



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Retrospective Analysis of Mortality in Tafamidis-Treated Japanese Patients with ATTRwt-CM Using the J-COSSA Registry
Protocol number	B3461129
Protocol version identifier	1.0
Date	25 June 2026
EU Post Authorization Study (PAS) register number	EUPAS1000001025
Active substance	ATC Code: N07XX08 - tafamidis
Medicinal product	VYNDAQEL® (tafamidis meglumine) VYNMAC® (tafamidis free acid)
Research question and objectives	Research question: What is the real-world overall survival among patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) treated with tafamidis in Japan, and how does overall survival vary by baseline prognostic factors and relate to baseline characteristics? To address the question, the study is conducted in two sequential stages. First stage (Stage 1) focuses on characterization of the registry data, including observed follow-up duration and patterns, and patient demographics and baseline characteristics. These results will be used to evaluate feasibility and provide important contextual information for the analyses and interpretation of results planned for the second stage (Stage 2). Objectives Stage 1: - To describe data availability and observed follow-up duration and patterns among patients with ATTRwt-CM treated with tafamidis included in the J-COSSA registry - To describe patient demographic and baseline characteristics of the study population across predefined analysis sets Objectives Stage 2: Primary objective: - To describe overall survival among patients with ATTRwt-CM following initiation of tafamidis treatment Secondary objectives: - To describe overall survival among patients with ATTRwt-CM following initiation of tafamidis treatment stratified with established baseline prognostic factors such as New York Heart Association (NYHA) class and National Amyloidosis Centre (NAC) ATTR stage Exploratory objectives:

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

	- To explore associations between baseline factors and mortality among patients with ATTRwt-CM following initiation of tafamidis treatment
Country(ies) of study	Japan
Author	████████████████████ ████████████████ ████████████████ ██

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS	3
2. LIST OF ABBREVIATIONS	5
3. RESPONSIBLE PARTIES	7
4. ABSTRACT	8
5. AMENDMENTS AND UPDATES	11
6. MILESTONES	12
7. RATIONALE AND BACKGROUND	12
8. RESEARCH QUESTION AND OBJECTIVES	13
9. RESEARCH METHODS	14
9.1. Study Design	14
9.2. Setting	14
9.2.1. Inclusion Criteria	15
9.2.2. Exclusion Criteria	15
9.2.3. Observation Period	16
9.2.4. Exposure and Study Time Definition	16
9.3. Variables	17
9.4. Data Sources	21
9.5. Study Size	22
9.6. Data Management	22
9.7. Data Analysis	23
9.8. Quality Control	27
9.9. Strengths and limitations of the research methods	28
9.10. Other Aspects	29
10. PROTECTION OF HUMAN PARTICIPANTS	29
10.1. Patient Information	29
10.2. Patient Consent	29
10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)	29
10.4. Ethical Conduct of the Study	29
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	29

PFIZER CONFIDENTIAL



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS.....	30
13. REFERENCES	30
14. LIST OF TABLES	31
15. LIST OF FIGURES	31
ANNEX 1. LIST OF STANDALONE DOCUMENTS	31
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS	31
ANNEX 3. ADDITIONAL INFORMATION.....	31



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	Six-minute walk test
ACE	Angiotensin-converting enzyme
AE	Adverse Event
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRv	Variant transthyretin amyloidosis
ATTRwt	Wild-type transthyretin amyloidosis
ATTRwt-CM	Wild-type transthyretin amyloid cardiomyopathy
AUC	Area Under the Curve
BMI	Body mass index
BNP	B-type natriuretic peptide
CI	Confidence interval
Cmax	Maximum plasma concentration
CRF	Case report form
DCT	Data Collection Tools
EC	Ethics Committee
EDC	Electronic data capture
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
GLS	Global longitudinal strain
HMA-EMA	Heads of Medicine Agencies-European Medicines Agency

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVST	Interventricular septal thickness
J-COSSA	Japan Cohort Study of Systemic Amyloidosis
JCS	Japanese Circulation Society
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Summary score
LVEF	Left ventricular ejection fraction
LVPWT	Left ventricular posterior wall thickness
MHLW	Ministry of Health, Labour and Welfare
NAC	National Amyloidosis Centre
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PASS	Post-Authorization Safety Study
RADDAR-J	Rare Disease Research in Japan
SAP	Statistical analysis plan
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
TAVI	Transcatheter aortic valve implantation
TnI	Troponin I
TnT	Troponin T
TTR	Transthyretin
YRR	Your Reporting Responsibility
eGFR	Estimated glomerular filtration rate

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

4. ABSTRACT

Retrospective Analysis of Mortality in Tafamidis-Treated Japanese Patients with ATTR-CM Using the J-COSSA Registry

Protocol Version 1.0, 25 June 2026

[REDACTED]
[REDACTED]

Rationale and Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and life-threatening condition characterized by myocardial deposition of misfolded transthyretin protein, leading to restrictive cardiomyopathy and heart failure. Tafamidis, a transthyretin stabilizer, has demonstrated efficacy in reducing all-cause mortality in patients with ATTR-CM in randomized controlled trials, leading to its approval in Japan in March 2019 for the treatment of ATTR-CM; however, evidence describing clinical outcomes of tafamidis treatment in routine clinical practice remains limited, particularly with respect to long-term outcomes derived from large-scale, multicenter data in Japan. In Japan, initiation of tafamidis requires physician and institutional certification and mandatory registration of treated patients in the nationwide Japan Cohort Study of Systemic Amyloidosis (J-COSSA) registry. This registry provides a unique opportunity to describe real-world clinical outcomes following tafamidis initiation on a national scale. This non-interventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

Research Question and Objectives

Research question:

What is the real-world overall survival among patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) treated with tafamidis in Japan, and how does overall survival vary by baseline prognostic factors and relate to baseline characteristics? To address the question, the study is conducted in two sequential stages. First stage (Stage 1) focuses on characterization of the registry data, including observed follow-up duration and patterns, and patient demographics and baseline characteristics. These results will be used to evaluate feasibility and provide important contextual information for the analyses and interpretation of results planned for the second stage (Stage 2).

