treatment guidelines and yield an estimate for the global prevalence of ATTR CM in HFpEF participants with a precision of ±2.5%. **Revision:** The empirical estimate for the prevalence of ATTR-CM in HFpEF participants is approximately 10%. The study will enroll approximately *2000* HFpEF participants within whom it is expected to detect *200* ATTR CM participants. Enrollment will be stopped if *200* ATTR CM participants are identified before *2000* HFpEF are enrolled. No formal sample size calculation was performed. A sample size of *2000* HFpEF participants would be sufficient to inform treatment guidelines and yield an estimate for the global prevalence of ATTR CM in HFpEF participants with a precision of ±2.5%. **Rationale:** Sample size was decreased to 2000 which is adequate to maintain the precision. • **Section 9 Statistical Analysis – Analysis by Scintigraphy, Analysis by Disease Status, Safety Analysis** **Revision:** Visit 2 will be deleted from Safety Analysis. **Rationale:** Study simplified to improve feasibility.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

TABLE OF CONTENTS

1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale

Transthyretin Amyloid Cardiomyopathy (ATTR-CM) occurs when transthyretin amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death.

The most frequent form of heart failure (HF) in patients with ATTR-CM is HF with preserved ejection fraction (HFpEF). HFpEF is also the most common form of heart failure in elderly patients and accounts for up to 50% of HF-related hospital admissions. It has recently been described that ATTR-CM is significantly underdiagnosed and may be more common than current prevalence estimates. The purpose of this study is to assess the prevalence of ATTR-CM in the HFpEF population.

Objectives and Endpoints

Primary Objective(s):	**Primary Endpoint(s):**
To assess the prevalence of ATTR-CM among patients with HFpEF within a clinically at-risk population.	Estimate of global prevalence of ATTR-CM in HFpEF patients. Diagnosis of ATTR-CM is defined by: • Cardiac Scintigraphy Grade 1, with confirmation of ATTR by cardiac biopsy, or: • Cardiac Scintigraphy Grade 2 or above.
Secondary Objective(s):	**Secondary Endpoint(s):**

To assess variations in prevalence of ATTR-CM (wild-type [WT] and hereditary) among patients with HFpEF at a country, regional, and global level.	• Estimate of prevalence of ATTR-CM in patients with HFpEF based on:
	  • Geographical or regional distribution;
	  • Age categories;
	  • Gender.
	• Proportion of patients with WT and hereditary forms among patients diagnosed with ATTR-CM.
	• Baseline characteristics of HFpEF patients

	with and without ATTR-CM: • New York Heart Association (NYHA) classification; • NT-proBNP.

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Overall Design

This study is a global, multi-center epidemiology study designed to estimate the global prevalence of ATTR-CM in participants with HFpEF within a clinically at-risk population.

Number of Participants

The empirical estimate for the prevalence of ATTR-CM in HFpEF participants is approximately 10%. The study will enroll approximately 2000 HFpEF participants within whom it is expected to detect 200 ATTR-CM participants. Enrollment will be stopped if 200 ATTR-CM participants are identified before 2000 HFpEF are enrolled. No formal sample size calculation was performed. A sample size of 2000 HFpEF participants would be sufficient to inform treatment guidelines and yield an estimate for the global prevalence of ATTR-CM in HFpEF participants with a precision of ±2.5%.

Statistical Methods

The primary endpoint is an estimate of the global prevalence of ATTR-CM in HFpEF participants. Diagnosis of ATTR-CM is defined as:

- Cardiac Scintigraphy Grade 1, with confirmation of ATTR by cardiac biopsy; or
- Cardiac Scintigraphy Grade 2 or above.

This global prevalence estimate will be obtained by dividing the number of participants who are diagnosed with ATTR-CM in the study by the total number of HFpEF participants evaluated. A 95% confidence interval on the estimate will also be calculated.

As secondary analysis, prevalence will be estimated for:

- Regions and countries;
- Age categories (60-64, 65-69, 70-74, 75-79, 80-85, >85);

- Gender (male, female).

Prevalence estimates along with 95% confidence interval (CI) will be generated for regions and countries with at least 50 participants. For regions and countries that enroll fewer than 50 participants, prevalence will not be estimated. Regions will be defined in the statistical analysis plan. The proportion of HFpEF participants who were diagnosed with wild-type and variant ATTR-CM will be descriptively summarized.

As a general rule, the secondary endpoints other than the prevalence estimates and all CCI reported as numerical values will be analyzed descriptively using mean, standard deviation, median, minimum, and maximum. Endpoints that are categorical will be summarized using frequency tables.