Objectives Stage 1:

- To describe data availability and observed follow-up duration and patterns among patients with ATTRwt-CM treated with tafamidis included in the J-COSSA registry
- To describe patient demographic and baseline characteristics of the study population across predefined analysis sets

Objectives Stage 2:

Primary objective:

- To describe overall survival among patients with ATTRwt-CM following initiation of tafamidis treatment



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Secondary objectives:

- To describe overall survival among patients with ATTRwt-CM following initiation of tafamidis treatment stratified with established baseline prognostic factors such as New York Heart Association (NYHA) class and National Amyloidosis Centre (NAC) ATTR stage

Exploratory objectives:

To explore associations between baseline factors and mortality among patients with ATTRwt-CM following initiation of tafamidis treatment

Study Design

This is a retrospective, observational, longitudinal, single-cohort study using secondary structured data collected in the J-COSSA registry, with an observation period from April 2019 to September 2025. The study is conducted in two sequential stages: a feasibility and data characterization stage (Stage 1) and an outcome analysis stage (Stage 2).

Population

This study will be conducted in a nationwide, multicenter, registry-based setting using data from the J-COSSA registry. The study population comprises patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) who initiated tafamidis treatment between April 2019 and September 2025 in Japan. Tafamidis initiation in Japan is restricted to certified physicians and institutions, and treating physicians are required to register treated cases in the J-COSSA registry under the national prescribing framework. Patients with a documented date of tafamidis initiation (index date) and post-index follow-up data will be included in the primary outcome analyses.

Variables

Exposure is defined as tafamidis treatment, including the following variables: date of initial tafamidis treatment (index date), date of last tafamidis treatment and tafamidis treatment duration. The outcome is all-cause death, defined based on the survival status and date of death variables. Key co-variables include demographics (Age, Gender), BMI, clinical staging (NYHA class, NAC ATTR stage), biomarkers (BNP, NT-proBNP, TnT, TnI, Creatinine, eGFR, Serum albumin), patient reported outcomes (KCCQ-OS, EQ-5D-5L), echocardiographic parameters (LVEF, IVST, LVPWT, E/e', GLS), comorbidities (Atrial fibrillation, Atrioventricular block, Sick sinus syndrome), medical history (hospitalization, permanent pacemaker, TAVI, catheter ablation), and concomitant heart failure medications (SGLT2i, β -blockers, ACE/ARB, ARNI, Digitalis glycoside, Calcium antagonist, Pimobendan, Loop-diuretics, Vasopressin V2 receptor antagonist).

Data Sources

Data are derived from the J-COSSA registry, a nationwide, multicenter, observational registry implemented on a secure national platform in Japan. Structured data are collected annually using predefined electronic case report forms. An anonymized dataset containing pre-specified variables will be extracted by the registry administrator and analyzed by Keio University School of Medicine.

Study Size

No formal sample size calculation was performed, as this is a descriptive registry-based study. Based on high-level information available from the J-COSSA registry prior to data extraction indicated that approximately 3,600 tafamidis-treated patients with ATTR-CM, predominantly ATTRwt-CM, had



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

been registered in the J-COSSA registry, of whom approximately 1,450 patients with documented dates of tafamidis initiation were expected to be potentially eligible for outcome analyses.

Data Analysis

Stage 1 analyses will descriptively summarize data availability, observed follow-up duration and patterns, and baseline patient characteristics. In Stage 2, overall survival following tafamidis initiation will be described using Kaplan–Meier methods, with cumulative survival probabilities estimated at 3-month intervals. Survival analyses stratified by established baseline prognostic factors, including NYHA class and NAC ATTR stage, will be conducted. Exploratory Cox proportional hazards models will be used to evaluate associations between baseline factors and mortality. No formal hypothesis testing is planned; effect estimates will be presented with 95% confidence intervals.

Milestones

Milestone	Planned Date
Start of data collection	2 Sep 2026
End of data collection	30 Sep 2026
Registration in the HMA-EMA Catalogues of RWD studies	1 Sep 2026
Final study report	28 Feb 2027



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

5. AMENDMENTS AND UPDATES

None.



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

6. MILESTONES

Milestone	Planned Date
Start of data collection	2 Sep 2026
End of data collection	30 Sep 2026
Registration in the HMA-EMA Catalogues of RWD studies	1 Sep 2026
Final study report	28 Feb 2027

7. RATIONALE AND BACKGROUND

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and life-threatening condition characterized by the deposition of misfolded transthyretin (TTR) protein in the myocardium, leading to restrictive cardiomyopathy and heart failure. ATTR-CM can arise from either wild-type TTR (ATTRwt) or variant TTR (ATTRv), with both forms contributing to significant morbidity and mortality, particularly among elderly populations (1-3).

Tafamidis is a first-in-class pharmacologic agent developed to stabilize the TTR tetramer and prevent its dissociation into monomers, a critical step in the pathogenesis of amyloid fibril formation. By binding selectively to the thyroxine-binding sites of TTR, tafamidis inhibits amyloidogenesis and thereby mitigates the progression of cardiac dysfunction (4).

The efficacy of tafamidis in treating ATTR-CM was demonstrated in the pivotal ATTR-ACT trial, a multicenter, double-blind, placebo-controlled study involving 441 patients. Tafamidis significantly reduced all-cause mortality and cardiovascular-related hospitalizations over a 30-month period, and preserved functional capacity as measured by the six-minute walk test (4). These findings have positioned tafamidis as a cornerstone therapy in the management of ATTR-CM, underscoring the importance of early diagnosis and phenotypic characterization of heart failure patients to identify those who may benefit from targeted treatment. Following this evidence, tafamidis meglumine 80 mg (4×20 mg) was approved in Japan in March 2019 for the treatment ATTR-CM. Subsequently, tafamidis free acid 61 mg was approved in Japan in September 2021. Tafamidis meglumine 80 mg and tafamidis free acid 61 mg have been shown to be bioequivalent at steady state, with Area Under the Curve (AUC) and Maximum plasma concentration (C_{max}) meeting predefined bioequivalence criteria (5); therefore, these formulations were not distinguished and were treated as equivalent tafamidis exposure in the present study.

Despite the robust evidence from randomized controlled trials and subsequent regulatory approvals, real-world data on clinical outcomes during tafamidis treatment remain limited. A retrospective cohort study conducted at Kochi University explored the use of tafamidis in patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) over a 12-18 months period, revealing notable differences in overall survival (log-rank test, $p = 0.012$) and in the event-free rate for cardiovascular-related hospitalization ($p = 0.002$) between tafamidis-treated patients ($n=38$) and non-treated patients ($n=44$) (6). In a separate retrospective, single-center observational study conducted at Kumamoto University, clinical outcomes of 125 ATTRwt-CM patients treated with tafamidis ($n=125$) were compared with untreated controls ($n=55$). Those receiving tafamidis had significantly lower all-cause mortality and fewer hospitalizations for heart failure compared with untreated patients, both in the overall group ($P < 0.01$) and in the propensity score-matched cohort ($P < 0.05$) (7). Despite these findings, the evidence is currently limited to single-site studies with relatively small sample sizes, which are prone to selection, information, and treatment biases, limiting their generalizability.