Analysis by Scintigraphy:

Participants who are diagnosed with ATTR-CM will be analyzed by scintigraphy grades (Grade 1, 2, or 3) using the 6-MWT, NT-proBNP, medical history, demographics (including age, TTR Genotype, gender and race), NYHA classification (Class I, II, III, or IV), and all CCI

Analysis by Disease Status:

Participants who are diagnosed with ATTR-CM will be analyzed by NYHA Classification (Class I, II, III, or IV) using the 6-MWT, NT-proBNP, medical history, demographics (including age, TTR Genotype, gender, and race) CCI CCI

Participants who are diagnosed with ATTR-CM will also be analyzed by 6-MWT quartile groups using NYHA classification (Class I, II, III, or IV), NT-proBNP, medical history, demographics (including age, TTR Genotype, gender, and race) CCI CCI

Analysis Comparing ATTR-CM participants with HFpEF patients without ATTR-CM:

HFpEF participants diagnosed with ATTR-CM will be compared with HFpEF participants not diagnosed with ATTR-CM descriptively using medical history, demographics (including age, TTR Genotype, gender, and race) CCI

Medical history data will be used to generate descriptive statistics for time from symptom onset to HFpEF diagnosis and time from symptom onset to ATTR-CM diagnosis.

Endpoints measuring proportion of participants (NYHA Classification and symptoms of interest from medical history) will be compared between HFpEF participants diagnosed with ATTR-CM and those that are not diagnosed with ATTR-CM. The Chi-square test will be used to compare the proportions between these 2 groups of HFpEF participants. Fisher's exact test will be used instead of the chi-square test if any one of the cells has ≤5 participants. Secondary CCI numerical endpoints that are normally distributed will be

compared between 2 groups of HFpEF participants using a t-test. Endpoints that are not normally distributed will be compared using the Wilcoxon rank sum test.

Safety Analysis:

Adverse events (AEs) and research related injuries (RRI) collected at Visit 1 or during follow-up, will be summarized overall and separately for HFpEF participants diagnosed with ATTR-CM and HFpEF participants not diagnosed with ATTR-CM.

1.2. Rationale

Transthyretin Amyloid Cardiomyopathy (ATTR-CM) occurs when transthyretin amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death.

The most frequent form of HF in patients with ATTR-CM is HF with preserved left ventricular ejection fraction (HFpEF).[1] HFpEF is also the most common form of HF in elderly patients and accounts for up to 50% of HF-related hospital admissions.[2,3] It has recently been described that ATTR-CM is significantly underdiagnosed and may be more common than current prevalence estimates. The purpose of this study is to assess the prevalence of ATTR-CM in the HFpEF population.

1.3. Schema

Not Applicable.

1.4. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the Section 8 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier	**Screening[b]**	**Visit 1[b]**	**Follow-up 1[bc]**	**Follow-up 2[b,f]**
Visit Day		**Day 1**	**14 Days Post Last Study Visit**	**6 Months Post Last Study Visit**
Visit Window	**Days -28 to -3**		**+10 Days**	**±30 Days**
Informed consent	X			
Review entrance criteria	X			
Echocardiography[a]	X			
Medical History	X			
Record current medications		X		X
Demography	X			
NYHA classification		X		
Physical Examination including height and body weight	X			
Vital Signs	X			
CCI				
Scintigraphy		X		
TTR genotyping[e]		X		
CCI				
Laboratory samples				
Cardiac Biomarkers (NT-proBNP)		X		
Serum/Urine tests for primary (light chain) amyloidosis[e]		X		
Blood and Urine specimens for ATTR-CM biomarkers		X		
CCI				
Inform participant of diagnosis			X	
Adverse Event reporting	X	X	X	
Vital Status				X
Subsequent diagnosis testing				X

Abbreviations: NYHA = New York Heart Association; CCI TTR – transthyretin; CCI nal

a. Echo performed if previous echo was ≥6 months prior to screening visit. If echo was performed within 6 months prior to screening and results are available, the echo can be used for study and does not need to be repeated.

b. May be performed by remote participant visit.

c. Participants should be followed for 14 days after the last study visit day to collect any AE/RRI information.

d. Or at early discontinuation.

e. Sample collected from all participants, only those samples from participants that are scintigraphy Grade 1, 2, or 3 will be analyzed.

f. For participants with scintigraphy grade 1, 2 or 3.

2. STUDY INTRODUCTION

2.1. Rationale

Transthyretin Amyloid Cardiomyopathy (ATTR-CM) occurs when transthyretin amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death.

The most frequent form of HF in patients with ATTR-CM is HF with preserved left ventricular ejection fraction (HFpEF).[4] HFpEF is also the most common form of HF in elderly patients and accounts for up to 50% of HF-related hospital admissions.[5,6] It has recently been described that ATTR-CM is significantly underdiagnosed and may be more common than current prevalence estimates. The purpose of this study is to assess the prevalence of ATTR-CM in the HFpEF population.

2.2. Background

Transthyretin (TTR) amyloidosis is a rare protein misfolding disease with a broad spectrum of manifestations. The condition is caused by the destabilization and dissociation of the native TTR tetramer which can result in misfolding and the formation of amyloid fibrils and progressive amyloid deposition in tissues.[7,8,9,10] This can occur in amounts sufficient to impair normal functioning. The 2 major phenotypes which form the spectrum of ATTR amyloidosis are transthyretin amyloid polyneuropathy (ATTR-PN), which primarily affects the peripheral and autonomic nerves, and ATTR-CM which primarily affects the myocardium. These clinical manifestations may occur in isolation or together. Both result in progressively impaired function, and ultimately in death.

ATTR-CM is a fatal disorder, characterized by the deposition of misfolded transthyretin amyloid fibrils in the ventricular walls (extra-myocardial), causing progressive disruption in the ability of the heart to effectively pump blood through the circulatory system. In ATTR-CM, the myocardium is the key site of ATTR deposition, and accumulation can lead to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure.

ATTR-CM can be inherited as an autosomal dominant trait caused by mutation in the TTR gene, or by deposition of wild-type transthyretin protein, previously called senile systemic or senile cardiac amyloidosis.[10,11] The median age of patients with wild-type ATTR-CM has been reported as 75 years of age at diagnosis.[12] In the Tafamidis for ATTR-CM Trial (ATTR-ACT) the average age of patients was 74.5 ±7.2 (standard deviation).[13] The hereditary (genetic variants) form of disease can affect multiple generations in a family and have a substantial emotional impact on patients and their families.[14] ATTR-CM is associated with genetic variants of TTR such as Val122Ile and Leu111Met (also known as familial amyloid cardiomyopathy) but may also occur in the absence of a specific mutation (i.e., wild-type TTR).[10,11] The Val122Ile mutation allele occurs in 3.3% to 4.0% of the US African-American population,[15,16] and is exceedingly rare in White patients. Median survival from diagnosis for patients with ATTR-CM has been reported as 41 months for patients with

a Val122Ile mutation and 46 months for patients with ATTR-CM due to wild-type TTR,[17] with most patients dying from cardiac causes, including sudden death, CHF, and myocardial infarction.[18,19] Untreated ATTR-CM is currently associated with mean progression to death within 24 to 36 months (median survival 25.6 months) of diagnosis for variants and up to 60 months (median survival 43.0 months) for wild type.[20]

The prevalence of ATTR-CM is defined as rare, but no prevalence estimates have been published. There are more than 120 mutations in the TTR gene which cause a variable phenotype determined by the relative extent of amyloid deposition in the myocardium and peripheral nerves.[21] Though prevalence of wild-type TTR is uncertain, studies using a non-biopsy approach to diagnosis[22,23] report a prevalence of 13% in HF patients with preserved ejection fraction,[24] 16% in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis,[25] and 5% of patients with presumed hypertrophic cardiomyopathy.[26]

ATTR-CM (due to wild-type or variant TTR) uniformly presents with the typical symptoms of HF (restrictive cardiac disease) including shortness of breath, dyspnea on exertion, orthostatic hypotension, syncope, and dysrhythmias including atrial fibrillation. Signs of ATTR-CM are evaluated via testing performed as part of routine HF assessment including electrocardiography, echocardiography, and cardiac biomarkers (e.g., N-terminal prohormone B type natriuretic peptide [NT-proBNP]). As the symptoms are very non-specific, a diagnosis of ATTR-CM may often be delayed for years.[27,28] An electrocardiogram (ECG) and echocardiogram aid in the diagnosis. Definitive confirmation of ATTR-CM has been typically achieved through a cardiac biopsy,[29] although cardiac magnetic resonance imaging (MRI) and scintigraphy are increasingly used to confirm evidence of disease. A non-biopsy approach using technetium-labeled bone scintigraphy tracers has been validated as a method for identification of patients with ATTR-CM. This approach is highly sensitive and specific for diagnosing ATTR-CM due to both hereditary and wild-type disease,[18,19,28] and can detect ATTR prior to an increase in left ventricular wall thickness or the development of the clinical syndrome of heart failure and a rise in cardiac biomarkers[30,31] and even predict prognosis.[21,30] Early identification and treatment is now more likely with the availability of effective diagnostic tools and therapy.

The most frequent form of HF in patients with ATTR-CM is HF with preserved left ventricular ejection fraction (HFpEF). HFpEF is also the most common form of HF in elderly patients and accounts for 50% of HF-related hospital admissions. It has recently been described that ATTR amyloidosis is significantly underdiagnosed, taking into consideration that both the clinical presentation and the symptoms are non-specific. The aim of this epidemiology study is to assess the prevalence of ATTR-CM in a clinically at risk HFpEF population.