To address existing evidence gaps and describe the clinical outcome in patients with ATTRwt-CM following tafamidis initiation, this study will leverage the national database which includes patients



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

with ATTRwt-CM treated with tafamidis in Japan. To ensure appropriate use of tafamidis, the Ministry of Health, Labour and Welfare (MHLW) has established prescribing requirements, and the Japanese Circulation Society (JCS) issued the 2020 Guideline on the Diagnosis and Treatment of Cardiac Amyloidosis (8). These include a certification system for prescribing physicians and facilities. In accordance with these requirements, physicians starting prescription of tafamidis in Japan must register all treated cases in the database of Japan Cohort Study of Systemic Amyloidosis (J-COSSA) registry (9), conduct ongoing follow-up, and submit annual clinical course reports to the JCS. As of January 2026, approximately 3,600 patients with ATTR-CM treated with tafamidis have been registered in the J-COSSA registry, which began enrollment in April 2020 (tafamidis was approved in Japan in March 2019).

Evidence from a broad patient population with ATTRwt-CM treated with tafamidis in real-world setting remains limited, including data on patients under-represented in clinical studies (such as advanced age, NYHA class IV, multiple comorbidities etc). This study has the potential to characterize clinical outcomes in these patient populations. This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research question:

What is the real-world overall survival among patients with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) treated with tafamidis in Japan, and how does overall survival vary by baseline prognostic factors and relate to baseline characteristics? To address the question, the study is conducted in two sequential stages. First stage (Stage 1) focuses on characterization of the registry data, including observed follow-up duration and patterns, and patient demographics and baseline characteristics. These results will be used to evaluate feasibility and provide important contextual information for the analyses and interpretation of results planned for the second stage (Stage 2).

Objectives Stage 1:

- To describe data availability and observed follow-up duration and patterns among patients with ATTRwt-CM treated with tafamidis included in the J-COSSA registry
- To describe patient demographic and baseline characteristics of the study population across predefined analysis sets

Objectives Stage 2:

Primary objective:

- To describe overall survival among patients with ATTRwt-CM following initiation of tafamidis treatment

Secondary objectives:

- To describe overall survival among patients with ATTRwt-CM following initiation of tafamidis treatment stratified with established baseline prognostic factors such as New York Heart Association (NYHA) class and National Amyloidosis Centre (NAC) ATTR stage

Exploratory objectives:



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

To explore associations between baseline factors and mortality among patients with ATTRwt-CM following initiation of tafamidis treatment

9. RESEARCH METHODS

9.1. Study Design

This study is a retrospective, observational, longitudinal single-cohort study using data from the J-COSSA registry. There is no comparison group in this study, therefore, there is no comparative effect measure.

In the J-COSSA registry, certified physicians are required to perform and document annual follow-up of patients, including confirmation of survival status and other assessments; however, as the registry is operated as an observational study embedded in routine clinical practice, the actual follow-up duration, follow-up patterns, and availability of key clinical variables may vary across patients and over time. To address the primary research objective of evaluating clinical outcomes following tafamidis initiation, the main analyses will be conducted in Stage 2. To support this objective, Stage 1 will be conducted to characterize data availability and completeness within the registry, including follow-up duration, follow-up patterns, and availability of key clinical variables at baseline and over time. These analyses will provide important context for the feasibility, interpretation, and robustness of the Stage 2 analyses.

The primary endpoint is time from tafamidis initiation to occurrence of death due to all causes. There is no secondary endpoint defined for this study. However, a stratified analysis of the primary endpoint is defined as the secondary objective (primary objective is un-stratified analysis of the primary endpoint). All-cause mortality will be summarized by Kaplan-Meier and survival probabilities at 3-month intervals over the follow-up period. Patients without death event will be censored at the date of discontinuation, the date of last confirmed survival, or the date of last recorded investigation, whichever occurs first.

The choice of a retrospective, observational, longitudinal single-cohort study design is driven by the study objective and the characteristics of the disease and data source. A single-cohort design without a comparison group was selected because ATTRwt-CM is a progressive condition that requires disease-modifying treatment, and tafamidis was the main disease-modifying therapy available in Japan during the data collection period. A retrospective observational approach is selected as the existing nationwide registry with established long-term follow-up and data elements aligned with the study objectives is available for this study, making a prospective design unnecessary. A longitudinal design is required to evaluate the time-to-event primary endpoint (all-cause mortality), which necessitates follow-up over time. This study design also has strengths related to the use of an existing nationwide registry, which enables the inclusion of a large patient population with established long-term follow-up, thereby supporting the evaluation of real-world overall survival in patients with ATTRwt-CM treated with tafamidis.

9.2. Setting

The study population is derived from the J-COSSA registry, which comprises patients with systemic amyloidosis across Japan, including patients with ATTRwt-CM. Because tafamidis initiation in Japan is restricted to JCS-certified physicians and treatment facilities, and registration into J-COSSA is required as part of the prescribing framework, the registry is designed to capture tafamidis-treated ATTRwt-CM patients nationwide, except for those who decline participation. Medical information—including demographics, diagnostic findings, comorbidities, biomarkers, echocardiographic parameters, clinical outcomes, and concomitant therapies—is recorded using an annual case report



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

form (CRF). A single CRF is generated for each patient for each registry year (e.g., baseline, 1st-year, 2nd-year, 3rd-year), and all CRFs are entered and maintained within an electronic data capture (EDC) system. An investigation date is recorded for each initial and follow-up visit CRF. The registry does not set the end of study period and any numbers of targets or caps for the sample size. New patients are added annually, and existing patients are followed longitudinally until withdrawal or death.

For the purpose of this study, the study population is defined by applying specific selection criteria to the registry population. Patients must have provided consent for registry participation, have a diagnosis of ATTRwt, and have received tafamidis in routine clinical practice following its commercial availability in Japan (from April 2019 to cut-off date). Given that tafamidis is indicated for cardiomyopathy in patients with ATTRwt, and that patients included in this study present with cardiac symptoms, the study population is expected to reflect tafamidis-treated patients with ATTRwt-CM in routine clinical practice. Patients who withdraw consent or whose diagnosis is subsequently revised are excluded to ensure the validity of the study population. All patients meeting the predefined inclusion and exclusion criteria will be included in the study population. Detailed inclusion and exclusion criteria are provided in Section 9.2.1. and Section 9.2.2..

Given the nationwide coverage of the registry and the requirement for J-COSSA registration as part of tafamidis prescribing (9), the overall study population (defined as the Overall Cohort) is expected to include a large proportion of tafamidis-treated ATTRwt-CM patients in Japan. Based on initial information obtained from the J-COSSA registry in January 2026, approximately 3,600 patients with ATTR-CM treated with tafamidis were registered with documented informed consent in the registry. Among these, approximately 1,450 patients had available information on the date of initial tafamidis treatment. This requirement for availability of tafamidis initiation is expected to significantly reduce the number of patients included in the analysis set relative to the overall registry population. As a result, the population included in the Outcome Analysis Set may represent a subset of the Overall Cohort. To evaluate the potential impact of this selection, patient demographics and baseline characteristics of the Outcome Analysis Set will be descriptively compared with those of the Overall Cohort.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Has recorded date of informed consent for entry into the registry
2. Is diagnosed with ATTRwt
3. Has a documented cardiac symptom
4. Has documented administration of tafamidis
5. Has an initial visit recorded in the J-COSSA registry with an investigation date on or after April 2019

In addition to the inclusion criteria 1 to 5 above, patients must meet the following inclusion criteria for inclusion in the Outcome Analysis Set:

6. Has a documented start date for the first tafamidis administration (index date) between April 2019 and September 2025.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

1. Has a record of withdrawal of informed consent for registry (withdrawal will be considered valid without dates)
2. Was determined not to have the diagnosis (ATTRwt) after registration.

In addition to the exclusion criteria 1 and 2 above, patients meeting the following criteria will not be included in the Outcome Analysis Set:

3. Has only an initial visit record and no post-index follow-up record.

Note: Patients with no follow-up data consist of two types. First is those whose follow-up data is unlikely to be entered into the registry, and thus no event can be expected to be reported. Second is those with short time from the index to the cutoff date. These patients can be considered at risk of observing an event, however, these patients would be censored at zero time since there is no follow-up data. As censored observations at time zero are excluded from standard survival analysis, excluding second type of patients would not affect the analysis.

9.2.3. Observation Period

Data for this study will be extracted from the J-COSSA registry. The study observation period is defined as Apr 2019 to September 2025, with September 2025 defined as the data cut-off date. The maximum follow-up period per patient is expected to be up to 5 nominal years.

9.2.4. Exposure and Study Time Definition

Exposure in this study is defined as initiation of tafamidis treatment, with follow-up time measured from the start date for the first tafamidis administration (the date of tafamidis initiation), which is defined as index date. Subsequent treatment discontinuation, interruption, or dose modification will not be accounted for in the primary analysis in the primary analysis. For each patient, end of follow-up is defined as the last of dates in 1 through 4 below with the following precedence order. If 1 (date of death) is recorded, this will be the end of follow-up. Otherwise, the end of follow-up is defined as the last date from 2, 3, or 4. Thus, death takes the precedence over other type of events. If an event in 1, 2, or 3 is reported but its event date is missing, then the investigation date from the follow-up CRF page will be substituted for the missing date.

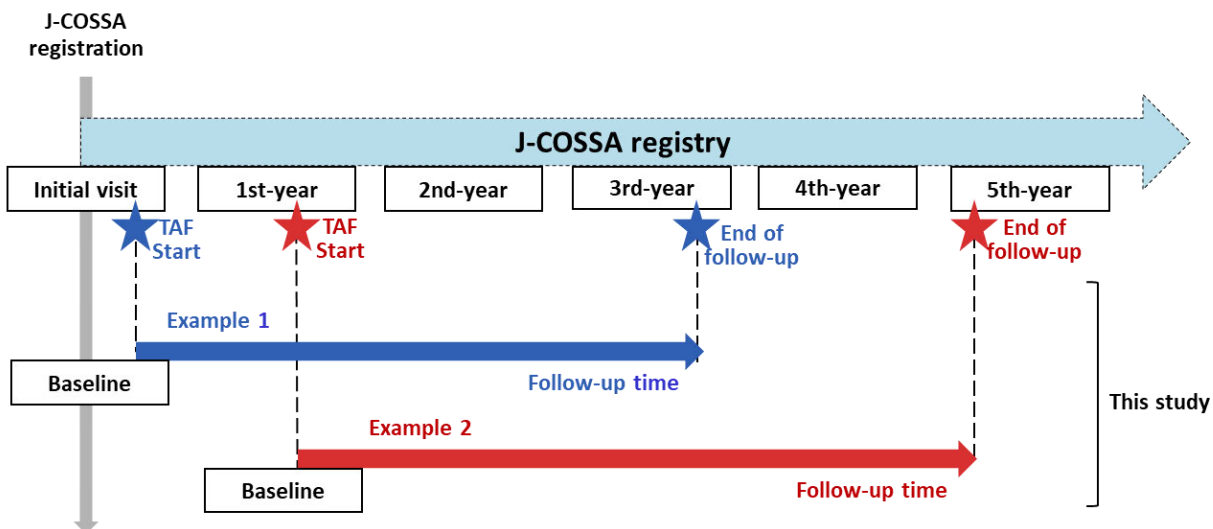
1. Date of death
2. Date of patient discontinuation from the registry
3. Date of last confirmed survival
4. Date of last recorded investigation/measurement

Last recorded date in 4 above includes dates of measurement and examinations recorded on each CRF page.

Baseline data are defined as clinical assessments obtained from the study visit in which the first tafamidis dosing is recorded. Due to the annual update structure of the J-COSSA registry, baseline data are not derived from a fixed time window but reflect the most recent assessments available at the time of the visit with first tafamidis dosing, which are generally expected to have been collected within approximately one year prior to that visit. Due to limitations of the registry data, baseline data may include measurements obtained after the index date. Furthermore, the study baseline visit may not correspond to the initial visit recorded in the J-COSSA registry. Details are described in [Section 9.7.](#)

Figure 1. Schematic illustration of patient follow-up in the J-COSSA registry and in this study.

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The panel represents patient-level follow-up period. (from index date to end of follow-up)

9.3. Variables

The study variables planned for Stage 2 in this study are described in Table 1 below. The final list of variables to be extracted and used for analysis may be refined based on the underlying data structure and feasibility assessment at Stage 1 and will be finalized in the statistical analysis plan (SAP) for Stage 2. For variables collected as year and month only in the registry, the date will be operationally defined as YYYY-MM-01 for analysis.