2.3. Benefit/Risk Assessment

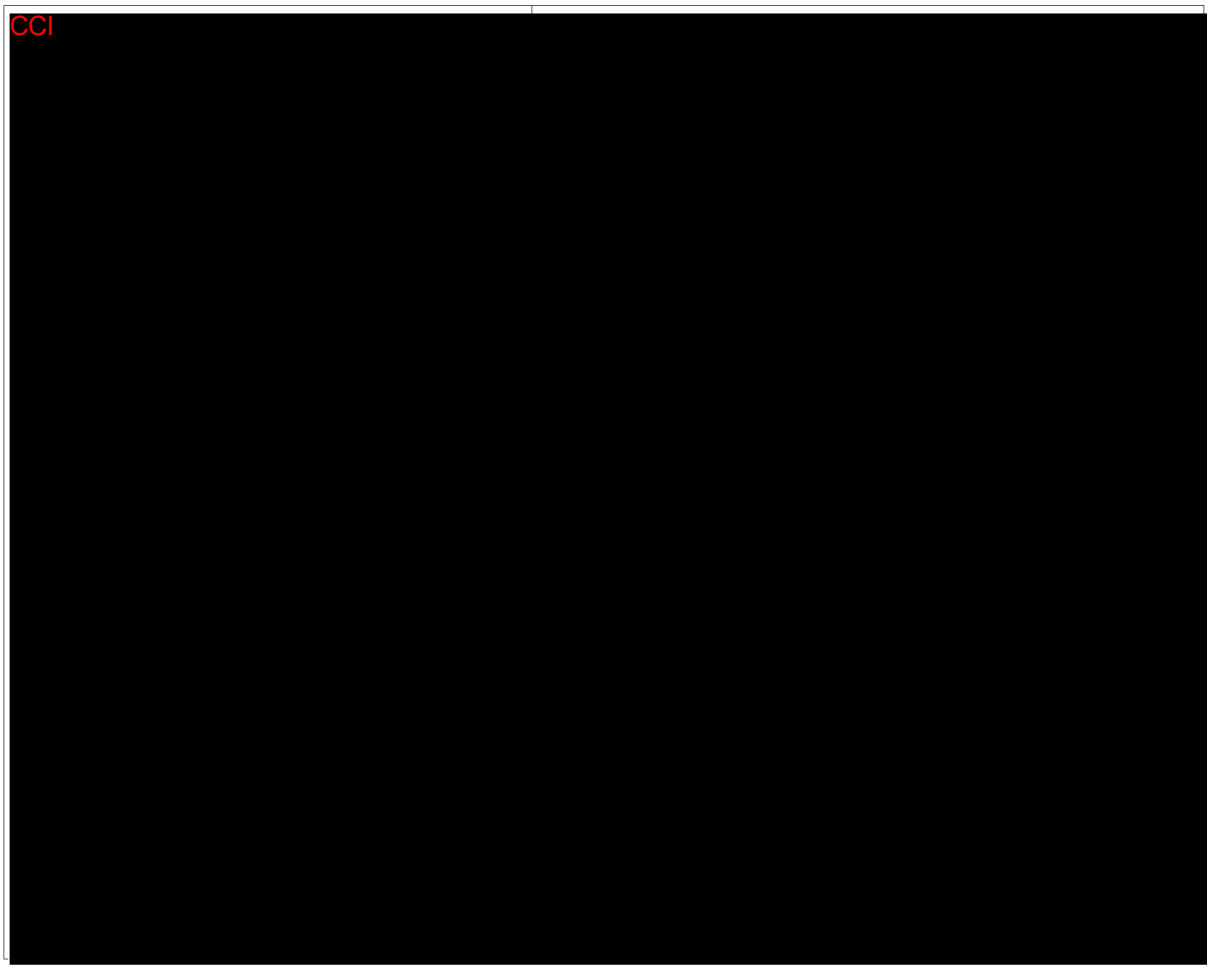
Participants in this study will already be diagnosed with HFpEF. Through participation in this study a further diagnosis of ATTR-CM will be assessed which will allow the health care provider to consider further treatment options for the participant. Potential risk includes those inherent from the procedures described.

3. OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
To assess the prevalence of ATTR-CM among patients with HFpEF within a clinically at-risk population.	Estimate of global prevalence of ATTR-CM in HFpEF patients. Diagnosis of ATTR-CM is defined as: • Cardiac Scintigraphy Grade 1, with confirmation of ATTR by cardiac biopsy, or: • Cardiac Scintigraphy Grade 2 or above.
Secondary Objective(s):	**Secondary Endpoint(s):**

To assess variations in prevalence of ATTR-CM (wild-type [WT] and hereditary) among patients with HFpEF at a country, regional, and global level.	• Estimate of prevalence of ATTR-CM in patients with HFpEF based on:
	  • Geographical or regional distribution;
	  • Age categories;
	  • Gender.
	• Proportion of patients with WT and hereditary forms among patients diagnosed with ATTR-CM.
	• Baseline characteristics of HFpEF patients with and without ATTR-CM:
	  • New York Heart Association (NYHA) classification;
	  • NT-proBNP.

CCI [redacted]



4. STUDY DESIGN

4.1. Overall Design

This study is a global, multi-center epidemiology study designed to estimate the global prevalence of ATTR-CM in participants with HFpEF within a clinically at-risk population. The study will enroll approximately 2000 patients.