Table 1. Variables of interest

Variable	Role	Operational Definition
Birth date	Demographics	Date (YYYY-MM-DD)
Age at index date	Demographics,	Continuous (years), Calculated with the index date and birthdate
Date of diagnosis	Baseline Characteristics	Date (YYYY-MM-01)
Age at diagnosis	Demographics	Continuous (years)
Gender	Demographics	Binary (Male/female)
Height	Baseline Characteristics	Continuous (cm)
Weight	Baseline Characteristics	Continuous (kg)
BMI	Baseline Characteristics	Continuous, Calculated with height and weight



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Variable	Role	Operational Definition
Diagnosis of ATTRwt	Baseline Characteristics	Category (ATTRwt only; all patients meet this criterion)
TTR genotype	Baseline Characteristics	Category (Wild type only; all patients meet this criterion)
Cardiac symptom	Baseline Characteristics	Category (present only; all patients meet this criterion), determined by treating physicians in routine clinical practice based on the presence of heart failure symptoms.
Tafamidis treatment: Date of initial tafamidis treatment	Index Date, Exposure	Date of initial tafamidis treatment (Year-Month-01)
Tafamidis treatment: Date of last tafamidis treatment	Exposure	Date of last tafamidis treatment (Year-Month-01)
Tafamidis treatment duration	Exposure	Continuous (days), Calculation is described in Section 9.7 .
Duration from diagnosis to start of tafamidis treatment	Baseline Characteristics	Category (days), Calculated with the date of disease diagnosis to the index date
VISIT Code	Visit information	Nominal category [INIT_001 (Baseline), INIT_002 (1 st follow-up year), INIT_003 (2 nd follow-up year), INIT_004 (3 rd follow-up year), INIT_005 (4 th follow-up year), INIT_006 (5 th follow-up year)] , defined as the follow-up year since patient enrollment into the registry
Investigation date	Visit information	Date (Year-Month-Date)
Follow-up period	Study Information	Continuous (days), Calculation is described in Section 9.7 .
Study discontinuation (patient-level)	Study Information	Category (discontinued, not discontinued), The date of discontinuation (Year-Month-Date)

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Variable	Role	Operational Definition
Survival status	Outcome, Primary Objective	Category (alive, deceased or unknown)
Date of last confirmed survival	Outcome, Primary Objective	Date (Year-Month-Date)
Date of death	Outcome, Primary Objective	Date (Year-Month-Date)
Disease severity: NYHA class	Baseline Characteristics, Secondary Objective	Category (I, II, III, IV)
Disease severity: (National Amyloidosis Centre) NAC ATTR stage	Baseline Characteristics, Secondary Objective	Category (I, II, III) *Patients were categorized into NAC ATTR stages based on NT-proBNP and eGFR values: stage I (NT-proBNP ≤ 3000 ng/L and eGFR ≥ 45 mL/min/1.73 m ²), stage III (NT-proBNP > 3000 ng/L and eGFR < 45 mL/min/1.73 m ²), and stage II (all remaining patients) (10).
Biomarker: B-type natriuretic peptide (BNP)	Baseline Characteristics	Continuous (pg/mL)
Biomarker: N-terminal pro-B-type natriuretic peptide (NT-proBNP)	Baseline Characteristics	Continuous (pg/mL)
Biomarker: Troponin T (TnT)	Baseline Characteristics	Continuous (ng/dL)
Biomarker: Troponin I (TnI)	Baseline Characteristics	Continuous (ng/dL)
Creatinine	Baseline Characteristics	Continuous (mg/dL)
eGFR	Baseline Characteristics	Continuous (mL/min/1.73m ²), Calculated from Creatinine, age and weight

PFIZER CONFIDENTIAL



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Variable	Role	Operational Definition
Serum albumin	Baseline Characteristics	Continuous (g/dL)
Six-Minute Walk Test (6MWT): Walk distance	Baseline Characteristics	Continuous (m)
KCCQ-OS (12 items)	Baseline Characteristics	Continuous
EQ-5D-5L	Baseline Characteristics	Category (1 to 5), Continuous (0 to 100 for Visual Analog Scale, 0 to 1 for utility score)
Echocardiographic parameter: Left Ventricular Ejection fraction (LVEF)	Baseline Characteristics	Continuous (%)
Echocardiographic parameter: IVST	Baseline Characteristics	Continuous (mm)
Echocardiographic parameter: LVPWT	Baseline Characteristics	Continuous (mm)
Echocardiographic parameter: E/e'	Baseline Characteristics	Continuous (mmHg)
Echocardiographic parameter: Global Longitudinal Strain (GLS)	Baseline Characteristics	Continuous (%)
Concomitant medication: SGLT2 inhibitor (SGLT2i)	Baseline Characteristics	Binary (used, not used)
Concomitant medication: β -blockers	Baseline Characteristics	Binary (used, not used)
Concomitant medication: ACE, ARB	Baseline Characteristics	Binary (used, not used)
Concomitant medication: ARNI	Baseline Characteristics	Binary (used, not used)
Concomitant medication: Digitalis glycoside.	Baseline Characteristics	Binary (used, not used)
Concomitant medication: Calcium antagonist	Baseline Characteristics	Binary (used, not used)
Concomitant medication: Pimobendan	Baseline Characteristics	Binary (used, not used)

PFIZER CONFIDENTIAL



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Variable	Role	Operational Definition
Concomitant medication: Loop-diuretics	Baseline Characteristics	Binary (used, not used)
Concomitant medication: Vasopressin V2 receptor antagonist	Baseline Characteristics	Binary (used, not used)
Medical History: History of hospitalization	Baseline Characteristics	Binary (present, not present)
Medical History: History of permanent pacemaker	Baseline Characteristics	Binary (performed, not performed)
Medical History: History of TAVI	Baseline Characteristics	Binary (performed, not performed)
Medical History: History of catheter ablation	Baseline Characteristics	Binary (performed, not performed)
Comorbidity: Atrial fibrillation	Baseline Characteristics	Binary (performed, not performed)
Comorbidity: Conduction disturbances, Atrioventricular block	Baseline Characteristics	Binary (present, not present)
Comorbidity: Sick sinus syndrome	Baseline Characteristics	Binary (present, not present)

9.4. Data Sources

The J-COSSA registry is a longitudinal, multicentre, observational registry collecting clinical data on patients with amyloidosis in Japan using an electronic data capture (EDC) system. The registry is implemented on the Rare Disease Research in Japan (RADDAR-J) platform, a national secure web-based system for rare disease data collection in Japan.

Study variables including exposure, outcome and covariate are derived from predefined CRFs, including annual follow-up forms. Information collected in the registry CRF includes patient demographics, diagnosis, comorbidities, medical history, cardiovascular-related parameters (including laboratory test results and echocardiographic findings), disease-subtype-specific-treatment, concomitant medications, medical history, quality of life measures, and clinical outcomes including survival status.