4.2. Scientific Rationale for Study Design

It has recently been described that ATTR amyloidosis is significantly underdiagnosed, taking into consideration that both the clinical presentation and the symptoms are non-specific. The most frequent form of HF in patients with ATTR-CM is HF with preserved left ventricular ejection fraction (HFpEF). The aim of this epidemiology study is to assess the prevalence of ATTR-CM in a clinically at risk HFpEF population. Inclusion of an age criteria of ≥60 years enables only at-risk HFpEF participants to be enrolled.

Definitive diagnosis of ATTR-CM may include invasive tissue biopsy. Extracardiac biopsy has a low diagnosis yield in ATTR amyloidosis, particularly in wild-type ATTR (ATTRwt). Therefore, in the setting of high clinical suspicion and a negative extracardiac biopsy, endomyocardial biopsy would be required. This invasive diagnostic approach carries

associated complications and delays in diagnosis.[22] Alternatively, noninvasive cardiac scintigraphy has marked a crucial change in the diagnostic workup of the disease. Data show that a Grade 2 or 3 uptake, in the absence of monoclonal proteins on serum and urine immunofixation electrophoresis and serum free light chain assay, is associated with 100% sensitivity and 100% specificity for cardiac ATTR amyloidosis.[22] In the case of Grade 1 uptake, histological confirmation through endomyocardial biopsy with typing of amyloid is required.

4.3. Justification for Dose

Not applicable.

4.4. End of Study Definition

The end of study is when all participants have completed all applicable study visits (including Follow-up Visit 2,) as shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male and female participants ≥60 years of age at time of screening.
2. Medical history of heart failure (HF) with:
    a. At least 1 episode with clinical evidence of HF (without hospitalization) by signs or symptoms of volume overload or elevated intracardiac pressures that required/requires treatment with a diuretic for improvement; OR
    b. 1 prior hospitalization for HF.
3. Left ventricular ejection fraction (LVEF) >40%.
4. End-diastolic interventricular septal wall thickness (IVST) ≥12 mm.
5. Willing and able to undergo scintigraphy.

6. Capable of giving signed informed consent as described in Section 10.1.2 which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

7. Participants who are willing and able to comply with all scheduled visits, laboratory tests, and other study procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Diagnosis of heart failure with reduced ejection fraction (HFrEF) (EF ≤40%).

2. Prior clinical history of myocardial infarction, CABG or multi-vessel obstructive coronary disease (>50% stenosis of ⩾2 epicardial coronary arteries).

3. Presence or history of any severe valvular heart disease (obstructive or regurgitant).

4. A confirmed diagnosis of a non-amyloid infiltrative cardiomyopathy (i.e., cardiac sarcoidosis, hemochromatosis), muscular dystrophies, cardiomyopathy with reversible causes, hypertrophic obstructive cardiomyopathy with known genetic etiology, or known pericardial constriction.

5. Any type of diagnosed amyloidosis (e.g., amyloid A amyloidosis, primary [light chain] amyloidosis) or prior diagnosis of ATTR-CM.

6. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

5.3. Schema

Not Applicable.

5.4. Lifestyle Requirements

Not applicable.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes screen failure details such as demography, eligibility criteria, and any SAE. Individuals who do not meet the criteria for participation in this study (screen failure) will be recorded as a screen failure but may be rescreened at a later date. Rescreened participants will be assigned a new screening number. Pfizer approval must be provided prior to re-screening a participant.

6. STUDY INTERVENTION

Not applicable.

6.1. Participant Compliance

Not applicable.

6.2. Study Intervention

No study treatment is administered. For the purposes of this protocol, study intervention refers to requirement for scintigraphy and biological specimens.

6.3. Study Intervention Storage

Not applicable.

6.4. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.5. Study Intervention Accountability

Not applicable.

6.6. Concomitant Treatment(s)

Not applicable.

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study and Vital Status Follow-up

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include *but are not limited to* the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;

- Study terminated by sponsor.

Due to assessment of vital status at the Follow-Up 2 Visit, a Release of Medical Information Form will be required of all participants for the purpose of access to medical records as well as for obtaining vital status follow-up with the participant's primary physician or with death registries. The signing of this Release of Medical Information Form is in addition to the Informed Consent Document. In some cases, sites may combine these 2 forms into a single form, as is their standard practice.

Participants should be questioned regarding their reason for withdrawal. A Follow-Up 2 Visit should be performed for those participants with ATTR-CM if consent has been obtained. The participant will be permanently discontinued from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly. If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.3. Withdrawal of Consent:

Participants who request to discontinue study participation must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from study procedures and/or study follow-up and entered on the appropriate case report form (CRF) page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Section 10.1.6 .

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant in the study should continue.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 63 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

Protocol-specified safety laboratory tests may be performed at a local laboratory if the study participant is unable to visit the study site, where allowable by law or local guidance. Local laboratory reference ranges need to be documented.

8.1.1. Screening Visit

The following procedures will be conducted during the Screening visit. Details of the assessments are located in Section 8.2:

- Informed consent.
- All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in this study.
- Echocardiography (unless obtained within 6 months prior to Screening Visit and results are available).
- Complete medical history.
- Measure vital signs (systolic and diastolic blood pressure supine and standing and pulse rate supine and standing).
- Demography (date of birth, age, gender, race and ethnicity).
- Full physical examination including weight and height measurements will be performed.
- Adverse event reporting.

8.1.2. Visit 1

The following procedure will be completed at Visit 1. Details of the assessments are located in Section 8.2:

- Record current medications.
- Record NYHA classification.

CCI [redacted]

- Perform scintigraphy.
- Collect blood, and urine samples for the following clinical laboratories:
  - NT-Pro-BNP
  - Serum/urine test for primary (light chain) amyloidosis;
  - ATTR-CM biomarker samples;

- TTR genotyping.

CCI [redacted]

- Adverse event reporting.

8.1.3. Follow-up 1 Visit

Participants will be informed of their diagnosis and collect any AE/RRI information within 14 days (+10 days) of study visit 1. This follow-up can be conducted remotely.

8.1.4. Follow-up 2 Visit

- Participants with scintigraphy of grade 1 or higher will be contacted to assess current medications and vital status. Participants with scintigraphy grade 1 will be asked if they have undergone a biopsy or other testing as follow up to scintigraphy since their last visit. Data will be collected on method of diagnosis and whether it confirmed the presence of ATTR-CM.

This post-study follow-up can be conducted remotely. This will occur 6 months after the Follow-up 1 Visit (+/- 30 days) or at early study discontinuation.

8.2. Assessments

8.2.1. Scintigraphy

All participants will undergo radionuclide cardiac scintigraphy at Visit 1 with a bisphosphonate radiotracer: ^{99m}Tc-DPD, ^{99m}Tc-PYP, or ^{99m}Tc-HMDP. Cardiac retention of all ^{99m}Tc-DPD, ^{99m}Tc-PYP, or ^{99m}Tc-HMDP will be determined by the central reader according to the grading:

Grade 0=absent cardiac uptake.

Grade 1=mild uptake less than bone.

Grade 2=moderate uptake equal to bone.

Grade 3=high uptake greater than bone.

Details of scintigraphy will be provided in a separate laboratory manual (Scintigraphy manual).

To confirm a diagnosis of ATTR-CM a participant with Grade 1 scintigraphy should undergo an endomyocardial biopsy.[20,32] If biopsy or other confirmatory testing is performed, data will be collected.

8.2.1.1. Management of Incidental Findings from Scintigraphy

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

Scintigraphy images will be reviewed by a central review facility. The purpose of this review is to evaluate images for diagnosis of ATTR-CM. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the principal investigator (PI). All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any adverse events (AEs) identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

8.2.2. Echocardiogram

Echocardiography (2D Doppler) will be performed and data collected for all participants at Screening unless one has been obtained within 6 months prior to Screening Visit and results are available. The assessment of end-diastolic interventricular septal thickness and left ventricular ejection fraction for study entry will be based on the echocardiogram performed at (or within 6 months prior to) the Screening visit as interpreted locally by the qualified reader (physician trained in echocardiography) at the site. If the Screening echocardiographic recording is not clear enough to accurately determine the end-diastolic interventricular septal wall thickness and left ventricular ejection fraction, it must be repeated. Each echocardiogram will be recorded and reviewed locally by the qualified reader at the clinical site, and the clinical significance of echocardiogram findings will be assessed by the investigator.

The following echocardiographic parameters should be collected if available:

1. End-diastolic interventricular septal wall thickness (mm).
2. End-diastolic left ventricular posterior wall thickness (mm).
3. Left ventricular ejection fraction (%).
4. Left atrial diameter, anterior-posterior (mm).
5. Left atrial diameter, medio-lateral (mm).
6. Left atrial diameter, superior-inferior (mm).
7. Left ventricular end systolic diameter (mm).

8. Left ventricular end systolic volume (mL).
9. Left ventricular end-diastolic diameter (mm).
10. Left ventricular end-diastolic volume (mL)..
11. E/A Ratio.
12. E/E' Ratio.

8.2.3. Cardiac Biomarkers: N-Terminal Pro-Hormone Brain Natriuretic Peptide (NT-proBNP) [redacted]

A 2.5 mL blood sample for NT-proBNP will be collected at Visit 1 and analyzed locally by the investigator site.

[redacted]

Specifications for sample collection can be found in the study laboratory manual.

8.2.4. Biospecimens for ATTR-CM Biomarker Identification and Validation

The following biospecimens for ATTR-CM biomarker research are required and will be collected from all participants in this study at Visit 1 as specified in the SoA (as allowed by local law):

- Collection of 56 mL blood including:
  - 2 K2EDTA plasma samples (10mL each),
  - 2 lithium heparin plasma samples (8mL each), and
  - 2 serum sample tubes (10mL each).
- Collection of 10 mL of urine.