Data is entered by investigators or trained site staff at participating institutions. The date of death, which is critical for the primary endpoint analysis in this study, is a mandatory data field for all patients for whom death has been documented. The survival status is also required to be completed in all visit records and is therefore consistently captured as long as follow-up data are available. To support the validity of the data used in this study, data entry and coding are conducted in accordance



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

with predefined registry procedures, including entry based on source documents and consistency checks within the EDC system. Collected data do not rely on algorithm-based definition, therefore, no additional validation procedures are required for outcome ascertainment.

For data extraction, investigators at Keio University School of Medicine will request the J-COSSA registry administrator (affiliated with St. Marianna University School of Medicine, Japan) to extract only the pre-specified data fields described in the data extraction request forms. Keio University School of Medicine will receive and securely store an anonymized dataset for analysis. The study sponsor will receive only aggregated analysis outputs from the primary investigator and will not obtain the raw registry dataset.

9.5. Study Size

This study does not prospectively define a target sample size, as it is a retrospective, non-interventional, descriptive analysis based on an existing registry database. No formal sample size or power calculation was performed, and no priori hypotheses or precision targets were specified for the primary endpoint.

The study will analyze data extracted from the J-COSSA registry database covering the period from April 2019 to September 2025. Based on high-level information obtained from J-COSSA registry in January 2026 indicated that approximately 3,600 patients with ATTR-CM treated with tafamidis were registered in the J-COSSA registry, of whom approximately 1,450 had a recorded date of tafamidis initiation (index date) and were potentially eligible for inclusion in the clinical outcome analysis. The study population predominantly consists of patients with wild-type ATTR-CM, with variant ATTR-CM representing only a small minority, consistent with published J-COSSA data showing that approximately 98% of patients have wild-type ATTR-CM (11).

Given that this is a retrospective registry dataset, ongoing query resolution and additional data entry may increase the number of eligible patients and improve data completeness by the final extraction.

9.6. Data Management

Data Collection

This study is a non-interventional study based on the secondary use of existing data collected in the J-COSSA registry, which contains structured data elements.

Data includes patient characteristics, diagnoses, comorbidities, medical history, pharmacological treatment (including tafamidis and concomitant medications), cardiovascular-related parameters (eg, echocardiographic measurements, biomarkers, and functional status), medical procedures, quality of life measures, and clinical outcomes (eg, death and hospitalization) recorded in predefined fields within the registry database. These data are originally captured through electronic CRFs and incorporated into the centralized registry database via the EDC system at each participating site, with data entry performed by investigators or trained site staff.

No new data collection will be performed for the purpose of this study. No additional paper-based or electronic CRFs or data collection tools (DCTs) will be used. All study analyses will be conducted using data extracted from the J-COSSA registry.

Data Vendor and Data Retrieval

The data source for this study is the J-COSSA registry, which is maintained and managed by the registry's governing organization (hereafter referred to as the data vendor or data store).



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Structured study data will be obtained through a database extract performed by the data vendor, in accordance with the study protocol, the statistical analysis plan and/or a pre-specified data extraction request. The study variables planned for this study are described in [Section 9.3.](#) As the study sponsor will not have direct access to the registry database, the final variable specifications to be extracted will be operationalized and implemented by the data vendor based on the SAP. Data extraction activities will be conducted as a one-time database extract at a prespecified timepoint agreed upon by the study sponsor and the data vendor.

The resulting study dataset will be transferred securely by the data vendor to Keio University School of Medicine, where data management and statistical analyses will be conducted, in a predefined electronic format suitable for statistical analysis. The study sponsor will not receive patient-level or record-level data from the J-COSSA registry and will receive only aggregated analysis results generated by Keio University School of Medicine.

Data Extraction and Abstraction Specifications

The scope and specifications of the data to be extracted include, but are not limited to, the following elements:

- Characteristics of patients to be included in the study dataset (eg, patients registered in the J-COSSA registry with specified diagnoses and/or having received tafamidis)
- The observation period and timeframe of the data to be evaluated
- Variables derived from structured data fields within the registry

These specifications will be defined to align with the study inclusion and exclusion criteria. Detailed technical specifications for data extraction are documented in the data extraction request forms. Completed versions of these forms will be included in or referenced by the SAP, as appropriate.

Data Handling and Preparation

Following receipt of the extracted dataset by Keio University School of Medicine, data quality checks and data preparation activities (eg, verification of data structure, identification of missing data, and logical and consistency checks across variables) will be performed prior to statistical analysis. Identified issues will be flagged and treated as missing or invalid for analysis.

Data management and statistical analyses will be performed using statistical software including SAS®, R and Python. All data management and handling activities will be conducted in accordance with applicable internal procedures, data protection requirements, and relevant regulatory and ethical guidelines.

9.7. Data Analysis

Prior to statistical analysis, the extracted dataset will undergo predefined data cleaning and preparation procedures, which include range checks, logical consistency checks across variables, and identification of implausible or inconsistent values. The thresholds for range checks and the criteria for identifying and handling discrepant or invalid data will be specified in advance and documented in the Data Management Plan prior to data preparation. Values identified as inconsistent, implausible, or otherwise invalid will be treated as missing for the purpose of analysis, as source data are not available for verification in this study.



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

No imputation of missing data will be performed for the primary analysis, except for specific variables for which imputation rules are explicitly defined in this protocol (e.g., imputation of tafamidis treatment end date as described above).

Definitions

Following nomenclature will be used in the analysis plan.

- **Nominal visit:** Identifier for the initial/follow-up CRF page (eg, initial visit, 1st year follow-up, 2nd year follow-up, etc.)
- **Investigation date:** The date represents the nominal visit recorded in each CRF page. This date does not necessarily correspond exactly to timing of patient encounters, tafamidis dosing, or individual clinical measurements.

The definition of index date and end of follow-up for this study are described in [Section 9.2.4](#).

The following analysis sets are defined:

- **Overall Cohort:** All patients satisfying the inclusion and exclusion criteria for the Overall Cohort ([Section 9.2.1](#), and [Section 9.2.2](#))
- **Outcome Analysis Set:** A subset of the Overall Cohort satisfying the eligibility criteria for the Outcome Analysis Set ([Section 9.2.1](#), and [Section 9.2.2](#)).
- **Supplemental Analysis Set:** A subset of Overall Cohort that is not included in the Outcome Analysis Set
- **Possible Delay Set:** A subset of outcome analysis set with possible data entry delay (see below)

Analysis of each clinical outcome in Stage 2 will be based on the Outcome Analysis Set. For outcomes requiring additional data availability (eg, baseline measurements), analyses will be restricted to the corresponding subset of the Outcome Analysis Set.