Details on processes for collection and shipment of these samples can be found in the study laboratory manual.

8.2.5. TTR Genotyping

Participants will require collection of a 4 mL blood sample for potential TTR genotype testing, subject to local laws and regulations, at Visit 1. If the participant is diagnosed with scintigraphy grades 1, 2, or 3 then the sample will be sent to a reference laboratory for analysis and complete genomic sequencing of the TTR gene.

8.2.6. Testing for Light Chain Amyloid

Specifications for testing samples are provided in the study laboratory manual. Blood and urine specimens for serum free light chains assay and the serum and urine electrophoresis with immunofixation will be obtained from all participants, but only analyzed for those with scintigraphy Grades 1, 2, or 3. As standard of care, participants with serum or urine test result indicative of monoclonal gammopathy of undetermined significance (MGUS) will require a confirmatory biopsy performed locally.

8.2.7. Medical History

A complete medical history is to be documented for all participants at the Screening visit. This medical history will document the specific symptoms the participant reports associated with ATTR-CM, as well as any additional co-morbid conditions or symptoms including but not limited to:

- Sprains/strains.
- Transthyretin amyloid polyneuropathy (ATTR-PN).
- Arthroplasty.
- Pacemaker or implantable cardioverter defibrillator (ICD).
- Carpal tunnel syndrome.
- Biceps tendon rupture.
- Lumbar spinal stenosis.
- Achilles tendon rupture (nontraumatic).
- Rotator cuff injury (nontraumatic).
- Atrial fibrillation/Atrial flutter.
- Heart block.
- Intracardiac thrombus.
- Embolic stroke.

8.2.8. Vital Signs

Vital signs (including systolic and diastolic blood pressure, and pulse rate) will be assessed and recorded at the Screening visit. Orthostatic blood pressure changes will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg. Rounding up to the nearest 5 or 10 mmHg is not permitted. The participant should be supine for at least 3 minutes before the supine blood pressure is obtained. Standing blood

pressure should then be measured approximately 2 minutes after the participant assumes the standing position.

The use of automated devices for measuring BP and pulse rate is acceptable, although when performed manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

8.2.9. Medications

A list of current medications will be collected at Visit 1 for all participants; and Follow-up 2 Visit for participants with scintigraphy grade 1, 2 or 3.

CCI [redacted]

8.2.11. NYHA Classification

The extent of participants' heart failure will be evaluated at Visit 1 using the New York Heart Association (NYHA) classification.

Class I: Participants with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Participants with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.

Class III: Participants with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV: Participants with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

CCI [redacted]

[redacted]

8.2.14. Physical Examination and Height and Weight Measurement

All participants will undergo a full physical examination at the Screening visit, including assessment of the following body systems:

General appearance	Neurological
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Skin
Nose	Musculoskeletal
Throat	Lungs
Genitourinary	

Measurement of height in centimeters (cm) or inches (in) and weight in kilograms (kg) or pounds (lbs.) will be performed at the Screening visit.

CCI

[redacted]

[redacted]

8.2.17. Vital Status

Participants, or their delegate, will be contacted at the Follow-up 2 Visit to determine vital status.

8.2.18. Subsequent Diagnosis of ATTR-CM

For participants who had scintigraphy grade 1 at Visit 1, information on subsequent diagnosis testing for cardiac amyloidosis and method thereof will be collected.

8.3. Safety

8.3.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Any AE that occurs from the time the participant provides informed consent through and including up to 14 days following the participant's last visit must be recorded. The investigator is required to assess whether the AE may be related to the participant's participation in the study. All AEs (i.e., serious and non-serious, including those attributed to qualifying procedure identified as research-related injury) are collected in the clinical study database.

The investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a research related injury requiring immediate notification to Pfizer as described below.

8.3.2. Research Related Injury

Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented and will be maintained by the sponsor.

The primary completion date (PCD) for the global prevalence estimate will be the date when all enrolled participants have either been diagnosed with ATTR-CM (scintigraphy grades 2 or 3), have scintigraphy grade 1 or found to be negative for ATTR-CM (scintigraphy grade 0) and have completed Follow-up Visit 1. Results will be reported after PCD and at the end of study (LPLV for participants with scintigraphy grade 1, 2 or 3).

The empirical estimate for the prevalence of ATTR-CM in HFpEF participants is approximately 10%. The study will enroll approximately 2000 HFpEF participants within whom it is expected to detect 200 ATTR-CM participants. Enrollment will be stopped if 200 ATTR-CM participants are identified before 2000 HFpEF are enrolled. No formal sample size calculation was performed. A sample size of 2000 HFpEF participants would be sufficient to inform treatment guidelines and yield an estimate for the global prevalence of ATTR-CM in HFpEF participants with a precision of ±2.5%.