For some patients whose follow-up ends at last date of confirmed survival or last recorded investigation/measurement date, rather than date of death or discontinuation, additional follow-up data may exist beyond the last follow-up visit but may not yet have been entered into the registry at the time of data cut-off. We set the allowance limit for determination of possible data entry delay to be 15 months; patients exceeding this allowance (>15 months) are classified as the Possible Delay Set. The allowance may be refined based on Stage 1 feasibility results.

Stage 1 analyses are intended not only to characterize data availability and completeness, but also to assess potential sources of bias relevant to Stage 2 analyses. Selection related to the availability of index date and follow-up data will be descriptively evaluated, while potential data entry delays will be addressed through sensitivity analyses excluding patients in the Possible Delay Set.

Detailed methodology for summary and statistical analyses will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the study sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

No statistical hypothesis testing will be conducted since the objective of this study is primarily descriptive. However, 95% confidence interval (95%CI) will be calculated for parameters of interest.

Stage 1 : Data characterization and completeness assessment

The following assessment is planned for Stage 1. If warranted by the planned assessment results, additional analyses or tabulations may be performed.

Inclusion/exclusion criteria and patient flow

- Each step of inclusion and exclusion condition will be evaluated. Patient flow will be tabulated, including Overall Cohort, Outcome Analysis Set, and Supplemental Analysis Set.

Index date, end of follow-up, and follow-up duration

- The last day of follow-up for each patient will be identified. Index dates and follow-up duration (days from index date to last date of follow-up) will be summarized for the Outcome Analysis Set.

Baseline visit

- The baseline visit, defined as the nominal visit where the index date is documented, will be identified for each patient in the Outcome Analysis Set. The registry year corresponding to the baseline visit will be tabulated.

Patient demographics and baseline characteristics

- Patient demographics and baseline characteristics will be summarized, where baseline is defined as the nominal visit of the first dosing of tafamidis, with or without an identified index date. The demographics and baseline characteristics are listed in [Table 1](#). Summaries will be provided for the Overall Cohort, Outcome Analysis Set, and Supplemental Analysis Set. For the Supplemental Analysis Set, summaries may be provided separately for the subset of patients not meeting inclusion criteria 6 for the Outcome Analysis Set and the subset of patients meeting exclusion criteria 3 for the Outcome Analysis Set.

Data completeness and missingness (baseline and nominal visit)

The following evaluation will be conducted for the Outcome Analysis Set.

- Missingness of the following variables at the baseline or initial visit will be summarized: birthdate, diagnosis date, gender, height, weight, BMI, diagnosis, disease severity, biomarkers, echocardiographic parameters, 6MWT, KCCQ-OS, EQ-5D-5L, comorbidities, concomitant medications, and medical histories. Detailed variables for disease severity, biomarkers, echocardiographic parameters, comorbidities, concomitant medications, and medical histories are provided in [Table 1](#).
- Missingness of measurement date of baseline factors at nominal baseline visit will be summarized. In addition, gaps between the investigation date and the available measurement dates at nominal baseline visit will be summarized.
- Missingness of outcome status for each nominal visit for all patients will be summarized. Category of outcome status (deceased, alive, unknown) will not be identified.

Missingness of key dates

- The number of patients without recorded date of death among those reported as deceased will be tabulated.
- The number of patients without recorded date of discontinuation among those reported as discontinued will be tabulated.



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

Exposure to tafamidis

The following evaluation will be conducted for the Outcome Analysis Set

- Tafamidis treatment status (yes/no) will be summarized for each nominal visit. In addition, among patients with any recorded tafamidis treatment, the number of patients with documented treatment end dates or ongoing treatment at the time of the last available dosing record will be tabulated.
- The last dosing date of tafamidis will be identified for each patient. The last dosing is defined as the recorded end date of tafamidis dosing at the last tafamidis dosing record prior to the data cut-off. If dosing status is ongoing or the end date of tafamidis dosing is not reported at the last tafamidis dosing record, the investigation date of the corresponding nominal visit will be used for imputation. Treatment duration will be summarized as the time from the index date to the date of last dosing.

Possible Delay Set

Possible delay in data entry into registry will be evaluated. Possible delay is defined as the gap between the date of last follow-up visit and the date of data cutoff of more than the allowance limit (gap > allowance). The number of patients in the Possible Delay Set will be summarized using allowance of >15, >18, and >24 months. The duration between the date of last follow-up visit and the date of data cutoff will also be summarized.

Stage 2: Analyses of clinical outcomes and other variables

Patient demographics and baseline characteristics

Patient demographics and baseline characteristics will be summarized for the Overall Cohort, Outcome Analysis Set, Supplemental Analysis Set, and Possible Delay Set. For the primary analysis, baseline is defined as the nominal visit at which the first dosing of tafamidis is recorded, regardless of whether an index date is recorded. To assess the appropriateness of the baseline definition, the temporal relationship between the index date and the date of baseline assessment will be evaluated by summarizing the time gap between the index date and the investigation date recorded at the nominal baseline visit. In addition, the number of patients whose baseline data were derived from annual reports recorded after the index date will be summarized, if applicable. As a sensitivity analysis, an alternative baseline definition may be applied.

Follow-up and exposure

Follow-up duration (days from index date to last date of follow-up) will be summarized.
Treatment duration of tafamidis (days from index date to end of dosing) will be summarized.

Mortality

Time from the index date to date of death will be analyzed using the time-to-event methods. Patients without death will be censored at the date of discontinuation, the date of last confirmed survival, or the date of last recorded investigation, whichever occurs first. The analysis will be based on the Outcome Analysis Set.

Primary analysis will use the Kaplan-Meier method to create survival plots and compute cumulative survival probabilities at 3-month intervals. As a secondary analysis, analyses stratified by established



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

baseline prognostic factors such as NYHA class and NAC ATTR stage will be conducted. In addition, other candidate baseline factors may be used for additional stratified or subgroup analyses.

As an exploratory analysis, Cox proportional hazards models will be used to assess the association between baseline factors and mortality to assess additional potential baseline prognostic factors. Baseline factors include established prognostic factors (eg, age, baseline NYHA class, baseline NAC ATTR stage) as well as additional clinical characteristics such as biomarker values, echocardiographic parameters, selected comorbidities, medical history and history of hospitalization. For continuous variables, potential cut-off values may be explored. The detailed list of potential prognostic factors will be described in the SAP.