The primary endpoint is an estimate of the global prevalence of ATTR-CM in HFpEF participants. Diagnosis of ATTR-CM is defined as:

- Cardiac Scintigraphy Grade 1, with confirmation of ATTR by cardiac biopsy; or

- Cardiac Scintigraphy Grade 2 or above.

This global prevalence estimate will be obtained by dividing the number of participants who are diagnosed with ATTR-CM in the study by the total number of HFpEF participants evaluated. A 95% confidence interval on the estimate will also be calculated.

As secondary analysis, prevalence will be estimated for:

- Regions and countries.
- Age categories (60-64, 65-69, 70-74, 75-79, 80-85, >85).
- Gender (male, female).

Prevalence estimates along with 95% CI will be generated for regions and countries with at least 50 participants. For regions and countries that enroll fewer than 50 participants, prevalence will not be estimated. Regions will be defined in the statistical analysis plan. The proportion of HFpEF participants who were diagnosed with wild-type and variant ATTR-CM will be descriptively summarized.

As a general rule, the secondary endpoints other than the prevalence estimates and all CCI reported as numerical values will be analyzed descriptively using mean, standard deviation, median, minimum and maximum. Endpoints that are categorical will be summarized using frequency tables.

Analysis by Scintigraphy:

Participants who are diagnosed with ATTR-CM will be analyzed by scintigraphy grades (Grade 1, 2, or 3) using the 6-MWT, NT-proBNP, medical history, demographics (including age, TTR Genotype, gender and race), NYHA classification (Class I, II, III, or IV), and all CCI

Analysis by Disease Status:

Participants who are diagnosed with ATTR-CM will be analyzed by NYHA Classification (Class I, II, III, or IV) using the 6-MWT, NT-proBNP, medical history, demographics (including age, TTR Genotype, gender, and race)CCI CCI

Participants who are diagnosed with ATTR-CM will also be analyzed by 6-MWT quartile groups using NYHA baseline classification (Class I, II, III, or IV), NT-proBNP, medical history, demographics (including age, TTR Genotype, gender, and race)CCI CCI

Analysis Comparing ATTR-CM participants with HFpEF patients without ATTR-CM:

HFpEF participants diagnosed with ATTR-CM will be compared with HFpEF participants not diagnosed with ATTR-CM descriptively using medical history, demographics (including age, TTR Genotype, gender, and race)CCI

Medical history data will be used to generate descriptive statistics for time from symptom onset to HFpEF diagnosis and time from symptom onset to ATTR-CM diagnosis.

Endpoints measuring proportion of participants (NYHA Classification and symptoms of interest from medical history) will be compared between HFpEF participants diagnosed with ATTR-CM and those that are not diagnosed with ATTR-CM. The Chi-square test will be used to compare the proportions between these 2 groups of HFpEF participants. Fisher's exact test will be used instead of the chi-square test if any one of the cells has ≤5 participants. Secondary CCI endpoints that are normally distributed will be compared between 2 groups of HFpEF participants using a t-test. Endpoints that are not normally distributed will be compared using the Wilcoxon rank sum test.

Safety Analysis:

Adverse events (AEs) and research related injuries (RRI) collected at Visit 1 or during Follow-up visits, will be summarized overall and separately for HFpEF participants diagnosed with ATTR-CM and HFpEF participants not diagnosed with ATTR-CM.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (e.g., advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional

additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This

verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.5. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.6. Study and Site Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.7. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

CCI

[redacted]

APPENDIX 2. ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
6-MWT	6-minute walk test
AE	adverse event
ATTR	transthyretin amyloid
ATTR amyloidosis	transthyretin amyloidosis
ATTR-ACT	Tafamidis for ATTR-CM Trial
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTR-PN	transthyretin amyloid polyneuropathy
ATTRwt	wild-type ATTR
BP	blood pressure
CABG	Coronary artery bypass grafting
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CRF	case report form
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EF	Ejection fraction
eGFR	estimated glomerular filtration rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
HCRU	Healthcare Resource Utilization
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD	informed consent document
ICH	International Council on Harmonisation
IRB	institutional review board
IVST	interventricular septal wall thickness
K2EDTA	potassium ethylenediaminetetraacetic acid
KCCQ	Kansas City Cardiomyopathy Questionnaire
Leu111Met	leucine replaced by methionine at position 111
LVEF	Left ventricular ejection fraction

Abbreviation	Term
mBMI	modified body mass index
MGUS	monoclonal gammopathy of unknown significance
MDRD	Modification of Diet in Renal Disease
MRI	magnetic resonance imaging
N/A	not applicable
NCT	National clinical trial number
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
PCD	primary completion date
PI	principal investigator
QTc	corrected QT interval
QTcF	corrected QT interval by Fredericia formula
RRI	research related injury
SAE	Serious adverse event
Scr	Serum creatinine
SoA	schedule of activities
TTR	transthyretin
US	United States
Val122Ile	valine replaced by isoleucine at position 122
WT	wild-type

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