As a sensitivity analysis, the primary analysis will be repeated with the outcome analysis set excluding patients in the Possible Delay Set. Additional “on treatment” analysis may be conducted with the follow-up time censored at the time of last tafamidis dosing (intervening treatment interruptions will not be considered).

9.8. Quality Control

Data preparation and all the planned analysis will be outsourced to Keio University School of Medicine, Tokyo, Japan. The study team affiliated in Keio University School of Medicine will develop SAP and perform data preparation and statistical analyses in accordance with the protocol developed by the study sponsor.

Data monitoring activities are limited to quality control procedures applied during data management and analysis, including data cleaning, data validation, and statistical programming quality control, as this study uses secondary data from an existing registry and does not involve on-site monitoring or source data verification.

During data preparation, data cleaning procedures are performed to identify missing data and potential anomalies, including checks for data completeness, consistency across variables, and identification of out-of-range or implausible values. Analytical datasets are created based on predefined derivation rules and are verified through documented processes, including consistency checks and internal validation of derived variables using the extracted dataset. Detailed data preparation procedures will be specified in the separate Data Management Plan and finalized prior to the initiation of data collection.

For quality assurance of analysis, Keio University School of Medicine will conduct code review of all modules of program and descriptive statistics review of all variables and all output results. Quality control procedures will be implemented to ensure the accuracy, consistency, and reliability of all statistical analyses conducted in this study. Independent programming, code review, and review of descriptive statistics and analysis outputs will be conducted by statisticians and analysts with access to the extracted dataset, as applicable. The level of independent programming will vary depending on the type of analyses. For Stage 1 analyses (data completeness and feasibility), single programming will be applied. For Stage 2 analyses (clinical outcome analyses), independent double programming will be implemented.

Data managers, statisticians and analysts involved in data preparation and analysis have appropriate academic qualifications, relevant professional experience, and have completed required training in clinical research, including GCP, data integrity, and CTR Quality Management System procedures. They are assigned defined roles (eg, Lead Biostatistician, Statistical Analyst, and Data Manager), and have documented training records and experience consistent with their responsibilities.

PFIZER CONFIDENTIAL



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

The specific quality control activities and programming approaches applied to individual analyses will be prospectively defined and documented in the SAP and/or the associated study programming plan. All data processing and analysis-related activities will be appropriately documented. Study records, including analysis datasets and statistical programming code, will be retained and archived in accordance with applicable sponsor and regulatory requirements to ensure reproducibility of results.

Data quality control procedures related to the collection, entry, and management of the registry data, are implemented by the J-COSSA registry owner in accordance with the predefined Data Management Plan and Quality Control Plan. These procedures include edit checks performed at the time of data entry, programmed logical checks based on predefined data validation rules, and external or manual checks of extracted data to identify missing or inconsistent entries, followed by query generation and resolution. These procedures support the accuracy, completeness, and integrity of the registry data. Source data verification and endpoint adjudication are not performed as part of this study, beyond the standard procedures applied within the registry.

9.9. Strengths and limitations of the research methods

Strengths of the research methods

Strengths of the study include the use of data from an existing, nationwide registry that has captured longitudinal clinical information following tafamidis initiation in routine clinical practice in Japan.

The J-COSSA registry collects a broad range of clinical information on an annual basis after tafamidis initiation, encompassing diverse aspects of patient management and outcomes beyond treatment exposure and survival status.

In accordance with the JCS's statement on the appropriate administration of tafamidis, responsibility for follow-up of the clinical course remains with the certified physician and institution that initiated treatment. This framework is intended to support continuity of clinical oversight after treatment initiation and to facilitate the longitudinal capture of key clinical information within routine practice.

At the same time, because the registry operates under real-world clinical conditions, the scope and completeness of longitudinal data collection may vary across patients and participating institutions. Such variability is inherent to real-world data collection; nevertheless, the registry provides a structured mechanism for capturing post-initiation clinical follow-up across a wide range of clinical settings.

Limitations of the research methods

This study is a single-cohort, registry-based study including only tafamidis-treated patients and does not include an untreated or comparative control group; therefore, it is descriptive in nature and not designed to evaluate the effectiveness of tafamidis. In addition, the primary analyses are anchored on tafamidis initiation and do not explicitly account for subsequent changes in treatment patterns, such as treatment discontinuation, interruption, or dose modification during follow-up.

Limitations related to the data source should also be considered. Because data are collected as part of routine clinical practice, some variables may have missing data. In addition, laboratory measurements are performed locally at each participating site, and standardized measurement methods and event definitions are not specified in the J-COSSA registry protocol. Cardiac symptoms are not defined using a standardized or prespecified criterion in the registry and are assessed by treating physicians as part of routine clinical practice, which may introduce variability in the assessment of this variable. Tafamidis initiation dates are recorded only at the year and month level in the registry; therefore, the index date is operationally defined as the first day of the recorded month, which may introduce minor



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

imprecision in time-to-event estimation. Also, baseline values defined using nominal visits may include measurements obtained after the index date for a small proportion of subjects.

Selection bias and limitations in generalizability should be acknowledged. As Stage 2 analyses include only patients with available index date and post-index follow-up data, the Outcome Analysis Set may differ from patients with the Overall Cohort, Supplemental Analysis Set and Possible Delay Set, with respect to patient demographics and characteristics. While this descriptive comparison may help contextualize the representativeness of the analytic population, any residual differences between the two groups may still limit the interpretability and generalizability of the study findings.

The J-COSSA registry data does not undergo independent third-party source data verification, and therefore inaccuracies or inconsistencies in recorded data cannot be ruled out. Moreover, data for this study will be extracted at a predefined cutoff timepoint, while the registry will continue thereafter and previously collected data may be updated. Consequently, study findings should be interpreted as reflecting a snapshot of the registry at the time of data extraction.

These limitations should be considered when interpreting study outcomes.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Ethical Guidelines for Medical and Biological Research Involving Human Subjects.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the



Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of clinical outcome analyses conducted in Stage 2 of this study are intended to be published in scientific literature or presented at a scientific congress. Findings from the Stage 1 feasibility assessment may be used, as appropriate, to inform the interpretation of the Stage 2 results. The study team will follow the International Committee of Medical Journal Editors (ICMJE) criteria to determine authors, and all authors who meet these criteria will be offered authorship. In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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Tafamidis
B3461129 NON-INTERVENTIONAL STUDY PROTOCOL
Version 1.0, 25 June 2026

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14. LIST OF TABLES

[Table 1. Variables of interest](#)

15. LIST OF FIGURES

[Figure 1. Schematic illustration of patient follow-up in the J-COSSA registry and in this study.](#)

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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